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Life Science Journal

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Identification of three fish species of genus *Plectorhynchus* from the Red Sea by their scale characteristicsAhmed S. A. Harabawy^{1, 3}, Imam A. A. Mekkawy^{2, 3} and Ali Alkaladi¹¹Biology Department, Faculty of Science, North Jeddah, King Abdulaziz University, Jeddah, Saudi Arabia.²Biology Department, Faculty of Science, Taif University, Taif, Saudi Arabia.³Zoology Department, Faculty of Science, Assiut University, Assiut, Egypt.harabawy2005@yahoo.com

Abstract: Scale characteristics and its detailed structure from different body regions were studied in three *Plectorhynchus* species in terms of morphometry and Scanning Electron Microscopic techniques. The present work has been suggested to the rarity of taxonomic and biological information about the three *Plectorhynchus* species, *P. gaterinus*, *P. pictus* and *P. schotaf* from the Red Sea. A wide spectrum of size-free intraspecific and interspecific variations was recorded and documented concerning the overall form of the scales and their morphometrics, scale surface morphology, the primary, secondary and tertiary radii counts, shape of interradian tongues and the first circuli, the interradian circuli, most outer lateral circuli, inner lateral circuli, denticles on circuli, interradian and intercircular grooves, segmentation and granulation pattern of the caudal field and the shape of ctenii. The quantitative scale characters of *Plectorhynchus* species are subjected to cluster analysis that revealed two main subclusters, the first includes *P. gaterinus* and *P. schotaf*, and the second subcluster includes *P. pictus*. In addition to the intraspecific variations, the highly significant interspecific variations in the morphometric indices also were evident from one body region to another ($P < 0.01$). The pattern of variations reflected by CVA referred to the partial discrimination between the three *Plectorhynchus* species considered. Among the scale characteristics used to differentiate between *Plectorhynchus* species are the overall shape of the lateral line canal, the relative position of its anterior and posterior openings and the cantilevered anterior extension of the canal.

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1. Introduction

The Red Sea has a unique environment as it is exposed to extreme natural influences, viz. intensive sun radiation, constant hot winds and subsequent high evaporation rate with negligible inflow of rivers. Like other tropical and subtropical seas, the Red Sea is characterized by a rich and highly diversified fauna and flora (Shiekh-Eldin, 1988; Ghisotti, 1995).

Coral reefs provide a home to thousands of species of different flora and fauna and found to be one of the most diverse and productive natural ecosystems. In spite of presence of a large variety of bony fishes living in and around the coral reefs in the Red Sea, so far, little is known about these fishes.

Lepidology, the use of scale morphology and squamation in fish classification, can be dating back to the mid-nineteenth century where the first use of fish scales in taxonomy; in this time the fishes were divided into four groups according to the structure of their scales: Placoidei, Ganoidei, Ctenoidei, and Cycloidei (Jawad, 2005).

The importance of scale structure as a research material in fish taxonomy and fisheries increased with great developments in the field of microscopy. Application of scanning electron

microscopy (SEM) to reveal morphology, ultrastructure and surface ornamentation of fish scales had facilitated its utility to distinguish the taxonomic groups over a continuum ranging from higher taxa to species.

Detailed structure of the fish scale can be helpful in describing the species, nomenclature, phylogeny, sexual dimorphism, age determination, growth studies, population dynamics, stock assessment, past environment experienced by the fish, migration, taxonomy, discriminating between hatchery-reared and wild populations, in understanding the pathology of a fish scale due to pollution of a water body, in addition to use the scales as a biosorbent to remove heavy metals from contaminated waste streams (Mekkawy *et al.*, 2007; Dapar *et al.*, 2012; Ganzon *et al.*, 2012; Prabu *et al.*, 2012).

Many authors have strongly emphasized on the validity of scale morphology and ultrastructural characteristics for fish taxonomy and phylogeny (Lippitsch, 1990, 1993; Mekkawy *et al.*, 1999, 2003, 2006, 2011; Mahmoud *et al.*, 2005; Harabawy *et al.*, 2007; Reza *et al.*, 2009; Esmaeili and Gholami, 2011; Dapar *et al.*, 2012 and Ganzon *et al.*, 2012). In addition to the systematic status, the functional

approach of the ultrastructure and superficial ornamentation of teleost scales also attracted the attention of the aforementioned recent authors.

Studies that use the morphometric characteristics of scales from different body regions in fish taxonomy were rare (e.g. Mekkawy *et al.*, 1999, 2003, 2006, 2011; Mahmoud *et al.*, 2005 and Harabawy *et al.*, 2007). Most of these studies aimed to establish a wide range of valuable scale characters that can reflect a well-defined taxonomic status and a well-founded phylogenetic tree of fish taxa.

The family Haemulidae (order Perciformes) represents one of the valuable and economical fish families in the Red Sea. Its members (Haemulids or grunts) are bottom-feeding, carnivorous, nocturnal fishes and use the reefs for shelter (Randall, 1992). Taxonomically, Haemulids appear as one of the problematic groups of marine fish families due to the fact that the traditional characters used in identification of fishes are relatively constant among certain species of haemulids. From a taxonomic point of view, the Red Sea region seems to be one of the least studied areas in concern with haemulids.

The present work aimed to screening and documenting the diversity of scale characteristics of three *Plectorhynchus* species: *P. gaterinus*, *P. pictus* and *P. schotaf* from the Red Sea at Jeddah and to answer the questions that were previously mentioned by Mekkawy *et al.* (2011) concerning the most useful scales characters for systematic purposes, the validity of the use of scale morphometrics in fish taxonomy, possibility to give an interpretations for the surface scale ornamentation in terms of systematic and functional approaches. In addition, what is the difference in scale characteristics of marine and freshwater fishes? The answers of such questions should present the bases for further work on scale characteristics and their exploitation for phylogenetic investigations for Haemulidae. Among the interesting scale characteristics considered in the present work were the overall form of the scales and their morphometrics, counts of radii, shape of interradii tongues and the first circuli, the interradii circuli, most outer lateral circuli, inner lateral circuli, denticles and grooves among circuli, granulation pattern of caudal field and form of ctenii. Do such characters reflect functional morphological aspects? This is also a question to be answered.

2. Materials and Methods

In the present work, 1160 scales from 27 specimens of three *Plectorhynchus* species, namely: *P. gaterinus* (Forsskål, 1775) (150 – 267 mm standard length (SL)), *P. pictus* (Tortonese, 1936) (200 – 280 mm SL) and *P. schotaf* (Forsskål, 1775) (188 – 245 mm SL) were examined to elucidate their scale characteristics. These specimens were collected

from the Red Sea at Jeddah, Saudi Arabia through the period from March to April 2012.

The scales were gently removed with fine forceps from the left side of the body from the following positions on the body: 1)- Region A, directly below the anterior part of the dorsal fin (BDFS). 2)- Region B, postoberculum (POS). 3)- Region C, below the lateral line, between the pectoral and pelvic fins (BLLS). 4)- Region D, caudal peduncle directly above the lateral line (CPS). In addition, anterior lateral line scales (ALLS), middle lateral line scales (MLLS) and posterior lateral line scales (PLLS) from caudal peduncle region. Morphometric measurements and radii counts were taken only from the scales of the first four regions (regions A, B, C and D). While scales forming the lateral line were examined to show the lateral line pattern, shape and characters of the lateral line canal.

Scales examined were cleaned by physical careful removing of the adhering tissues debris without damage in the scale surface. Then they were immersed in a solution of 10% ammonia for 24-36 hr to soften adhering tissues and to clean them. Cleaned scales were dried on a filter paper and kept between two glass slides.

Fig. 1 shows the structure of a sectioned scale, types of radii and the morphometric measurements considered. The primary, secondary and tertiary radii were counted to reveal intraspecific and interspecific variations. The morphometric measurements were treated in terms of indices (L1/L, L2/L, L1/L2 and W/L) whereas, L: scale length; L1: rostral field length; L2: caudal field length; W: scale width.

To clarify intraspecific and interspecific variations of three *Plectorhynchus* species, ANOVA (Design:Species+Region+Species*Region, ($R^2=0.97-0.99$)), canonical variate analysis and clustering analysis were applied on the morphometric indices of scales using SPSS package, release 9.0.0 (1998) with the assumption of homogeneity of variance.

Scanning Electron Microscopy (SEM) was used to study the morphology and microstructures of the scales in the rostral, lateral, and caudal regions. The cleaned and dried scales that are used for Scanning Electron Microscope (SEM) examination were mounted and fixed by sticker tape on a specimen holder and coated with a 30-nm layer of gold. The electron micrographs were produced on GAOL, GSM5400LV, SEM in back scattering mode and on a Stereo Scan Cambridge Mark 2A (15 KV) in Assiut University Electron Microscope Center, Assiut, Egypt.

Also the shape of overall granulation area in the caudal field was studied according to the shape of rostro-caudal separation line, the posterior rim and the

shape of granulation area in the caudal field by using light microscope.

3. Results

Scale surface morphology and morphometrics:

All scales of *Plectorhynchus* species are mainly of the ctenoid and sectioned type (i. e. with well-developed radii) on all parts of the body of the three species investigated. No simple scales (i. e. without or with only weakly developed radii) were recorded. The surface of scales is divided into three distinct fields, anterior or rostral field from the focus to anterior margin, posterior or caudal field from the focus to the posterior margin and lateral fields (Fig. 1). The scales of *Plectorhynchus* species studied show a characteristic surface ornamentation which in its simplest case consists of ridges (circuli) and grooves, forming nearly circular rings around a center called focus except in the caudal region that have no circuli and alternatively, contains ctenii and granulation segments. The variable scale shape has its effect on the arrangement of the circuli. The regenerated scales (without any ornamentation at least at the central part of the scale) were recorded. The largest scales are recorded in post operculum region (POS) below the lateral line, while the smallest ones are found in caudal peduncle region and on the belly.

In the rostral part of the scale, the circuli are partitioned by deep and narrow grooves that run radially (radii) between the focus and anterior rim. The radii on the scales of *Plectorhynchus* can be categorized into three types depending on their origin and end on the scale including: primary, secondary and tertiary (Fig. 1). In comparison to the tertiary radii, the relative number of primary and secondary radii is more in number.

Morphometrics and counts of radii:

Table 1 shows the basic statistics of the scale morphometric indices (relative to scale length, L) from four different body regions. This table reveals the interspecific variations among the three *Plectorhynchus* species considered. Based on the size-free morphometric indices clustering of these species (Fig. 2) refers to their division into two main subclusters, the first includes *P. gaterinus* and *P. schotaf*, and the second subcluster includes *P. pictus*. Highly significant interspecific variations in these indices were evident in different body regions scales ($P < 0.01$) (Table 1).

In each species, Tables 2-4 reveal intraspecific variations in these scale morphometric characteristics of the four body regions considered. From Table 2, one can note that, in *P. gaterinus*, the indices L1/L and L1/L2 show significant difference between scales of the four body regions ($P \leq 0.05$). But W/L index revealed highly significant variations ($P < 0.01$). While L2/L index reflected insignificant

variation ($P > 0.05$). Tables 3 and 4 showed that in both *P. pictus* and *P. schotaf* respectively, only one index (W/L) revealed highly significant variations ($P < 0.01$) while the rest of indices show insignificant differences ($P > 0.05$) between scales of the four body regions of both.

The pattern of variations reflected by CVA referred to the partial discrimination between the three *Plectorhynchus* species on CVI only (Fig. 3) due to the discriminating power of L1/L index that has the higher loading value on CVI (Table 5).

The percentages of occurrence and basic statistics of the primary, secondary and tertiary radii counts are given in Tables 6, 7 and 8. Table 6 shows variations in the primary radii counts among the three *Plectorhynchus* species studied. These counts are ranged between 2-7, 1-9 and 4-9 in *P. gaterinus*, *P. pictus* and *P. schotaf* respectively. The secondary radii counts varied between 0-7, 0-7 and 0-3 in *P. gaterinus*, *P. pictus* and *P. schotaf* respectively. The tertiary radii ranged between 0-2, 0-5 and 0-2 in *P. gaterinus*, *P. pictus* and *P. schotaf* respectively. Such counts were size free in species considered ($P > 0.05$). The patterns of distribution of such size-free counts revealed significant scale interspecific variations of *Plectorhynchus* species using G – statistics test ($P < 0.01$).

Scanning electron microscope studies:

Rostral field:

At the rostral rim of all scales of *Plectorhynchus* species studied, tongue-like projections are found in the inter-radial space and are free of circuli near the rim (Fig. 4a). On the same scale, such tongues may be convex or straight or both are found; the 1st inter-radial circulus is rounded or relatively straight (Fig. 4a).

The radial grooves in the rostral field of the scales of *Plectorhynchus* species have two different forms. In the first form, the groove appeared as a deep irregular groove, some strong ridges on each side of the groove are touched and some others are short. This form was recorded in scales of *P. gaterinus* and *P. pictus* (Fig. 4b). In the second form, the groove is relatively shallow with narrow split; this form was recorded in *P. schotaf* (Fig. 4c).

Inter-radial circuli, grooves and denticles:

The spaces between the circuli are called intercircular spaces (grooves). Such grooves were flat and wide relative to the circulus thickness in most of scales of *Plectorhynchus* species studied (Fig. 5). The circuli found between radii (in the interradian space) bear small denticles or tooth-like structures that can be seen only under high magnification and are called lepidonts. Three different characteristic types of denticles or lepidonts were identified on the inter-radial circuli (Fig. 5a-c). Type 1: The circuli bear

denticles of variable size; the free ends of these denticles are oriented backwardly. Such form was recorded in *P. gaterinus* (Fig. 5a). Type 2: The circuli bear strong denticles with very pointed ends (claw-like ends) oriented backwardly (Fig. 5b). Such form was recorded only in *P. pictus*. Type 3 is characterized by denticles with rounded ends that have flat dorsal surface and is oriented backwardly (Fig. 5c). This type was recorded in *P. schotaf*. In addition, growing small denticles were recorded in the three species studied.

The outer lateral circuli:

In all scales of *Plectorhynchus* species studied, the most outer lateral circuli (the first to second ones) are relatively free of denticles (Fig. 6). The outer circuli may be thick (Fig. 6a) or thin (Fig. 6b and c) with sculptured surface. The grooves between the outer circuli are flat. Such grooves were recorded in *P. gaterinus* and *P. schotaf* (Fig. 6a and c). Other grooves appear as V-shape enclosed by wide thickened circuli in all scales of *P. pictus* (Fig. 6b). The denticles of the outer lateral circuli have tubercular shape and gradually take their specific shape in the inner lateral circuli towards the focus.

The inner lateral circuli and denticles:

The inner lateral circuli of *Plectorhynchus* species are separated by flat grooves enclosed by thickened circuli. These grooves were recorded in scales of *P. gaterinus* and *P. pictus* (Fig. 7a and b). V-shape grooves enclosed by wide thickened circuli are recorded in scales of *P. schotaf* (Fig. 7c). The inner circuli bear denticles of variable shape and size on their dorsal sides. These denticles were differentiated into three different categories (Fig. 7a-c): 1- strong conical denticles with the tip bent anteriorly towards the center of the scale and show a neck-like narrowing (Fig. 7a), this type of denticles was recorded in *P. gaterinus*; 2- short small spine-like denticles with pointed ends and unequal interval distances between them on the same circulus (Fig. 7b), these denticles are specific for *P. pictus* and 3- canine-like denticles with ends bend slightly towards the focus and separated by equal interval distances (Fig. 7c), these were recorded in *P. schotaf*.

Focus region:

The focus of the scales of the both species *P. gaterinus* and *P. pictus* is located in front of the separation line, while in scales of *P. schotaf*, the focus penetrates the granulation area to be behind the separation line (Figs. 8 and 11). The focus region shows unique patterns of circuli and tubercular ridges (Fig. 8a-c). The focal circuli of *P. gaterinus* are smooth and do not bear any denticles (Fig. 8a), while those of *P. pictus*, bear small irregular denticles (Fig. 8b). In contrast, in scales of *P. schotaf*, the central part of the focus has no circuli and appears as

irregular tubercular ridges with different shapes and sizes (Fig. 8c).

Caudal field:

Segmentation of the caudal field and ctenii:

Figures 9-10 reveal that the posterior field of the scales appears as rows of segments arranged in parallel radial lines and ending as long ctenii at the posterior rim of the scale. According to the pattern of segmentation, shape and arrangement of segments and shape and size of ctenii, three patterns of scales were identified in *Plectorhynchus* species considered. In *P. gaterinus*, the segments of each row occupied alternative position with the adjacent ones. Each segment has two equal lateral folds and is tightly connected to other one with little intersegmental matrix layer; the outer row extends posteriorly into long pointed ctenii (Figs. 9a and 10a). In *P. schotaf*, the segments are sculptured and have irregular shapes without specific pattern and extend posteriorly into ctenii of various shapes and sizes. The segments are spaced and have a wide matrix layer connects between them (Figs. 9b and 10d). In case of *P. pictus*, the segments of each row are adjacent to each other and the ctenii are long and pointed (Fig. 9c) or have a wide edges with very sharp lateral processes (Fig. 9d). Each segment has two lateral folds, one longer than the other. The segments are connected to each other by ligaments-like tendons (Fig. 10b). In all scales of the three *Plectorhynchus* species studied, old segments are located internally close to the focus and have corroded or resorbed appearance whereas the youngest segments are well developed, externally located and extending to the posterior rim (Fig. 9d). Some pores were recorded in the caudal field of scales of *Plectorhynchus* species studied (Fig. 8c).

The separation line, the posterior rim and the shape of granulation area:

The separation line is the border between rostral and caudal field. At which the circuli do not invade the posterior field of the scale because the circuli have dead ends or merge together and the inter-circular grooves become broader. Therefore, the area of granulation in the caudal field is sharply separated from the anterior rostral field and is easily recognizable.

According to the separation line, the shape of posterior rim and the shape of granulation area, three forms were identified in sectioned scales in *Plectorhynchus* species (Fig. 11). Form 1: The separation line is convex and the posterior rim is rounded, so the granulation area is similar to a convex lens. This form was specific for *P. gaterinus* (Fig. 11a). Form 2: The separation line is zigzag-shaped and the posterior rim is rounded. Such form was specific for *P. pictus* (Fig. 11b). Form 3: The separation line has □-shape and the posterior rim has

V-shape, therefore the granulation area is homboidal in shape, this form was specific for *P. schotaf* (Fig. 11c).

Lateral line canal:

Figure 12 shows the characteristics of the lateral line canal of *Plectorhynchus* species studied. The lateral line canal is a simple tube embodied within the matrix of the scale. It is divided into a rostral wide tube extend anteriorly and a caudal narrow tube that extend posteriorly to end just before the posterior margin (*P. gaterinus* and *P. schotaf*) (Fig. 12a) or reach the posterior margin of the scale (*P. pictus*) (Fig. 12b and c). The rostral wide tube slightly deviates anteriorly from the anteroposterior axis of the scale (oblique). The anterior opening is

hidden by a cap-like projection cantilevered over it. The anteriorly projecting cap-like extensions are adorned by two forward-projecting spines from the antero-dorsal and antero-ventral corners of the cover. The posterior opening of caudal narrow tube occurs on the inner surface of the caudal region. In *P. pictus*, a series of pores are found at the lateral side of the wide rostral canal and the posterior opening occurs at the scale's posterior margin at the bases of ctenii (Fig. 12c), but in *P. gaterinus* and *P. schotaf*, no pores are found and the posterior opening occurs just before the posterior margin (Fig. 12a). The length of the lateral-line canals vary along the lateral line and gradually decreases to be just a simple short straight tube in caudal peduncle lateral line scales.

Table 1: Basic statistics, mean \pm SD (Range) of the morphometric indices of scales from four body regions of the three *Plectorhynchus* species from the Red Sea, Jeddah, Saudi Arabia. The postopercular scales (POS), below dorsal-fin scales (BDFS), below lateral line scales (BLLS) and caudal peduncle scales (CPS).

Region	Index	Mean \pm SD (Range)		
		<i>P. gaterinus</i> (N=40)	<i>P. pictus</i> (N=50)	<i>P. schotaf</i> (N=45)
Region A (BDFS)	L1/L**	66.7 \pm 5.28(57.03–74.07) a	72.03 \pm 3.46(62.44–78.98) b	68.52 \pm 2.29(63.73–72.43) c
	L2/L**	33.31 \pm 5.3(25.93–42.97) a	27.98 \pm 3.47(21.02–37.56) b	31.48 \pm 2.27(27.37–36.08) c
	L1/L2**	205.9 \pm 52.74(60.61–285.61) a	262.91 \pm 46.22(166.22–375.81) b	219.25 \pm 22.89(176.63–264.66) a
	W/L**	84.92 \pm 4.73(77.62–100) a	94.51 \pm 7.42(78.68–107.33) b	80.08 \pm 7.17(67.02–93.7) c
		<i>P. gaterinus</i> (N=40)	<i>P. pictus</i> (N=50)	<i>P. schotaf</i> (N=45)
Region B (POS)	L1/L**	66.36 \pm 3.1(61.57–76.9) a	71.42 \pm 3.68(61.87–79.05) b	69.66 \pm 3.07(64.97–77.08) c
	L2/L**	33.64 \pm 3.09(23.1–38.43) a	28.57 \pm 3.67(21.17–38.13) b	30.35 \pm 3.06(22.92–35.03) c
	L1/L2**	200.08 \pm 31.92(160.2–332.87) a	256.13 \pm 49.56(162.28–373.47) b	233.05 \pm 36.23(185.5–336.26) c
	W/L**	98.64 \pm 5.02(89.45–108.99) a	109.69 \pm 8.18(92.43–131.23) b	93.42 \pm 4.6(81.72–104.13) c
		<i>P. gaterinus</i> (N=40)	<i>P. pictus</i> (N=50)	<i>P. schotaf</i> (N=45)
Region C (BLLS)	L1/L**	64.89 \pm 4(60.03–72.36) a	71.6 \pm 2.6(66.67–77.88) b	69.02 \pm 4.24(63.28–81.82) c
	L2/L**	35.13 \pm 3.94(27.92–39.97) a	28.38 \pm 2.59(22.14–33.41) b	30.97 \pm 4.25(18.18–36.93) c
	L1/L2**	188.46 \pm 34.46(150.21–259.18) a	255.34 \pm 34.66(200–350.53) b	229.85 \pm 53.54(171.35–450) c
	W/L**	86.25 \pm 6.58(66.61–98.42) a	102.54 \pm 8.5(88.84–122.57) b	87.05 \pm 4.77(76.86–100) a
		<i>P. gaterinus</i> (N=40)	<i>P. pictus</i> (N=50)	<i>P. schotaf</i> (N=45)
Region D (CPS)	L1/L**	63.9 \pm 4.97(51.74–71.46) a	72.34 \pm 2.33(67.42–75.83) b	68.25 \pm 3.3(61.97–75.61) c
	L2/L**	36.13 \pm 4.97(28.54–48.26) a	27.71 \pm 2.29(24.17–32.58) b	31.77 \pm 3.3(24.39–38.03) c
	L1/L2**	181.91 \pm 38.15(107.2–250.41) a	263.48 \pm 29.76(206.9–313.7) b	218.35 \pm 35.11(162.98–310.08) c
	W/L**	78.42 \pm 6.62(66.67–95.66) a	87.72 \pm 5.45(75.13–100) b	75.4 \pm 4.02(65.82–82.99) c

**= The differences are highly significant at 0.01 level.

Table 2: Basic statistics, mean \pm SD (Range) of the morphometric indices of scales from four body regions of *P. gaterinus* from the Red Sea, Jeddah, Saudi Arabia. The postopercular scales (POS), below dorsal-fin scales (BDFS), below lateral line scales (BLLS) and caudal peduncle scales (CPS).

Index	Region A (BDFS)	Region B (POS)	Region C (BLLS)	Region D (CPS)
	Mean \pm SD (Range) (N=40)	Mean \pm SD (Range) (N=40)	Mean \pm SD (Range) (N=40)	Mean \pm SD (Range) (N=40)
L1/L*	66.7 \pm 5.28 (57.03–74.07) a	66.36 \pm 3.1 (61.57–76.9) a	64.89 \pm 4 (60.03–72.36) ab	63.9 \pm 4.97 (51.74–71.46) b
L2/L ⁿ	33.31 \pm 5.30 (25.93–42.97) a	33.64 \pm 3.09 (23.1–38.43) a	35.13 \pm 3.94 (27.92–39.97) a	36.13 \pm 4.97 (28.54–48.26) a
L1/L2*	205.9 \pm 52.74 (60.61–285.61) a	200.08 \pm 31.92 (160.2–332.87) ab	188.46 \pm 34.46 (150.21–259.18) ab	181.91 \pm 38.15 (107.2–250.41) b
W/L**	84.92 \pm 4.73 (77.62–100) a	98.64 \pm 5.02 (89.45–108.99) b	86.25 \pm 6.58 (66.61–98.42) a	78.42 \pm 6.62 (66.67–95.66) c

n= Insignificant difference at 0.05 level.

*= The differences are significant at 0.05 level.

**= The differences are highly significant at 0.01 level.

Table 3: Basic statistics, mean \pm SD (Range) of the morphometric indices of scales from four body regions of *P. pictus* from the Red Sea, Jeddah, Saudi Arabia. The postopercular scales (POS), below dorsal-fin scales (BDFS), below lateral line scales (BLLS) and caudal peduncle scales (CPS).

Index	Region A (BDFS)	Region B (POS)	Region C (BLLS)	Region D (CPS)
	Mean \pm SD (Range) (N=50)	Mean \pm SD (Range) (N=50)	Mean \pm SD (Range) (N=50)	Mean \pm SD (Range) (N=50)
L1/L ⁿ	72.03 \pm 3.46 (62.44–78.98) a	71.42 \pm 3.68 (61.87–79.05) a	71.6 \pm 2.60 (66.67–77.88) a	72.34 \pm 2.33 (67.42–75.83) a
L2/L ⁿ	27.98 \pm 3.47 (21.02–37.56) a	28.57 \pm 3.67 (21.17–38.13) a	28.38 \pm 2.59 (22.14–33.41) a	27.71 \pm 2.29 (24.17–32.58) a
L1/L2 ⁿ	262.91 \pm 46.22 (166.22–375.81) a	256.13 \pm 49.56 (162.28–373.47) a	255.34 \pm 34.66 (200–350.53) a	263.48 \pm 29.76 (206.9–313.7) a
W/L ^{**}	94.51 \pm 7.42 (78.68–107.33) a	109.69 \pm 8.18 (92.43–131.23) b	102.54 \pm 8.50 (88.84–122.57) c	87.72 \pm 5.45 (75.13–100) d

n= Insignificant difference at 0.05 level.

**= The differences are highly significant at 0.01 level.

Table 4: Basic statistics, mean \pm SD (Range) of the morphometric indices of scales from four body regions of *P. schotaf* from the Red Sea, Jeddah, Saudi Arabia. The postopercular scales (POS), below dorsal-fin scales (BDFS), below lateral line scales (BLLS) and caudal peduncle scales (CPS).

Index	Region A (BDFS)	Region B (POS)	Region C (BLLS)	Region D (CPS)
	Mean \pm SD (Range) (N=45)	Mean \pm SD (Range) (N=45)	Mean \pm SD (Range) (N=45)	Mean \pm SD (Range) (N=45)
L1/L ⁿ	68.52 \pm 2.29 (63.73–72.43) a	69.66 \pm 3.07 (64.97–77.08) a	69.02 \pm 4.24 (63.28–81.82) a	68.25 \pm 3.3 (61.97–75.61) a
L2/L ⁿ	31.48 \pm 2.27 (27.37–36.08) a	30.35 \pm 3.06 (22.92–35.03) a	30.97 \pm 4.25 (18.18–36.93) a	31.77 \pm 3.30 (24.39–38.03) a
L1/L2 ⁿ	219.25 \pm 22.89 (176.63–264.66) a	233.05 \pm 36.23 (185.5–336.26) a	229.85 \pm 53.54 (171.35–450) a	218.35 \pm 35.11 (162.98–310.08) a
W/L ^{**}	80.08 \pm 7.17 (67.02–93.7) a	93.42 \pm 4.60 (81.72–104.13) b	87.05 \pm 4.77 (76.86–100) c	75.4 \pm 4.02 (65.82–82.99) d

n= Insignificant difference at 0.05 level.

**= The differences are highly significant at 0.01 level.

Table 5: Standardized canonical variates derived from CVA of certain morphometric characters of the scales of the three *Plectorhynchus* species from the Red Sea, Jeddah, Saudi Arabia.

characters	CVI	CVII
L1/L	0.737	-2.535
L2/L	0.057	0.368
L1/L2	0.036	2.344
W/L	0.642	0.686
Eigenvalue	0.772	0.193
% of Variance	80%	20%

Table 6: Percentages of occurrence and basic statistics of the primary radii counts of the postopercular scales (POS), below dorsal-fin scales (BDFS), below lateral line scales (BLLS) and caudal peduncle scales (CPS) of the three *Plectorhynchus* species from the Red Sea at Jeddah, Saudi Arabia.

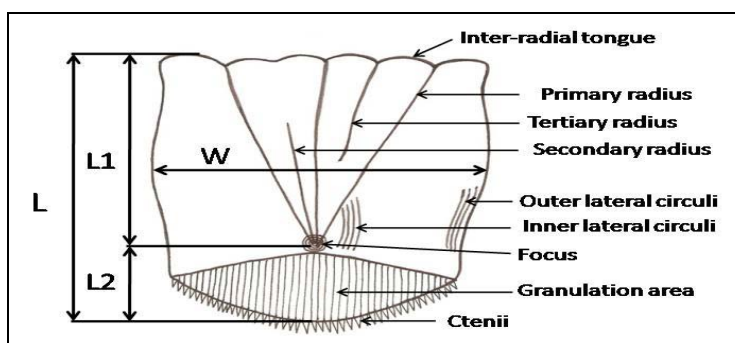
Species	Scales	N	Primary radii counts									Mean \pm SD
			1	2	3	4	5	6	7	8	9	
<i>P. gaterinus</i>	BDFS	82	0	0	6.1	20.73	59.76	12.2	1.22	0	0	4.82 \pm 0.77
	POS	69	0	4.35	17.39	31.88	40.58	4.35	1.45	0	0	4.28 \pm 1
	BLLS	68	0	1.47	7.35	39.71	44.12	7.35	0	0	0	4.49 \pm 0.8
	CPS	55	0	0	1.82	16.36	50.91	29.09	1.82	0	0	5.13 \pm 0.77
<i>P. pictus</i>	BDFS	90	0	0	1.11	8.89	35.56	38.89	13.33	2.22	0	5.61 \pm 0.94
	POS	99	2.02	3.03	12.12	27.27	26.26	24.24	5.05	0	0	4.66 \pm 1.3
	BLLS	96	0	0	5.21	11.46	25	40.63	12.5	3.13	2.08	5.61 \pm 1.22
	CPS	87	0	0	0	2.3	14.94	41.38	32.18	6.9	2.3	6.33 \pm 0.97
<i>P. schotaf</i>	BDFS	79	0	0	0	2.53	39.24	45.57	12.66	0	0	5.68 \pm 0.73
	POS	69	0	0	0	2.9	24.64	50.72	21.74	0	0	5.91 \pm 0.76
	BLLS	70	0	0	0	0	27.14	52.86	17.14	1.43	1.43	5.97 \pm 0.8
	CPS	53	0	0	0	0	26.42	49.06	24.53	0	0	5.98 \pm 0.72

Table 7: Percentages of occurrence and basic statistics of the secondary radii counts of the postopercular scales (POS), below dorsal-fin scales (BDFS), below lateral line scales (BLLS) and caudal peduncle scales (CPS) of the three *Plectorhynchus* species from the Red Sea at Jeddah, Saudi Arabia.

Species	Scales	N	Secondary radii counts								Mean±SD
			0	1	2	3	4	5	6	7	
<i>P. gaterinus</i>	BDFS	81	4.94	18.52	33.33	32.1	11.11	0	0	0	2.26±1.05
	POS	69	0	0	4.35	27.54	40.58	17.39	8.7	1.45	4.03±1.06
	BLLS	68	0	10.29	20.59	47.06	17.65	4.41	0	0	2.85±0.98
	CPS	55	3.64	10.91	45.45	34.55	5.45	0	0	0	2.27±0.87
<i>P. pictus</i>	BDFS	90	77.78	17.78	3.33	1.11	0	0	0	0	0.28±0.58
	POS	99	5.05	20.2	22.22	24.24	14.14	10.1	3.03	1.01	2.7±1.55
	BLLS	96	22.92	36.46	23.96	7.29	9.38	0	0	0	1.44±1.19
	CPS	87	78.16	17.24	4.6	0	0	0	0	0	0.26±0.54
<i>P. schotaf</i>	BDFS	79	81.01	17.72	1.27	0	0	0	0	0	0.2±0.43
	POS	69	59.42	28.99	10.14	1.45	0	0	0	0	0.54±0.74
	BLLS	70	85.71	12.86	1.43	0	0	0	0	0	0.16±0.4
	CPS	53	83.02	13.21	3.77	0	0	0	0	0	0.21±0.49

Table 8: Percentages of occurrence and basic statistics of the tertiary radii counts of the postopercular scales (POS), below dorsal-fin scales (BDFS), below lateral line scales (BLLS) and caudal peduncle scales (CPS) of the three *Plectorhynchus* species from the Red Sea at Jeddah, Saudi Arabia.

Species	Scales	N	Tertiary radii counts						Mean±SD
			0	1	2	3	4	5	
<i>P. gaterinus</i>	BDFS	81	70.37	27.16	2.47	0	0	0	0.32±0.52
	POS	69	78.26	21.74	0	0	0	0	0.22±0.42
	BLLS	68	97.06	2.94	0	0	0	0	0.03±0.17
	CPS	55	100	0	0	0	0	0	0±0
<i>P. pictus</i>	BDFS	90	34.44	35.56	21.11	4.44	1.11	3.33	1.12±1.17
	POS	99	77.78	17.17	5.05	0	0	0	0.27±0.55
	BLLS	96	68.75	19.79	11.46	0	0	0	0.43±0.69
	CPS	87	54.02	37.93	5.75	2.3	0	0	0.56±0.71
<i>P. schotaf</i>	BDFS	79	92.41	7.59	0	0	0	0	0.08±0.27
	POS	69	81.16	14.49	4.35	0	0	0	0.23±0.52
	BLLS	70	94.29	4.29	1.43	0	0	0	0.07±0.31
	CPS	53	88.68	7.55	3.77	0	0	0	0.15±0.46

**Fig. 1: A diagrammatic structure of *Plectorhynchus* scale showing the different regions, terms and morphometric measurements used in the present work; L: scale length; L1: rostral field length; L2: caudal field length; W: scale width.**

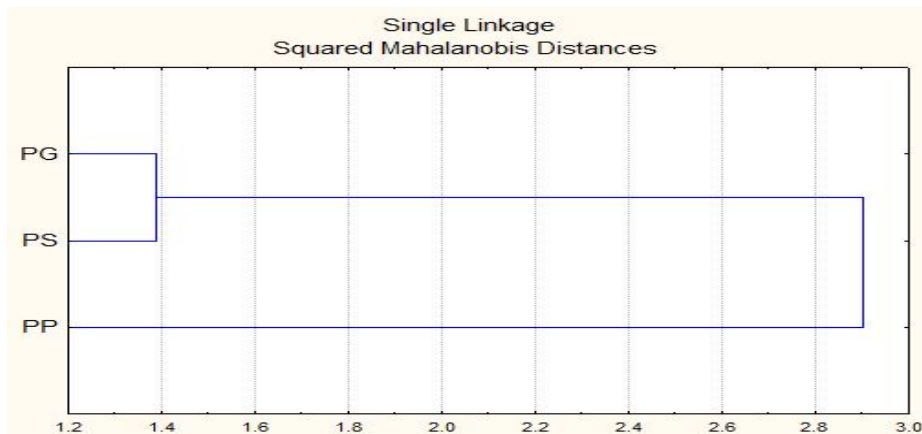


Fig. 2 : Clustering (Single Linkage, squared Mahalanobis distance) of three *Plectorhynchus* species from the Red Sea, Jeddah, Saudi Arabia based on scale morphometric indices. *P. gaterinus* (PG), *P. pictus* (PP) and *P. schotaf* (PS).

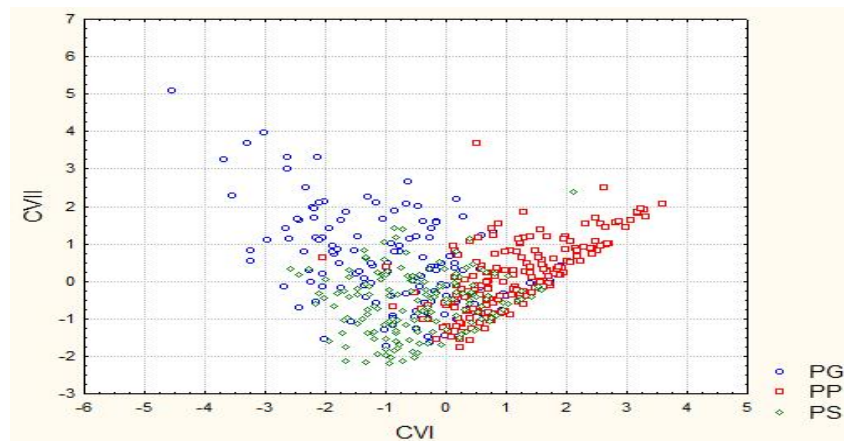


Fig. 3: Plots of scores of CVI and CVII derived from CVA carried out on indices of certain morphometric characters of the scales of three *Plectorhynchus* species from the Red Sea, Jeddah, Saudi Arabia. *P. gaterinus* (PG), *P. pictus* (PP) and *P. schotaf* (PS).

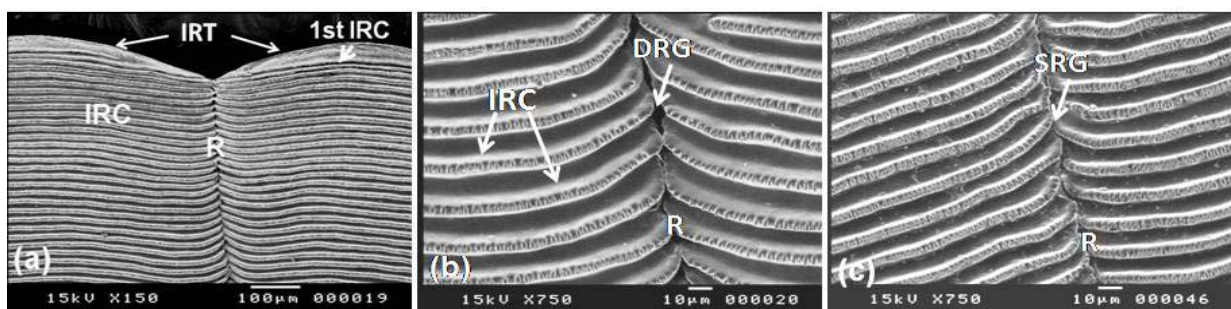


Fig. 4: Scanning electron micrographs show (a): the inter-radial tongues (IRT), 1st inter-radial circulus (1st IRC), inter-radial circuli (IRC) and radii (R) in the rostral field of the scales recorded in the three *Plectorhynchus* species considered; (b): deep radial grooves (DRG) with irregular split recorded in *P. gaterinus* and *P. pictus* and (c): shallow radial grooves (SRG) with very narrow split recorded in *P. schotaf* only.

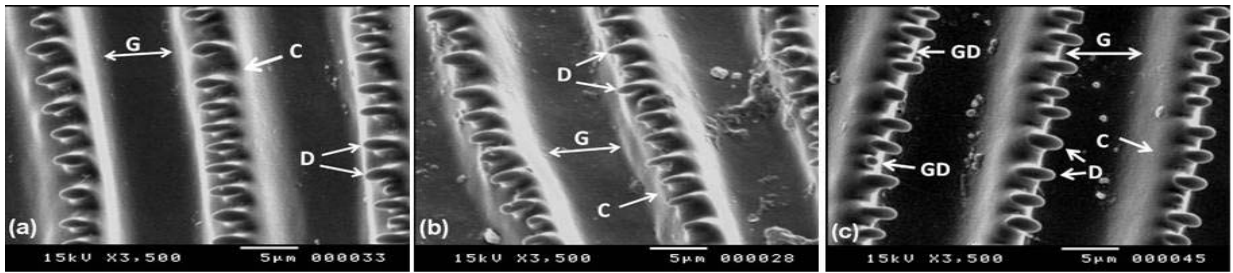


Fig. 5: Scanning electron micrographs show the inter-radial circuli (C), lepidonts or denticles (D), growing denticles (GD) and grooves (G) of the three *Plectorhynchus* species considered (a): recorded in *P. gaterinus*, (b): in *P. pictus* and (c): in *P. schotaf*.

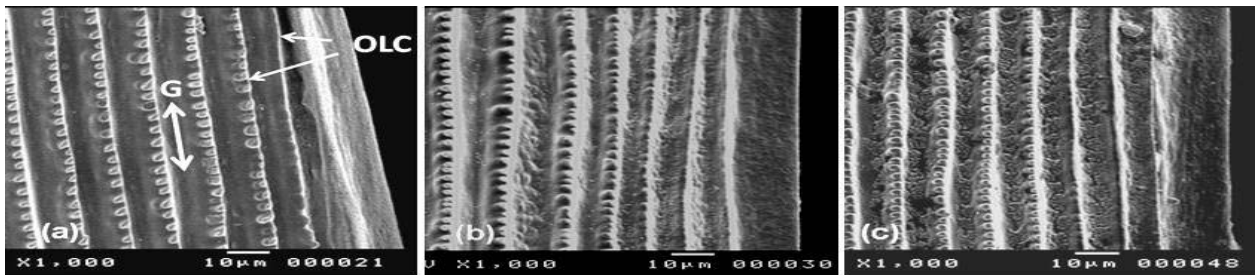


Fig. 6: Scanning electron micrographs show the most outer lateral circuli (OLC) and grooves (G) of the three *Plectorhynchus* species considered. (a): recorded in *P. gaterinus*, (b): in *P. pictus* and (c): in *P. schotaf*.

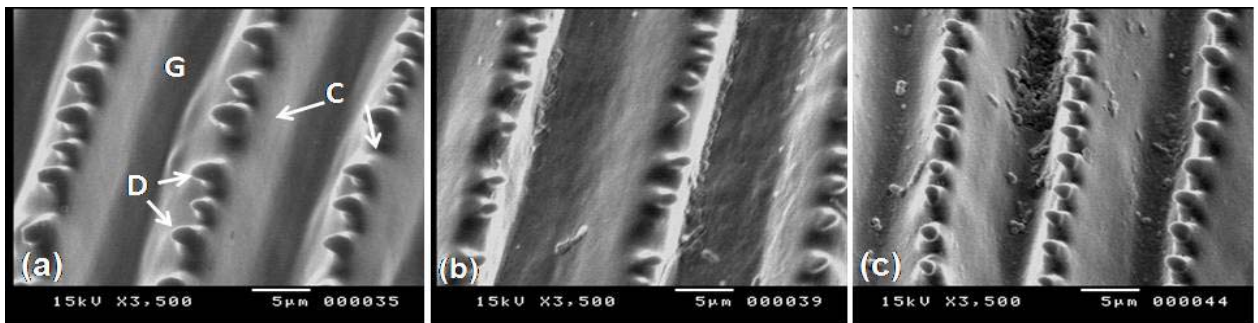


Fig. 7: Scanning electron micrographs show the inner lateral circuli (C), denticles (D) and grooves (G) of the three *Plectorhynchus* species considered. (a): recorded in *P. gaterinus*, (b): in *P. pictus* and (c): in *P. schotaf*.

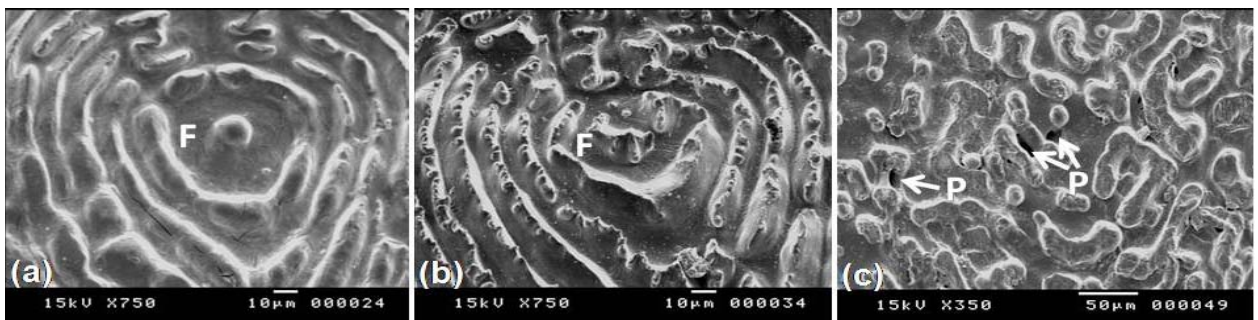


Fig. 8: Scanning electron micrographs show the focus region (F) in the scales of the three *Plectorhynchus* species considered. (a): the focus with arranged smooth circuli recorded in *P. gaterinus*, (b): the arranged focal circuli bear small irregular denticles recorded in *P. pictus* and (c): the focus has no circuli and appears as tubercular ridges with different shapes and sizes in *P. schotaf*, note the presence of pores (P).

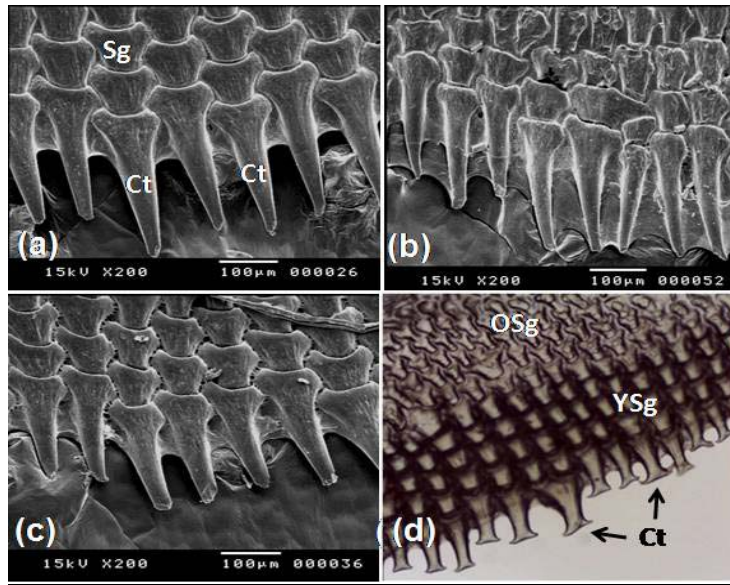


Fig. 9: Scanning electron micrographs (a-c) and photomicrograph (d) show the different forms of ctenii (Ct) and granulation segments (Sg) identified in the caudal field of the scales of the three *Plectorhynchus* species; (a): ctenii recorded in *P. gaterinus*; (b): in *P. schotaf* and (c&d): in *P. pictus*, old segments (OSg) are located internally and have a corroded appearance, the youngest segments (YSg) are well developed and located externally.

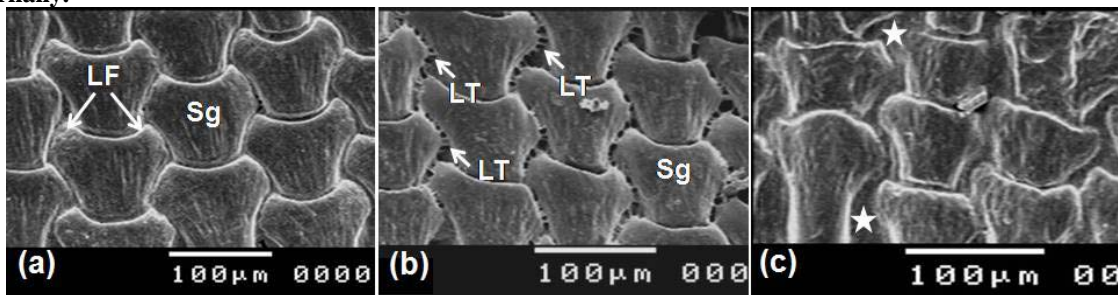


Fig. 10: Scanning electron micrographs show the different forms of segments (Sg) identified in the caudal field of the scales of the three *Plectorhynchus* species; (a): recorded in *P. gaterinus*, the segments occupied alternative position with the adjacent ones, each segment has two equal lateral folds (LF) and tightly connected to each other, (b): in *P. pictus*, the segments are adjacent to each other, has one long lateral fold and connected by ligaments-like tendons (LT) and (c): in *P. schotaf*, irregular sculptured segments are spaced and connected by a wide matrix layer (stars).

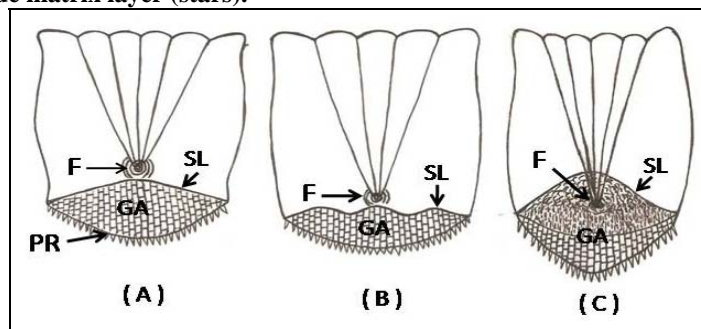


Fig. 11: Forms of scales identified in three *Plectorhynchus* species from the Red Sea, Jeddah, Saudi Arabia; according to the rostro-caudal separation line (SL), the posterior rim (PR) and the shape of granulation area (GA) in the caudal field. (A): specific for *P. gaterinus*; (B): specific for *P. pictus* and (C): specific for *P. schotaf*, note the location of the focus (F).

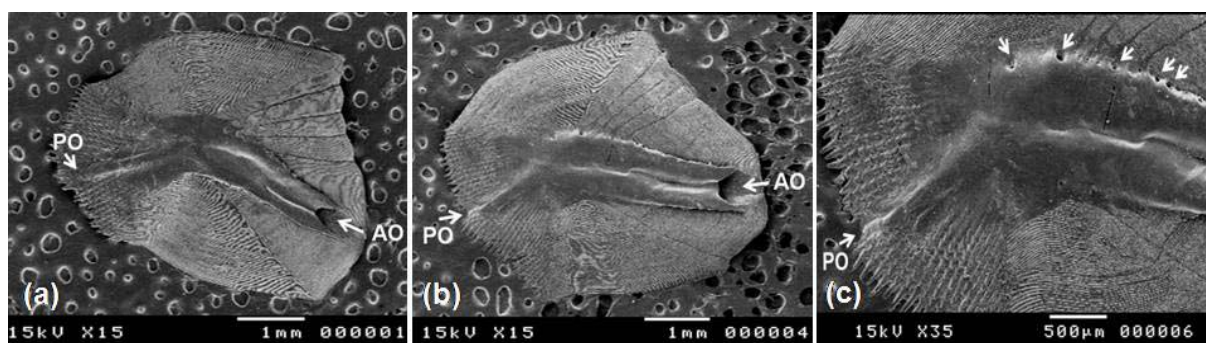


Fig. 12: Scanning electron micrographs show the characteristics of the lateral line canal of the three *Plectorhynchus* species considered. (a): recorded in both *P. gaterinus* and *P. schotaf*, the posterior opening (PO) occurs just before the posterior rim and (b & c): recorded in *P. pictus*, showing a series of pores (arrows) at the lateral side of the canal and the posterior opening (PO) occurs at the scale's posterior margin at the bases of ctenii.

4. Discussion

Fish scales are bony structures that grow shingle-like from pockets within the skin (Schneider *et al.*, 2000). As fish grow the scales also increase in size, producing characteristic growth rings (circuli) at the scale margin (Cheung, 2007). Once circulus deposited on the scale, it remains unchanged over the entire life span of the scale (Sire and Arnulf, 2000; Sire and Akimenko, 2004).

In the present work, intraspecific and interspecific relationships were reflected on the bases of quantitative scale characters by clustering of the three *Plectorhynchus* species in terms of the size-free morphometric indices of the scales. The cluster analysis of the present work revealed that there are two main subclusters, the first includes *P. gaterinus* and *P. schotaf*, and the second subcluster includes *P. pictus*. Mekkawy *et al.* (1999, 2006, 2011); Mahmoud *et al.* (2005); Mekkawy and Abdel-Rahman (2005) and Harabawy *et al.* (2007) used similar systematic values of morphometric characteristics of scales in other teleosts.

The presence of primary, secondary, and tertiary radii is considered as a growth phenomenon. It is weakly influenced by genetic factors (Lippitsch, 1990). The higher number of radii is correlated with the better nutritive conditions of the fish (Tandon and Johal, 1996). Radii represent the line of scale flexibility (Esmaeili and Gholami, 2011). There is no significant correlation between number of radii and fish size and consequently were size free for all species considered in the present work. The patterns of distribution of such size-free counts revealed significant interspecific variations of *Plectorhynchus* species considered. However, the number of radii is correlated to fish size in some other teleosts such as *Mullus surmuletus* and *M. barbatus* (Javad and Al-Jufail, 2007). On the other hand, the number of radii remains constant on a given scale during ontogeny as

recorded in greater lizard fish by Javad and Al-Jufail (2007).

The environment is recognized as a powerful force in modeling the morphology of an organism during ontogeny (Ganzon *et al.*, 2012). The epidermal cover of the three *Plectorhynchus* species studied like other swimming fishes undergo friction forces due to water flow in coral reefs habitats. The interradial circuli with their denticles and those of lateral fields may play an important role to offer a resistance to these frictional forces by mechanical anchoring.

In the present study, the shape of the first interradial circuli was convex, straight, or concave. Such shape variations are characteristic for different species (Lippitsch, 1990, 1993; Mahmoud *et al.*, 2005; Mekkawy *et al.*, 2006; Harabawy *et al.*, 2007 and Mekkawy *et al.*, 2011); but in some cases seems to be modified by external factors (Lippitsch, 1990).

Denticles are important fine structures seen on the interradial and inner lateral circuli. They are not homologous to breeding tubercles and contact organs (Esmaeili and Niknejad, 2007). Improbability to make lepidonts as contact organs (to facilitate contact between males and females during reproduction) was due to their microscopic size and the covered position (Delmater and Courtenay, 1974). In the present work, it was noted that all denticles on the interradial circuli were oriented posteriorly towards the scalar focus, while those found on the inner lateral circuli are oriented at right angle on the longitudinal axis of the scale towards the scale center. This means that the denticles are oriented in different directions. Therefore, they may be involved in the mechanical anchoring of the scale into the covering dermis (i.e. they may act as minute hooks preventing movement or detachment of the scale) as already proposed for other teleosts (Gabr and Sakr, 1992; Mekkawy *et al.*, 1999, 2003; Mahmoud *et al.*, 2005; Harabawy *et al.*, 2007 and Mekkawy *et al.*, 2011).

This explains why isolated scales always have a well defined strip of skin adhering to it after removal (Lanzing and Bower, 1973). Jawad (2005) stated that the small-sized processes located on the circuli cannot anchor the scale in the dermis as securely as can the well-developed denticles. On the other hand, Zylberberg and Meunier (1981) proposed that the scale is anchored in the surrounding tissue by the bundles of collagen fibers connecting the upper part of the scale to the overlying dermis.

Concentration of the denticles on the interradiial and inner lateral circuli of scales of *Plectorhynchus* species considered in addition to the absence or rarity of such denticles in the most outer lateral circuli may suggest that the anchoring is more important in the radial part of the rostral field and near the focus and is less important in the outer part of the outer lateral field (the newly formed circuli) as proposed by Mekkawy *et al.* (2011). Also, as all of the denticles are not oriented to a specific direction, they constitute multidirectional anchoring. These findings agree with those reported by Mekkawy *et al.* (1999, 2003, and 2011) and Harabawy *et al.* (2007).

The surface structures of the overlapped region of the scales are stable after their formation (Esmaeili and Gholami, 2011). This stability may suggest that the shape, size and spacing of the circuli and denticles and other surface characteristics may provide useful criteria for systematic purposes. But, this hypothesis requires test and refinement by comparisons of such characteristics in different related species. Concerning this point, a wide spectrum of lepidonts (denticles) of different size and shape in many fish genera and species were recorded by many authors (e.g. Lippitsch, 1990, 1992, 1993; Mekkawy *et al.*, 1999, 2003, 2006; Mahmoud *et al.*, 2005; Harabawy *et al.*, 2007 and Mekkawy *et al.*, 2011). These authors suggested that such denticles might characterize genera and may even distinguish some taxa at the specific level reaching to species level. In spite of being carnivores inhabiting the bottoms and use the reefs for shelter, *Plectorhynchus* species are subjected to various environmental factors. Their size-free scale characters and ornamentation also were stable. So, the impacts of such environmental factors were omitted and the size-free fixed scale characters are expressions of their divergent evolution and were not controlled by the environmental factors. Accordingly, the intraspecific and interspecific variations in *Plectorhynchus* species could be genetically controlled.

The position of the focus on the scale remains the same throughout the life of the individual species (Ganzon *et al.*, 2012). The focus area sculpture was among the fine features of scales studied by SEM. This area may be smooth or have a

granulate sculpture that varies in shape and size between teleosts (Lippitsch, 1992). In the present work the focus of scales has different locations and different shapes among *Plectorhynchus* species studied. The focus shows unique patterns of circuli and tubercular ridges in *P. gaterinus* and *P. pictus* or has no circuli and appears as irregular tubercular ridges with different shapes and sizes in *P. schotaf*. Lippitsch (1992) believed such focus area to be formed by disintegration of circuli.

Granulation patterns, shape and size of segments and ctenii and overall caudal field of the scales of *Plectorhynchus* species studied were constant with fish size and exhibited interspecific variations. The large degree of morphological variations exhibited between species and genera of the same family and a complete change in morphology for several species outside the family were evident (Mekkawy *et al.*, 2006; Mahmoud *et al.*, 2005; Harabawy *et al.*, 2007 and Mekkawy *et al.*, 2011). These findings suggest and emphasized on the importance of the caudal field of scales as a taxonomic character not only at the level of species or genera but also at families level (Delamater and Courtenay, 1974; Mekkawy *et al.*, 1999, 2003, 2006; Mahmoud *et al.*, 2005; Harabawy *et al.*, 2007 and Mekkawy *et al.*, 2011). In contrast, Esmaeili and Gholami (2011) stated that the tubercles and ridges of the free caudal region change in shape and increase in surface and thickness during ontogeny. Consequently, the ornamentation patterns are specific to different ontogenetic stages and this should be taken into account in systematic studies.

In the present work, SEM observations revealed that the reduction in length or resorption process of the ctenial spines (ctenii) is not severe and almost stops after the tip of the spine length has been resorbed as recorded by Jawad (2005). Therefore, such resorption process may lead to segmentation of the caudal field of the scales of *Plectorhynchus* species considered. Hughes (1981) and Roberts (1993) interpreted the mechanism of spine loss as a progressive resorption rather than a sudden amputation. A severe resorption leading to complete disappearance of the spine was recorded in some other teleost fishes (Roberts, 1993). Jawad (2005) reported that the resorption of ctenial spines, as a character, seems to be a characteristic of broader taxonomic groups such as genera and families rather than isolated species within these groups.

The caudal field of the scales of the three *Plectorhynchus* species was found perforated by a number of pores. A similar finding was recorded by Harabawy (2002), Mahmoud *et al.* (2005), Mekkawy and Abdel-Rahman (2005) and Mekkawy *et al.*, 2006 and 2011). Harabawy (2002) postulated that such

pores may act as minute canaliculi through which the mucus can pass to cover the fish body and other substances can be released into the water when the skin is damaged. The mucus is significantly decreasing the friction between the fish and water and it promotes the healing of wounds (Holčík, 1989). Mahmoud *et al.* (2005) added that these pores may represent a part of the lateral line system.

The anterior opening of the lateral line canal of *Plectorhynchus* species studied is hidden by an evelike extension cantilevered over it. Anterior opening is wider than the posterior one. Delamater and Courtenay (1973) reported as a possible working hypothesis that the cantilevered anterior extension of the canal could help in detection of water motion speed and direction. A wide range of structural variation of lateral line canal was recorded in different teleost species by many authors (e.g. Mekkawy, 1980; Khalil *et al.*, 1982; Mekkawy *et al.*, 1999, 2003, 2006; Mahmoud *et al.*, 2005; Harabawy *et al.*, 2007 and Mekkawy *et al.*, 2011). It ranged from a simple direct or slightly oblique perforation to an extended canal with or without simple to highly complex cantilevered extensions acting as covers anterior opening. Also, it may be a complex branched canal (Harabawy *et al.*, 2007). In contrast, no definite structural lateral line canal was recorded in *Epinephelus* species studied by Mekkawy *et al.* (1999) or in *Cephalopholis* species and *variola louti* studied by Mekkawy *et al.* (2006). Such canals formed by some type of body scale arrangement to appear as a false lateral line canal.

It is apparent that both gross differences and details of such variation may be important in identification of groups (orders, families, genera and species), especially when combined with other equally impressive characters of scale structure (Delamater and Courtenay, (1972). Delamater and Courtenay (1974), Mekkawy (1980), Khalil *et al.* (1982) and Mahmoud, *et al.* (2005) also used the variable position of the anterior and posterior openings of the lateral line canal to differentiate between some fish species belonging to the same genus or different genera. Khalil *et al.* (1982) and Mahmoud, *et al.* (2005) recorded some pattern of displacement of the lateral line canal, and in turn their openings on the scales directed toward the caudal end. The latter authors found such pattern of displacement to be valuable in species identification of seven *Lethrinus* species but not in an obvious way.

In the present work it was noted that the qualitative and quantitative (morphometrics and radii counts) characters of the scales exhibit a lot of species-specific characters for each species of the three *Plectorhynchus* species studied. This may indicate that such qualitative and quantitative scale

characters are genetically fixed and more stable. In contrast, Mahmoud, *et al.* (2005) and Harabawy *et al.* (2007) recorded that such qualitative characters exhibit species-specific characters for each species studied by them than that of morphometric ones. These authors mentioned that this situation may indicate that the qualitative scale characters are genetically fixed and more stable than the quantitative ones.

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Reproductive Performance and Milk Yield Of Friesian Dairy Cows Affected By L-Tyrosine Treatment During Early Postpartum Period

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Abstract: A total of 24 Friesian cows between the 1st and 3rd parity and average body weight (LBW) of 512.6 ±15.5 kg were divided into three similar groups (n=8 each) based on their BW, parity and milk production of the previous season. Cows of the 1st group (G1) were fed concentrate feed mixture (CFM) (control group). Cows of the 2nd group were received oral dose of L-tyrosine 50 g/cow at day 21(G2) while those of the 3rd group (G3) were received the same dose of G2 but on day 40. Throughout the experimental period, cows were machine milked and daily milk yield was individually recorded for the 1st four months. Milk composition and somatic cell count were determined. Estrus was detection and cows in heat were inseminated. Also, number and length of estrous cycles from calving up to conception were recorded. Postpartum 1st ovulation (PPOI), 1st estrus (PPEI) and 1st service (PPSI) intervals, number of services per conception (NSC), days open (DO) and conception rate (CR%) were calculated. Pregnancy was diagnosed by rectal palpation on day 60 post-insemination. Results revealed that L-tyrosine treatment improved significantly ($P<0.05$) daily milk production of G2 and G3 by 11.5 and 11.8% compared to G1. G3 had higher ($P<0.05$) percentages of fat, protein and lactose as compared to G1 (3.83, 3.22 and 4.37 vs. 3.72, 2.89 and 4.14%), respectively. G2 had higher ($P<0.05$) percentages of protein and lactose (3.13 and 4.45%, respectively) compared to G1, while fat percentage was similar to G1. Treated cows with L-tyrosine showed lower ($P<0.05$) somatic cell count in milk as compared to G1. Postpartum estrous interval was shorter ($P<0.05$), by 10.78 days in G2 than G1, While, those of G3 showed longer period (+ 7.72 day) than G1. Days open in G2 and G3 cows was shorter ($P<0.05$) by 19.68 or 13.3 day, respectively, than G1. Number of services per conception was less ($P<0.05$) in G2 (1, 50) and G3 (1.87) than in G1 (2.43). Conception rate increased ($P<0.05$) in G2 and G3 compared with those of control (50 vs. 75 and 100%).

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1. Introduction

Use of organic substances is believed having positive effect on animal productivity and reproductive performance through enhancing the release of sex hormones (Gabr, 2009). One of these substances is L-tyrosine, which involves in the catecholamine and thyroxin formation (Hammel and Russe, 1987). In addition it serves as a precursor for the synthesis of dopamine, norepinephrine, and epinephrine and is a specific brain neurotransmitter implicated in the control of GnRH and LH (Ramirez *et al.*, 1984).

Tyrosine may be involved in stimulating GnRH *via* influencing synthesis of norepinephrine (Gibson and Wurtman, 1986 and Acworth *et al.*, 1988), a neurotransmitter that stimulates GnRH release (Ramirez *et al.*, 1984 and Terasawa *et al.*, 1988).

The relationship between tyrosine and reproduction has been reported previously (Gabr, 2009). In dairy cows, tyrosine treatment resulted in expressing estrus within several days in more than 85% of the cows followed by normal estrous cycles (Munsterer, 1987).

In sows, exogenous tyrosine increased LH pulse frequency in growth-restricted lambs (Hall *et al.*, 1992), induced follicular growth, estrus and ovulation

in anovulatory dairy cows (Hammerl, 1986 and Munsterer, 1987) and improved expression of estrus (Hammerl and Russe, 1987).

The aim of the present work was to study the effect of post-partum L-tyrosine treatment on milk yield and reproductive performance of Friesian cows during the first four months postpartum.

2. Materials and Methods

The present study was carried out at Sakha Animal Production Research Station, belonging to the Animal Production Research Institute, Agricultural Research Center, Ministry of Agriculture and Land Reclamation, Egypt during the period from July to November 2010.

Animals and management:

A total of 24 healthy Friesian cows with an average of 512.6±15.5 kg body weight (BW), between 28 and 56 months of age and 1-3 parities were used in this study. All cows were chosen at early postpartum period (10 days post calving). At the beginning of the experimental period, the experimental cows were divided into three similar groups, 8 in each. Multiparous cows (n=5 in each group) were divided according to their BW, parity and milk production of

the previous season, while primiparous cows (n=3 in each group) were allotted based only on their BW.

Experimental cows were fed according to their BW and milk production. The 1st group (G1) was served as a control, while cows in 2nd (G2) and 3rd (G3) groups were received an oral dose of L-tyrosine (50 g/cow) at day 21 and 40 of postpartum period, respectively. All cows were housed in separately semi-open yards.

Feeding system:

Experimental cows were fed a diet containing concentrate feed mixture, rice straw and corn silage according to the recommendation of NRC (2001) for dairy cows based on their live body weight and milk yield.

Experimental procedures:

Milk yield and composition:

Cows were machine milked twice daily at 6:00 and 17:00 h. Daily milk yield (morning and evening) was individually recorded for the 1st four months of lactation. Milk samples were monthly collected to determine milk composition using Milkoscan (Model 133B) and somatic cell count (Foss Electronic 360, Slangerupgade, Denmark).

Detection of estrus and insemination:

Beginning of day 10 postpartum, an infertile bull was introduced to cows of each group for 20 minutes three times daily at 6, 12 and 15 h to recognize the onset of the 1st estrus. Estrus was identified when cows showed complete receptivity to the teaser and stood quietly to be mounted. Cows those be recognized to be on heat were artificially inseminated.

Number and length of estrous cycles from calving up to conception were recorded. Postpartum 1st ovulation (PPOI), 1st estrus (PPEI) and 1st service (PPSI) intervals, number of services per conception (NSC), days open (DO) and conception rate (CR%) were calculated. Conception rate was calculated as the proportion of Conceived cows relative to inseminated cows multipliable by 100.

Pregnancy was diagnose by rectal palpation which taken place on day 60 post-insemination.

Statistical analysis:

The obtained data were statistically analyzed using SAS (2004). The significant differences among treatment groups were tested using Duncan's Multiple Range Test (Duncan, 1955). The statistical model was

$$Y_{ij} = U + A_i + e_{ij}$$

Where:

Y_{ij} = Observed traits

U = Overall mean

A_i = Experimental group 1-3 (1= G1, 2= G2 and 3=G3)

e_{ij} = Random error

Conception rate values were statically analyzed using Chi square test.

3.Results and Discussion

Milk yield:

L-tyrosine treatment in G2 and G3 increased ($P<0.05$) daily milk production during the 1st four months of lactation, compared to G1 (Table 1). It is of interest to note that treatment of L-tyrosine on 21 (G2) or 40 (G3) day-postpartum improved ($P<0.05$) protein and lactose percentages as compared to G1. This however, treatment on day 40 postpartum (G3) affected fat percentage compared to G1. This indicates that L-tyrosine treatment has a positive reflection on the yield of fat and protein (Table 1). Meanwhile it reduces ($P<0.05$) the somatic cell count.

The present results come in agreement with the findings of **Rae and Ingalls (1984)** reporting an increase in milk production as a result of tyrosine treatment. This is mostly attributed to the increase in blood supply (**Mephram, 1982**) and the energy intake of mammary gland cells (**Anderson, 1979 and Wurtman, 1982**), in addition to its effect on increasing growth hormone via its effect on brain catecholamine's (**Martin, 1980**). This explanation is supported by the previous findings of **Machlin (1973) and Peel et al. (1981)** who found that administration of exogenous growth hormone increases milk production.

The observed increase in milk protein yield in treated groups may be attributed to elevation in the supply of tyrosine to the mammary gland, to from milk protein (**Mephram, 1982**).

Reproductive traits:

Data in Table (2) indicated that G2 showed the significantly shorter PPEI and DO, in addition lower NS/C and the highest CR compared to G1 and G3. Except PPEI, which was the longest in G3, the other reproductive traits of G3 came between G1 and G2.

Such trend is in agreement with the results of **Hammerl (1986)** in which reported higher conception rate (69 %) after treating anestrous cows with L-tyrosine compared to 26% in the control group. This may be due to the involvement of tyrosine in stimulating GnRH release via stimulating synthesis of norepinephrine (**Wurtman et al., 1981; Gibson and Wurtman, 1986 and Acworth et al., 1988**), and /or neurotransmitter that stimulates GnRH release (**Ramirez et al., 1984 and Terasawa et al., 1988**).

Ovarian activity:

Results in Table (3) showed that L-tyrosine treatment in G2 and G3 decreased ($P<0.05$) average number of estrus cases and ovulatory cycles per cow during the ovulatory cycles compared with the control group. On the other hand, the no statistical differences in average number of total ovulations, silent ovulations per cow, ovulatory cycle length during the ovulatory cycles were observed among experimental groups.

The finding in Table 3 show that L-tyrosine inhibit follicular growth in the ovary which leads to

decrease in the mentioned parameters. Another explanation, the decrease in no. of cycles may be due to increase in the milk yield as a result of elevation in prolactin level which suppress FSH release from anterior pituitary gland. The low number of estrus per cow was associated with that exogenous tyrosine treatment induced follicular growth and ovulation in anovulatory dairy cows (Wetzel, 1985; Hammerl, 1986 and Munsterer, 1987).

L-tyrosine may involve stimulation of GnRH release because availability of tyrosine influences synthesis of norepinephrine (Wurtman *et al.*, 1981), a neurotransmitter that stimulates

hypothalamic GnRH release and pulsatile and preovulatory release of LH from pituitary gland (Ramiez *et al.*, 1984 and Terasawa *et al.*, 1988). The catecholamines may mediate effects of other neurotransmitters and gonadal steroids on release of GnRH (Kalra and Kalra, 1983; Ramirez *et al.*, 1984 and Yen and Vale, 1990).

In conclusion, the present study indicated the beneficial effects of L-tyrosine treatment on day 21 post-partum on milk yield and reproductive performance of Friesian cows during the first four months of lactation.

Table (1): Yield and composition of milk (Mean \pm MSE) as affected by time of L-tyrosine treatment as calculated throughout the first 120 day post-partum.

Item	Experimental groups (n=8)			\pm MSE
	G1	G2	G3	
Average daily milk yield (kg/day):				
Actual milk yield	14.22 ^b	16.43 ^a	16.53 ^a	0.24
4% fat corrected milk	13.27 ^b	15.05 ^a	15.69 ^a	0.22
Milk composition (%):				
Fat	3.72 ^{ab}	3.64 ^b	3.83 ^a	0.036
Protein	2.89 ^b	3.13 ^a	3.22 ^a	0.041
Lactose	4.14 ^b	4.45 ^a	4.37 ^a	0.035
Component yields (g/day):				
Fat	50.02 ^b	56.88 ^{ab}	59.33 ^a	2.68
Protein	39.07 ^b	48.98 ^a	50.75 ^a	4.24
Lactose	56.88 ^b	69.52 ^a	68.77 ^a	3.21
Somatic cell count (10³/ml):	394.53 ^a	311.92 ^b	290.11 ^b	19.14

^a and ^b: Means within the same row with different superscripts are significantly different ($P < 0.05$).

G1= Control, G2= Cows received oral dose of L-tyrosine (50 g/cow) at day 21 of postpartum period and G3= Cows received oral dose of L-tyrosine (50 g/cow) at day 40 of postpartum period.

Table (2): Reproductive traits (Mean \pm MSE) as affected by time of L-tyrosine treatment throughout the first 120 days post-partum

Item	Experimental groups (n=8)			\pm MSE
	G1	G2	G3	
Postpartum 1 st estrus interval (day)	35.62 ^b	24.84 ^c	43.24 ^a	1.30
Number of services per conception	2.43 ^a	1.50 ^b	1.87 ^{ab}	0.20
Days open (day)	75.93 ^a	56.25 ^b	62.8 ^{ab}	4.10
Conception rate (%)	50 ^c	100 ^a	75 ^b	-

^a and ^b: Means within the same row with different superscripts are significantly different ($P < 0.05$).

Table (3): Postpartum ovarian activity and progesterone (P4) concentration of cows in different experimental groups.

Item	Experimental group (n=8)			\pm MSE
	G1	G2	G3	
Total number of ovulations/cow	4.05	3.03	3.29	0.41
Number of silent ovulations/cow	0.76	0.00	1.01	0.35
Total number of estrus cases	3.94 ^a	2.53 ^b	2.27 ^b	0.27
Number of ovulatory cycles/cow	3.94 ^a	2.27 ^b	2.53 ^b	0.23
Ovulatory cycle length (day)	20.9	21.51	22.95	3.62

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Lowering Effect of Ginger and Selenium on Oxidative Stress in Experimental Rats

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Abstract: The effect of combination of ginger and selenium on oxidative stress in rats was studied. Oxidative stress was induced in rats by single intraperitoneal injection of potassium bromate (KBrO₃) at a dose 125 mg/kg b.wt. Seven groups (n=7) of rats were used in this study. One of them was kept negative control and the others were given KBrO₃. One was kept positive control and the others were given orally ginger, selenium and their combination for 8 weeks.

Results showed that rats with oxidative stress had significant decreases in weight gain and feed efficiency, blood hemoglobin and packed cell volume; serum GSH, SOD and CAT and liver SOD, GST and GPX. There were also increases in liver AST and ALT, serum uric acid, urea nitrogen, creatinine, MDA and NO concentrations. Administration of ginger powder or extract in combination with selenium increased weight gain, feed efficiency, hemoglobin content and packed cell volume. It reversed the biochemical markers of oxidative stress, lipid peroxidation and liver and kidney functions to normal levels

In conclusion, combination of ginger plant with selenium produces a protective effect in rats with oxidative stress. Therefore, intake of ginger with selenium may be useful for patients who suffer from oxidative stress.

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1. Introduction

Oxidative stress arises from an imbalance between the production of reactive oxygen species and the ability of the system to remove or repair the damage caused and restore the prevailing reducing environment (Halliwell and Gutteridge, 1999). Free radicals such as superoxide and nitric oxide (NO) are also produced as second messengers, particularly by immune cells. Superoxide reacts rapidly with nitric oxide by nitric oxide synthase to produce peroxynitrite, whereas hydrogen peroxide slowly decomposes to the highly reactive hydroxyl radical. Both peroxynitrite and hydroxyl radicals are highly reactive oxidizing agents, capable of damaging proteins, lipids, and DNA. Such damage includes changing protein conformation, altering cellular membrane dynamics by oxidation of unsaturated fatty acids, and alterations in DNA and RNA species (Beckman and Koppenol, 1996). Potassium bromate (KBrO₃) is widely used as a food additive in the bread-making process and found in drinking water samples as a by-product of ozone disinfection. KBrO₃ induces renal carcinogenesis and act as a tumor promoter in carcinogen-initiated animals. Renal cell tumors have been observed in male and female rats after exposure to this compound due to

oxidative stress generated by KBrO₃ (Fuji *et al.*, 1984 and Kurokawa *et al.*, 1990).

Dietary intake of antioxidants can inhibit or delay the oxidation of susceptible cellular substrate so prevent oxidative stress. Phenolic compounds such as flavonoids, phenolic acids, diterpenes and tannins have received much attention for their high antioxidative activity (Rice-Evans *et al.*, 1996).

Ginger (*Zingiber officinale Roscoe*) is one of the most commonly used herbal supplements and its substantial use in folk remedies for different medical conditions has been documented. Traditionally, ginger has been used to treat a wide range of ailments. Phytochemical studies showed that ginger is rich in a large number of biologically active substances, including gingerols and shogaols (White, 2007). Ginger contains antioxidants such as gingerols, shogaols and some related phenolic ketone derivatives. Ginger extract contains monoterpenes and sesquiterpene. Ginger extract has antioxidative properties and scavenges superoxide anion and hydroxyl radicals (Cao *et al.*, 1993 and Krishnakanta and Lokesh, 1993).

Selenium is a trace element that that is essential to good health but required only in small amounts. Selenium acts by several mechanisms, including detoxifying liver enzymes, exerting anti-

inflammatory effects, and providing antioxidant defense. Selenium is found in minute amounts in foods, with the richest sources being from meats, fish, whole grains, and dairy products. The selenium content of vegetables is dependent on the soil in which they are grown is a trace mineral (Thomson, 2004 and Yiming *et al.*, 2005).

The objective of the present study was to evaluate the antioxidant activity of ginger and selenium on potassium bromate - induced oxidative stress in rats.

2. Material and Methods

A – Material:

Forty-nine adult male rats of Sprague Dawley Strain weighing 175 ± 10 gm were obtained from Helwan farm, Cairo, Egypt. The basal diet was prepared according to NRC (1995). Fresh ginger plant was obtained from local market in Cairo. Selenium powder and potassium bromate ($KBrO_3$) were purchased from El-Gomhoryia Company, Cairo Egypt.

B- Methods:

1-Preparation of ginger powder and ethanolic extract:

Ginger plant were dried with hot air ($40-60^\circ C$) and grinded into powder and added to the diet as 5 % of the constituent of fiber. 270 g of fresh ginger were chopped with 300 mL ethanol by using a blender for 15 min. at average speed. The mixture was macerated during 24hrs at $4^\circ C$. The resultant extract was filtered using a $0.45 \mu m$ pore size cellulose acetate membrane.

2- Biological design:

After adaptation period (one week), the rats were randomly allocated into seven groups, of seven rats each. The first group was fed on basal diet only and kept as a control (-ve). The other six groups were injected by a single intraperitoneal dose of potassium bromate at dose 125 mg/kg body weight to induce oxidative stress (Khan and Sultana, 2004). One group of rats was left without treatment served as a control (+ve). The other groups were treated by ginger powder, ginger extract, selenium; ginger powder with selenium and ginger extract with selenium.

The food intake was calculated daily and the body weight gain was recorded weekly (Chapman *et al.*, 1950). Feed efficiency ratio (FER): FER = weight gain (g)/ feed intake (g) was then calculated. At the end of experiment (8 weeks), the rats were anesthetized, blood sample were collected into clean centrifuge tubes to obtain serum. Livers were immediately removed and rinsed with saline, blotted on filter paper and stored at $-70^\circ C$ pending for biochemical analyses.

Hemoglobin (Hb) and packed cell volume (PCV) were estimated in heparinized blood according to Drabkin (1949) and Mc Inory (1954) respectively. Activity of serum ALT and AST enzymes and concentrations of creatinine, uric acid and urea were estimated according to Reitman and Frankel (1957), Bonsens and Taussky (1984), Fossati *et al.* (1980) and Kanter (1975.), respectively. Blood glutathione (GSH), malondialdehyde (MDA), nitric oxide (NO) and free radicals were determined according to Afzal *et al.* (2002) , Placer *et al.*(1966), Green *et al.* (1981) and Borg (1976), respectively. Catalase and superoxide dismutase (SOD) were estimated according to Luck (1965) and Winterbourn *et al.* (1975), respectively. Liver superoxide dismutase (SOD), glutathione transferase (GST) and glutathione peroxidase (GPX) were determined according to Beauchamp and Fridovich (1971), Habig *et al.* (1974) and Tapple (1978), respectively.

C-Statistical analysis

The collected data were subjected to statistical analysis using computerized SPSS program (Version 15) according to Godfrey (1986).

3. Results

Table (1) showed that control (+ve) rat group had significant ($p < 0.5$ and 0.01) decreases in weight gain, food intake and FER when compared to the control (-ve) group. In ginger powder, ginger extract and selenium groups there were significant ($p < 0.5$ and 0.01) decreases in weight gain and FER, while ginger powder with selenium and ginger extract with selenium groups showed a significant ($p < 0.5$) decrease in FER when compared to the control (-ve) group. In all treated groups there were significant increase in final weight, weight gain, food intake and FER compared to the control (+ve) group.

Table (2) revealed that control (+ve) rat group had significant ($p < 0.01$) decreases in Hb and PCV values compared to control (-ve) group. All treated groups had no significant decreases in Hb and PCV values compared to control (-ve) group, but showed a significant increase in other parameters compared to control (+ve) group.

Table (3) showed that control (+ve) rat group had significant ($p < 0.001$) increases in serum AST, ALT, creatinine, uric acid and urea nitrogen values compared to control (-ve) group. Ginger powder, ginger extract and selenium groups showed a significant ($p < 0.01$) increases in serum ALT, creatinine, uric acid, AST and urea nitrogen ($p < 0.05$) values compared to control (-ve) group. Ginger powder with selenium group showed a significant ($p < 0.05$) increases in creatinine and uric acid, while ginger extract with selenium group showed a significant increase in uric acid ($p <$

0.05) when compared to the control (-ve) group. All treated groups showed significant decreases in AST, uric acid and urea concentrations, but ginger powder or extract with selenium groups had a significant decrease in serum ALT and creatinine compared to control (+ve) group.

Table (4) showed that control (+ve) rat group had significant increases in blood MDA, NO and free radical ($p < 0.001$) and a significant decrease in GSH ($p < 0.001$). Ginger powder and selenium groups caused a significant ($p < 0.05$) decrease in GSH at compared to control (-ve) group. All treated groups showed a significant ($p < 0.05$) increase in NO level compared to control (-ve) group. There were a significant increase in GSH and significant decreases in MDA, NO and free radicals when compared to the control (+ve) group.

Table (5) showed that control (+ve) rat group had significant ($p < 0.001$) decreases in activity of serum SOD and catalase, but ginger powder and selenium groups showed a significant ($p < 0.05$) decrease in serum SOD and catalase at compared to control (-ve) group. All treated groups showed significant increases in serum SOD and catalase when compared to the control (+ve) group.

Table (6) showed that control (+ve) rat group had significant ($p < 0.001$) decreases in liver SOD, GST and GPX. Ginger powder and selenium groups had significant ($p < 0.05$) decreases in liver SOD, GST and GPX, while ginger extract group showed a significant ($p < 0.05$) decrease in liver GPX compared to the control (-ve) group. All treated groups showed significant increases in liver SOD, GST and GPX compared to the control (+ve) group.

Table (1): Mean values \pm SD of body weight gain, food intake and food efficiency ratio (FER) of the experimental groups

Groups Variables	Control (-ve)	Control (+ve)	Ginger powder	Ginger extract	Selenium	Ginger powder+ selenium	Ginger extract+ Selenium
Initial weight(g)	175.77 \pm 5.14 ^a	179.61 \pm 6.31 ^a	181.31 \pm 5.21 ^a	183.67 \pm 4.99 ^a	182.31 \pm 4.36 ^a	180.35 \pm 4.66 ^a	183.35 \pm 5.11 ^a
Final weight(g)	263.27 \pm 17.76 ^a	215.36 \pm 3.71 ^{b*}	242.06 \pm 13.88 ^a	247.72 \pm 16.21 ^a	244.19 \pm 15.66 ^a	252.49 \pm 14.28 ^a	263.87 \pm 12.77 ^a
Weight gain (g)	87.50 \pm 8.65 ^a	35.75 \pm 1.21 ^{c***}	60.75 \pm 6.11 ^{b*}	64.05 \pm 7.18 ^{b*}	61.88 \pm 7.13 ^{b*}	72.14 \pm 8.11	80.52 \pm 12.77
Food intake(g/w)	19.31 \pm 1.36 ^a	17.74 \pm 1.21 ^{b*}	19.15 \pm 1.31 ^a	19.55 \pm 1.26 ^a	18.88 \pm 1.21 ^a	18.96 \pm 1.25 ^a	19.59 \pm 1.14 ^a
FER	0.075 \pm 0.003 ^a	0.033 \pm 0.004 ^{d***}	0.052 \pm 0.001 ^{c**}	0.054 \pm 0.002 ^{c**}	0.054 \pm 0.001 ^{c**}	0.063 \pm 0.003 ^{b*}	0.068 \pm 0.004 ^{b*}

Significant with control group * $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$

Mean values in each row having different superscript (a, b, c, d) are significant

Table (2): The Mean values \pm SD of blood Hb and PCV of the experimental rats

Groups Variables	Control (-ve)	Control (+ve)	Ginger powder	Ginger extract	Selenium	Ginger powder+ selenium	Ginger extract+ Selenium
Hb (g/dl)	13.20 \pm 1.21 ^a	8.99 \pm 0.88 ^{c**}	11.14 \pm 1.27 ^{ab}	12.21 \pm 1.11 ^a	11.21 \pm 1.30 ^{ab}	12.36 \pm 1.31 ^a	12.59 \pm 1.27 ^a
PCV %	37.36 \pm 3.14 ^a	28.16 \pm 2.96 ^{b***}	33.77 \pm 4.17 ^a	35.61 \pm 4.96 ^a	34.21 \pm 5.21 ^a	35.51 \pm 6.11 ^a	35.75 \pm 5.61 ^a

Significant with control group * $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$

Mean values in each row having different superscript (a, b, c, d) are significant

Table (3): The Mean values \pm SD of serum ALT, AST, creatinine, uric acid and urea nitrogen of the experimental groups

Groups Variables	Control (-ve)	Control (+ve)	Ginger powder	Ginger extract	Selenium	Ginger Powder+ Selenium	Ginger extract+ Selenium
AST (μ /ml)	35.36 \pm 3.71 ^c	59.11 \pm 5.91 ^{a***}	43.71 \pm 4.98 ^{b*}	45.21 \pm 5.11 ^{b*}	47.31 \pm 3.98 ^{b*}	39.67 \pm 3.61 ^c	33.67 \pm 3.51 ^c
ALT (μ /ml)	22.16 \pm 3.14 ^{bc}	33.18 \pm 4.11 ^{a**}	31.41 \pm 4.18 ^{a**}	32.36 \pm 3.21 ^{a**}	30.14 \pm 4.26 ^{a**}	25.14 \pm 5.51 ^b	26.17 \pm 6.59 ^b
Creatinine (Mg/dl)	0.77 \pm 0.02 ^c	1.55 \pm 0.33 ^{a**}	0.96 \pm 0.18 ^{ab*}	0.98 \pm 0.17 ^{ab*}	1.21 \pm 0.12 ^{a**}	0.88 \pm 0.06 ^{b*}	0.79 \pm 0.08 ^c
Uric acid (Mg/dl)	2.11 \pm 0.54 ^d	5.35 \pm 1.21 ^{a***}	3.25 \pm 0.78 ^{bc*}	3.67 \pm 0.77 ^{bc*}	4.78 \pm 0.88 ^{b**}	3.21 \pm 0.89 ^{bc*}	3.17 \pm 1.01 ^{bc*}
Urea nitrogen (Mg/dl)	32.14 \pm 3.61 ^c	63.14 \pm 5.69 ^{a***}	45.67 \pm 4.35 ^{b*}	41.33 \pm 5.31 ^{b*}	49.29 \pm 6.11 ^{b*}	35.67 \pm 4.14 ^c	33.21 \pm 3.81 ^c

Significant with control group * $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$

Mean values in each row having different superscript (a, b, c, d) are significant

Table (4): The Mean values \pm SD of blood GSH, MDA, NO and free radicals of the experimental groups

Groups Variables	Control (-ve)	Control (+ve)	Ginger powder	Ginger extract	Selenium	Ginger Powder+ Selenium	Ginger extract+ Selenium
GSH (mmol/l)	7.58 \pm 0.78 ^a	3.11 \pm 0.16 ^{c**}	5.99 \pm 0.28 ^{b*}	6.31 \pm 0.43 ^{ab}	5.36 \pm 0.82 ^{b*}	6.37 \pm 0.77 ^{ab}	6.59 \pm 0.76 ^{ab}
MDA (mmol/l)	3.03 \pm 0.44 ^b	6.11 \pm 0.67 ^{a***}	4.11 \pm 0.55 ^b	4.36 \pm 0.65 ^b	4.21 \pm 0.54 ^b	3.66 \pm 0.38 ^b	3.76 \pm \pm 0.54 ^b
NO (mmol/l)	2.67 \pm 0.78 ^a	15.65 \pm 2.81 ^{a***}	7.36 \pm 1.36 ^{b*}	5.26 \pm 1.01 ^{bc*}	6.14 \pm 1.21 ^{b*}	5.11 \pm 1.11 ^{bc*}	4.19 \pm 0.55 ^{c*}
Free radicals	25430.11 \pm 336.78 ^c	75365.43 \pm 547.81 ^{a***}	34361.31 \pm 272.36 ^{bc}	27353.20 \pm 301.27 ^c	30411.31 \pm 411.14 ^{bc}	26732.20 \pm 317.21 ^c	24351.71 \pm 273.71 ^c

Significant with control group * $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$

Mean values in each raw having different superscript (a, b, c, d) are significant

Table (5): The Mean values \pm SD of serum SOD and catalase (CAT) of the experimental groups

Groups Variables	Control (-ve)	Control (+ve)	Ginger powder	Ginger extract	Selenium	Ginger Powder+ Selenium	Ginger extract+ Selenium
SOD (mmol/l)	214.25 \pm 25.17 ^a	120.71 \pm 12.14 ^{d***}	178.16 \pm 13.61 ^{c*}	196.21 \pm 11.17 ^{ab}	175.31 \pm 12.61 ^{c*}	199.36 \pm 13.21 ^{ab}	204.36 \pm 15.55 ^a
CAT (μ /l)	60.36 \pm 6.37 ^a	19.86 \pm 2.16 ^{c**}	41.16 \pm 4.71 ^{b**}	53.21 \pm 6.21 ^a	49.21 \pm 4.59 ^{b**}	55.61 \pm 6.03 ^d	54.25 \pm 5.21 ^a

Significant with control group * $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$

Mean values in each raw having different superscript (a, b, c, d) are significant

Table (6): The Mean values \pm SD of some liver SOD, GST and GPX of the experimental groups

Groups Variables	Control (-ve)	Control (+ve)	Ginger powder	Ginger extract	Selenium	Ginger Powder+ Selenium	Ginger extract+ Selenium
SOD (μ /mg)	105.87 \pm 9.14 ^a	41.26 \pm 3.22 ^{c***}	77.11 \pm 8.08 ^{b*}	91.14 \pm 9.29 ^a	76.31 \pm 7.85 ^{b*}	99.88 \pm 9.43 ^a	110.14 \pm 10.21 ^a
GST (μ /mg)	2.41 \pm 0.24 ^a	0.65 \pm 0.08 ^{c**}	1.36 \pm 0.22 ^{b*}	1.78 \pm 0.33 ^{ab}	1.03 \pm 0.25 ^{b*}	1.96 \pm 0.32 ^a	2.49 \pm 0.43 ^a
GPX (μ /mg)	99.67 \pm 9.26	35.36 \pm 4.21 ^{c**}	66.38 \pm 7.28 ^{b*}	70.11 \pm 8.14 ^{b*}	69.36 \pm 7.19 ^{b*}	82.13 \pm 9.17	95.45 \pm 9.18 ^a

Significant with control group * $P < 0.05$ ** $P < 0.01$ *** $P < 0.001$

Mean values in each raw having different superscript (a, b, c, d) are significant

4. Discussion

Free radicals are natural by-products of oxygen metabolism that may contribute to the development of chronic diseases such as cancer and heart diseases. Lipid peroxidation is a complex process that damages the cell structure and function. Peroxidation of membrane lipids initiates the loss of membrane integrity; membrane bound enzyme activity and cell lyses (Pryor and Squadrito, 1995). Oxidative damage in tissues can be limited by the defense system of the host. These defenses appear to be inducible by nutrients/non-nutrients in the diet. Low levels of tissue antioxidant enzymes are likely to result in high levels of tissue damage that are reflected as lipid peroxides, protein carbonyls, etc. Conversely, elevated levels of antioxidant enzymes would reduce this oxidative damage to tissues. The presence of selenium helps induce and maintain the glutathione antioxidant system. Selenium is incorporated into proteins to make selenoproteins, which are important

antioxidant enzymes. The antioxidant properties of selenoproteins help prevent cellular damage from free radicals. Other selenoproteins help regulate thyroid function and play a role in the immune system (Combs and Gray, 1998 and McKenzie *et al.*, 1998). Selenium is a component of the enzymes glutathione peroxidase. It is also found in three deiodinase enzymes, which convert one thyroid hormone to another. Selenium is a component of the unusual amino acids selenocysteine and selenomethionine. In humans, selenium is a trace element nutrient that functions as cofactor for reduction of antioxidant enzymes, such as glutathione peroxidase and certain forms of thioredoxin reductase found in animals and some plants (Gladyshev and Hatfield, 1999 and Burk, 2002). Antioxidant effects of selenium can also be accounted for by its role in the selenium-dependent thioredoxin reductases. These enzymes reduce intermolecular disulfide bonds and regenerate ascorbic acid from dehydroascorbic

acid. Selenium also plays a role in the functioning of the thyroid gland and in every cell that uses thyroid hormone, by participating as a cofactor for the three known thyroid hormone deiodinases, which activate and then deactivate various thyroid hormones and their metabolites (Petit *et al.*, 2003, Koehrl *et al.*, 2005 and Dennert *et al.*, 2011).

It is well known that spices possess antioxidant activity and prevent oxidation of lipids in foodstuffs. Kikusaki and Nakatani (1993) reported that chemical constituents like gingerols and shogaols present in ginger exhibited high antioxidative activity. Sekiwa *et al.* (2000) reported that a novel glucoside related to gingerdiol from ginger had antioxidative activity using the linolenic acid model system. Consumption of ginger stimulated liver tissue of rats to increase defense enzymes such as superoxide dismutase, catalase and glutathione. In addition, these enzymes modulate the oxidative damage within the tissues which can be quantitated in terms of lipid peroxidation and protein oxidation. The significant reduction of MDA in liver and kidney tissues of ginger - fed rats confirmed that ginger enhanced antioxidant system (Nirmala *et al.*, 2008). Ginger-free phenolic and ginger hydrolyzed phenolic fractions exhibited free radical scavenging, inhibition of lipid peroxidation, DNA protection and reducing power abilities indicating strong antioxidant properties (Khanom *et al.*, 2003). The pretreatment for 20 days with ethanolic *Z. officinale* extract enhances the antioxidant defense (catalase, superoxide dismutase, and tissue glutathione) in isoproterenol-induced oxidative myocardial necrosis in rats and exhibited cardio protection property (Ansari *et al.*, 2006). Moreover, Ginger extract has antioxidative properties and scavenges superoxide anion and hydroxyl radicals (Cao *et al.*, 1993). Gingerol derived from ginger, at high concentrations, inhibits ascorbate-ferrous complex that in turn induces lipid peroxidation (Rice-Evans *et al.*, 1996). The effects of oral ingestion of bromobenzene-induced hepatotoxicity on the liver function tests of male rats have been demonstrated. El-Sharaky *et al.* (2009) reported that activities of AST and ALT were significantly elevated in bromobenzene-induced hepatotoxicity treated rats compared to the control group. Serum levels of bilirubin and total proteins measure the excretory and synthetic functions of liver. Serum bilirubin was greatly increased while the total proteins were significantly decreased in bromobenzene treated rats compared to untreated control group. This indicates an injury, impaired functions and damage of liver because of oral ingestion of bromobenzene. In addition, the decline in renal mitochondrial function following subchronic and chronic exposure to potassium bromate based on

the oxidative stress mode of action of bromate. Bromate toxicity in male rat kidney included changes in energy consumption and utilization in renal cells that involve up-regulation of glycolytic processes, possibly resulting from altered mitochondrial function (Abd El-Ghany *et al.*, 2011).

In conclusion, the present study demonstrates that ginger powder and extract exert significant antioxidant effects and these effects were amplified with coadministration of selenium. Therefore, intake of ginger plant in combination with selenium may be beneficial for amelioration of oxidative stress which is a predisposing risk factor of many diseases.

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Decolonization of Methicillin Resistant *Staphylococcus aureus* Nasal Carriage Among Health Care Workers

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Abstract: Methicillin-resistant *Staphylococcus aureus* (MRSA) has evolved as one of the most important causes of hospital infections worldwide. Screening for carriage of (MRSA) is fundamental to modern-day nosocomial infection control. Effective decolonization decreases the risk of subsequent staphylococcal infection and controls the spread of MRSA. The aim of this study was to identify the frequency of MRSA nasal carriage among health care workers in Assiut University Hospitals and to determine the efficacy of combined local mupirocin ointment and oral rifampin and trimethoprim /sulfamethoxazole for nasal MRSA decolonization for implementing various infection control policies to control the spread of MRSA in our Hospitals. Swabs were taken from the anterior nares of the 150 health care workers in different departments in Assiut University Hospitals, Egypt. Identification of *Staphylococcus aureus* was done by the conventional bacteriological methods. Methicillin resistance was detected by growth on oxacillin resistance screening agar base (ORSAB). For those who showed nasal carriage of MRSA, topical application of mupirocin & oral treatment with rifampin and trimethoprim/ sulfamethoxazole were administered for 5 days. Screening was carried out 48 hours, 1 month, 6 months and 9 months after the treatment cycle was completed. Out of 150 health care workers, 45.3% (68) were MRSA carriers. Post treatment screening showed a reduction in the number of carriers. After 48hs post treatment, they were 11.8%, followed by 1.5% after 1month. Recolonization occurred at 6 and 9 months post treatment (23.5% and 14.7% respectively) but were still less than before treatment. We conclude that we have a high percentage of MRSA nasal colonization among the studied health care workers. A single treatment cycle of combined local mupirocin, oral rifampin and trimethoprim/ sulfamethoxazole resulted in successful MRSA decolonization in the early post treatment period (within 1 month) with no documented adverse effects. However, nasal MRSA recolonization occurred again in the late post treatment period (≥ 6 months). Screening and treatment should be made an essential protocol to decrease the number of carriers transmitting MRSA to the hospital settings.

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1. Introduction

Methicillin-resistant *Staphylococcus aureus* (MRSA) continues to be a global problem in infection control. For many years it has been a major cause for nosocomial infections in many countries (Simor et al, 2002). These strains show resistance to a wide range of antibiotics, thus limiting the treatment options to few agents, such as vancomycin and teicoplanin (Peacock, 2005). It is therefore important to keep the prevalence of MRSA carriage and MRSA infections low (Wertheim and Vos, 2005).

All MRSA carriers are not the same; carriage may be transient, intermittent, or persistent for months to years (Vandenbergh et al, 1999). The anterior nares have been thought to be the most frequent site of MRSA carriage and should be targeted for surveillance screening in healthy health care workers (HCW) (Buehlmann et al, 2008). Nasal carriage of *S. aureus* is a known risk factor for subsequent infection. Transmission from health-care personnel to patients was evaluated in many studies, some of which reported a clear molecular and

epidemiological evidence of MRSA transmission from health-care workers to patients (Richardson et al, 1990). Some studies have even described outbreaks of MRSA among patients associated with colonised health-care workers (Dawson et al, 1997). Other studies considered transmission likely (Albrich and Harbarth, 2008).

Decolonization may be defined as treatment to eradicate *S. aureus* or MRSA carriage. There is a controversy regarding the effectiveness of MRSA decolonization, and it is not recommended in some studies (Buehlmann et al, 2008). In other studies, the potential benefits of decolonization were ensured and include decreased risk of subsequent staphylococcal infection and prevention of staphylococcal transmission to reduce endemic rates of infection or manage outbreaks (Andrew et al, 2009).

Eradication therapy varied between studies. Several topical and systemic antimicrobial agents have been used for MRSA decolonization, with limited success rates (Simor et al, 2007). A variety of agents, both topical and systemic, have been used

for decolonization. Although, mupirocin (Bactroban Nasal, GlaxoSmithKline) has been most commonly used (Andrew et al, 2009) yet resistance to the use of mupirocin alone has been reported (Wertheim and Vos, 2005). Chlorhexidine baths have been used in combination with intranasal mupirocin in uncontrolled trials and during outbreaks (Sandri et al, 2006). The use of combination therapy has been effective in treating MRSA in the nares and at other sites. Such combinations included the use of oral antibiotics plus rifampin which ensures excellent penetration into secretions and tissues (Bradley, 2005). However, development of resistance of *S. aureus* to rifampin after treatment with a regimen containing rifampin ranged from 0-40% (Falagas et al, 2007). The wide-scale use of systemic antibiotics has been associated with the development of drug resistance and the loss of valuable therapeutic agents for subsequent treatment of infection. Eradication of MRSA is not guaranteed or permanent. Thus “decolonization” rather than “eradication” may be a more appropriate term. The effect of any eradication or decolonization strategy seems to last 90 days at most, although more prolonged follow-up has been infrequent (Loeb et al, 2003). We carried out this study to identify the frequency of MRSA nasal carriage among health care workers in Assiut University Hospitals and to determine the efficacy of combined local mupirocin ointment and oral rifampin and trimethoprim /sulfamethoxazole for nasal MRSA decolonization for implementing various infection control policies to control the spread of MRSA in our Hospitals.

2. Material and Methods

This is a prospective cohort study with a follow-up period of 9 months. A total of one hundred and fifty health care workers from different departments and units of Assiut University Hospitals were enrolled in the study after taking their consents. The HCW recruited in the study were from the operative room of the Ophthalmology department (n=4), the Trauma Intensive Care Unit (n=61) and the Neonatal Intensive Care Unit (n= 85).

Nasal Swabs

Table 1: Frequency of MRSA nasal carriage among health care workers in different departments.

Number of screened healthcare workers in different units	Number (%) of MRSA nasal carriers
• Operative room of Ophthalmology dept. (n=4)	4 (100)
• Trauma Intensive Care Unit (n=61)	49 (80.3)
• Neonatal Intensive Care Unit (n=85)	15 (17.6)
Total (150)	68 (45.3)

MRSA: Methicillin Resistant *Staphylococcus aureus*

The frequency of detection of nasal MRSA colonization in HCW in different departments is presented in table (2). Screening was done 48hs , 1

A swab from both anterior nares was obtained from each health care worker according to Abed El-Jalil et al (2008) for MRSA detection . Colonization was defined as MRSA identified from the nares of these persons in the absence of MRSA infection (Como-Sabetti et al, 2006).

Culture , Identification and Screening for MRSA

Nasal swabs were immediately plated on mannitol-salt agar and incubated at 35°C for 72 hrs. Mannitol fermenting colonies were examined by Gram stain and tested for catalase production and coagulase test. Isolates which showed positive growth on mannitol salt agar were subcultured on oxacillin resistance screening agar base (ORSAB, Oxoid Limited , Basingstoke, England) to detect oxacillin resistant strains (Simor et al, 2002).

Treatment of colonized health care workers

Colonized health care workers were treated with local mupirocin twice per day for 5 days as recommended by the manufacturer (Turixin®, GlaxoSmithKline, Munich, Germany). In addition they received oral rifampin, 600 mg and oral TMP/SMX, 160 mg/ 800 mg given twice a day for five days (Ellison et al, 1984).

Post treatment screening

Post treatment screening was done according to the German recommendation on MRSA patients issued by the Robert-Koch Institut (Anonym, 1999). A minimum wash-out period of 48 h was required between the last treatment and the first set of screening swabs. Successful decolonization was considered to have been achieved if results were negative for 3 consecutive sets of cultures (24 h between each). Follow up screening was repeated after 1month, 6 months and 9 months after the treatment cycle was finished. Health care workers in the Ophthalmology Operative Room (n=4) refused to continue screening after 1 month post treatment.

3. Results

A total of one hundred and fifty health care workers were screened for MRSA nasal carriage. Sixty eight (45.3%) were found to be colonized as shown in table (1).

month, 6 months, and 9 months post treatment. Health care workers from the Operative room of the

Ophthalmology department didn't continue screening after 1 month post treatment.

Table 2: Frequency of MRSA nasal carriers after combined treatment in different departments .

Departments	No. (%) of HCW with MRSA nasal colonization				
	Before treatment	24 hs post treatment	1 month post treatment	6 months post treatment	9 months post treatment
Operative room of ophthalmology dept.	4	1 (25)	0 (0)	-	-
Trauma Intensive Care Unit	49	6 (12.2)	1 (2)	13 (26.5)	6 (12.2)
Neonatal Intensive Care Unit	15	1 (6.7)	0 (0)	3 (20)	4 (26.7)
Total	68	8 (11.8)	1 (1.5)	16 (23.5)	10 (14.7)

HCW: Health care workers.

MRSA: Methicillin Resistant *Staphylococcus aureus*

4. Discussion

Screening for carriage of methicillin resistant staphylococcus aureus (MRSA) is fundamental to modern-day nosocomial infection control, both for epidemiologic investigation and day-to-day decision on barrier isolation (Safdar et al, 2003).

Although many body sites such as hands, rectum, perineum, axillae, vagina, pharynx, gastrointestinal tract, and intact or inflamed skin are frequently colonised for varying time periods, the main reservoir of MRSA is the anterior nares. Among nasal *S. aureus* carriers, approximately one-half also carry the organism on their skin (Wertheim et al, 2005).

Eradicating MRSA nasal carriage from epidemiologically-implicated health care workers (HCWs) has been used on a number of occasions to control MRSA outbreak (Ben Ayed et al, 2010).

As routine decolonization is not a policy in our hospitals, we reported a very high rate of nasal carriage (45.3%). Our results were much higher than those of the study at Ain Shams University hospital, Egypt, which reported the rate of nasal MRSA carriage to be 20% (Abdel Rahman et al, 2010). In another study at Nazami Hospital in Iran, the prevalence of nasal carriage of MRSA in HCWs was only 5.3% (Askarian et al, 2009). The mean nasal MRSA carriage in health-care workers in many studies was 4.1% (Bertin et al, 2006; Seybold et al, 2006). In an Italian hospital MRSA carriage was reported in only 1.5% among HCW (Orsi et al, 2008). In countries such as The Netherlands that routinely decolonize MRSA carriers, very low prevalences of MRSA carriage are reported due to the routine decolonization which has been underestimated in the past as a strategy to control the spread of MRSA (Buehlmann et al, 2008).

It is well known that staphylococcal dispersal from asymptomatic personnel of MRSA to patients, is mainly dependent on whether the person is a nasal carrier (Hare and Thomas, 1956). It is therefore recommended that screening of health-care workers should not be restricted to outbreak settings because

there is a trend for higher colonisation rates in settings with endemic MRSA (Albrich and Harbarth, 2008). Such settings with endemic MRSA as in our hospitals. These settings have lower awareness of the threat of the bacteria (Harbarth et al, 2008). Compliance with hand hygiene and contact precautions among health-care workers were repeatedly shown to be poor in hospitals with endemic MRSA (WHO, 2005)

Evidence indicating an association between nasal *S. aureus* carriage and subsequent *S. aureus* infection has led to the development of decolonization programs aimed at decreasing the *S. aureus* infection rate (Wertheim et al, 2005). Studies of pooled data in systematic reviews or meta-analyses, strongly support the efficacy of decolonization in patients at high risk of infection (Bode et al, 2010).

Mupirocin has no structural similarities with existing systemic antibiotics that might lead to the development of cross-resistance, and in its topical form, it has minimal toxicity (Bradley et al, 2005). It has become the topical agent of choice for the elimination of MRSA carriage. However, the increased use of this antibiotic has been followed by reports of MRSA out break with both low and high-level mupirocin resistance (Simor et al, 2007). It was reported that single-cycle of mupirocin decolonization, even when effective, was followed by recolonization in many studies (Harbarth et al, 2008; Robicsek et al, 2009). So, additional cycles may be needed to prolong the effect, but the use of multiple cycles may increase the risk of MRSA resistance to mupirocin (Simor et al, 2007).

In the present study we evaluated the efficiency of a combination therapy consisting of local mupirocin, oral rifampin (600 mg) and oral TMP/ SMX (160 mg/ 800 mg) all given twice a day for five days (Ellison et al, 1984). The effectiveness of TMP-SMX as a treatment for MRSA infections was proved by Grim et al (2005). It is reported that *S. aureus* can be internalized by human cells and can survive intracellularly (Garzoni et al, 2007). So,

some systemic antibiotics, especially rifampin and cotrimoxazole, may achieve better tissue and intracellular levels, leading to higher MRSA eradication rates (**Yamaoka , 2007**).

The effect of the decolonization strategy used in this study was evaluated after 48hs, 1 month , 6 months and 9 months post treatment. Nasal MRSA colonization rates among HCW decreased after 48 hs post treatment (to 25% in the operative room of the Ophthalmology dept, 12.2% in the Trauma Intensive Care Unit and 6.7% in the Neonatal Intensive Care Unit). Maximum decolonization was achieved after 1 month post treatment when the majority became free while only 2% of the HCW remained nasal carriers in the Trauma Intensive care Unit. However, recolonization was detected again at 6 months post treatment ranging from 20% to 25.5% in the neonatal and Trauma Intensive Care Units respectively. Our findings are consistent with **Loeb et al (2003)**, who reported that the effect of any eradication or decolonization strategy seems to last 90 days at most.

Many investigations stated that follow-up lasted at least 4 weeks after completion of therapy, suggesting that success of decolonisation might be overestimated in some studies (**Blok et al, 2003**). We emphasize on that as we found an excellent success of decolonization after 1 month (98.5% , 67/68), but recolonization was detected at 6 and 9 months post treatment (23.5% and 14.7% respectively). Recolonization may be acquired from the hospital environment or from colonized extranasal sites or from subclinical infections (**Simor et al, 2007**).

In the current study, the efficacy of MRSA decolonization was on the basis of a single decolonization course. We reported a very high percentage of decolonization by this regimen which was much higher than that reported by other studies after a single decolonization course which achieved success in only 46.7% of patients (**Buehlmann et al, 2008, Simor et al 2007**).

In accordance with Roccaforte et al (1988) who used rifampin, TMP/SMX and Bacitracin local ointment, we found the regimen used in this study for decolonization to be safe and effective on short term follow up. However, relapse limits its value. In addition, **Richard et al, (1984)** evaluated a regimen consisting of rifampin and TMP/SMX only. They reported that this regimen decreased the number of MRSA-colonized patients, but not permanently as recolonization occurred again more than 6 months after treatment.

In settings of high endemicity or frequent outbreaks, decolonization therapy aims to reduce MRSA prevalence (rather than achieve MRSA eradication) and obtain outbreak termination. Therefore, shorter follow-up periods may be preferred

because they likely reflect the true effect of decolonisation therapy rather than the chances of reinfection. By contrast, when MRSA prevalence is low and outbreaks are rare, the goal of decolonisation therapy is to prevent MRSA from becoming endemic and to ensure that health-care workers remain free of MRSA after decolonisation. In these settings extended follow-up may be indicated (**Albrich and Harbarth, 2008**).

By referral to many studies, the duration of therapy did not affect treatment success and decolonisation occurred in 90% of health-care workers treated for 5 days, 82% for 7 days, 93% for 10 days, and 85% for 14 days (Blok et al, 2003).

Many regimens were reported with various degrees of success. A recent systematic review of 23 randomized, placebo-controlled trials was performed to assess the efficacy of decolonization in an overall population (healthy volunteers, health care workers, and patients) comprising both MRSA and MSSA carriers (**Ammerlaan et al, 2009**). The intervention consisted of topical decolonization alone or in combination with systemic treatment. Decolonization eliminated nasal carriage in 90% of the study participants overall. However, efficacy was lowest in the studies that assessed topical decolonization alone in patients admitted with MRSA carriage (**Harbarth et al, 1999**). Higher success rates have been achieved with topical decolonization accompanied with, or followed by, systemic decolonization (**Simor et al, 2007**).

In a multicenter, randomized, controlled trial, decolonization consisted of nasal mupirocin ointment, chlorhexidine soap, and a 7-day course of rifampin and doxycycline (**Simor et al, 2007**). The success rate was 47% after 1 decolonization cycle and 76% after 2 cycles. In places like Pakistan where mupirocin is not routinely available, oral fluoroquinolones, like oral levofloxacin in combination with topical gentamycin ointment can be used for decolonization of staphylococcal carriage (**Akhtar , 2010**). Other regimens include, a 7-day regimen of nasal mupirocin, chlorhexidine body wash, and oral rifampicin and doxycycline that resulted in successful MRSA eradication at 3 months' post-treatment in 74% (64 / 87) of patients regardless of the presence of extranasal MRSA colonization (**Simor et al, 2007**). In the study of **Buehlmann et al (2008)**, a combination consisting of mupirocin nasal ointment, chlorhexidine mouth rinse and full body wash with chlorhexidine soap for 5 days in addition to vancomycin, cotrimoxazole, rifampin and fusidic acid were used for eradication of MRSA carriage after a mean (\pm SD) of 2.1 ± 1.8 decolonization cycles. This study reported a success rate of 87%.

Measures used to control the spread of MRSA include screening, decolonization of carriers, patient isolation in a single room, hand decontamination, and protective clothing (Siegel et al, 2007).

Work restrictions for health-care workers with MRSA varied in different studies, colonised or infected personnel were allowed to work without restrictions other than education as the condition in our hospitals and emphasis on hand hygiene and standard precautions. Other institutions instructed the health-care workers to work only in dedicated MRSA areas or where MRSA was present. In other studies, colonised or infected health-care workers were temporarily removed from patient care for varying durations until documentation of negative follow-up cultures was obtained (Bertin et al, 2006). In settings with endemic MRSA or limited resources as in our hospitals, priority should be given to HCW in high-risk units such as ICUs, burn units, or surgical wards (Patel and Madan, 2000).

We conclude that we have a high percentage of MRSA nasal colonization among the studied health care workers. A single treatment cycle of combined local mupirocin, oral rifampin and trimethoprim/sulfamethoxazole resulted in successful MRSA decolonization in the early post treatment period (within 1 month) with no documented adverse effects. However, nasal MRSA recolonization occurred again in the late post treatment period (≥ 6 months). Screening and treatment should be made an essential protocol to decrease the number of carriers transmitting MRSA to the hospital settings.

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Effect of Genetic Counseling on Consanguineous Spouses Attending Maternal and Child Health Centers

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Abstract: Consanguineous spouses relation plays an important role in the prevalence of genetic disorders. Genetic counseling is directed towards reducing the number of children born with genetically determined disorders. **Aim:** The study aimed to evaluate the effect of genetic counseling on knowledge of consanguineous spouses' related to genetic disorders and making decision toward reproductive health. **Research design:** This is a quasi-experimental study. **Setting:** This study was carried out at maternal and child health centers affiliated to Ministry of Health in El-Qaliobia governorate. **Sample:** A purposive sample of one hundred spouses with 1st, 2nd or 3rd degree of consanguinity relation who attended the previously mentions MCH centers. **Tools:** Two tools were used for data collection; the first tool was an interviewing questionnaire to collect data about sociodemographic characteristics of spouses; past and present health history of spouse and spouses knowledge related to genetic disorders, genetic counseling and making decision toward reproductive health. The second tool obtained from record review of laboratory investigations regarding to genetic tests. **Results:** This study proved that genetic counseling helps in increasing spouses' knowledge regarding purpose of genetic counseling, genetic disorders, how it will be inherited and the risk of having an affected child. Approximately one third of spouses conducted genetic investigations, 10 Out of 18 Pregnant women received antenatal care (more than half), and very few of them had using family planning methods. The study also showed significant statistical correlations between spouses' performances of genetic investigations and their monthly income. **Conclusion:** The finding of this study showed that genetic counseling increased spouses' knowledge regarding the effects of consanguinity marriage on their offspring's and helps them to make proper reproductive decision through suggestion of reproductive choices. **Recommendations:** The study recommended that, genetic clinics should be accessible in all maternal and child health centers especially in rural areas supplied with necessary facilities and coordinated team work for conducting genetic investigations and genetic counseling program.

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Keywords: Consanguinity relation, Genetic disorders, genetic investigations, Genetic counseling.

1. Introduction

Consanguineous marriage refers to unions contracted between biologically-related individuals. In clinical genetics, a consanguineous marriage means union between couples who are related as second cousins or closer. In population genetics, consanguinity may refer to union of individuals with at least one common ancestor such as those occurring within small towns and tribes (Seronson and Chevront, 2010). Consanguineous marriage is widely favored in large majority of Egyptian population estimates of consanguinity ratios in different parts of Egypt rated from 29% -50%. The highest incidence is that in the rural areas. Research worldwide has indicated that consanguinity could have an effect on some reproductive health parameters such as postnatal mortality and rates of congenital malformation (Mokhtar and Abdel Fattah, 2008). Genetic disorders are diseases that are not acquired or caused from infection or trauma, but rather children inherit the gene from their parents. It could be congenital. It can be seen the disease at birth

immediately but sometimes ,if the children have the gene, the disease will develop later on (El-Sobkey,2007).These disorders include the sickle cell gene, thalassemia,the hemophilia, inborn errs of metabolism and red cell enzymopaties (Vessey and Jackson,2009). Genetic counseling services have been recommended by the World Health Organization to reduce the prevalence of genetic disorders (WHO, 2010). Genetic counseling is a process of communication between patients and trained professionals intended to provide patients who have genetic disease or risk of such a disease with information about their condition and its effect on their family. This allows patients and their families to make informed reproductive and other medical decisions (Michie et al., 2007).

Nurse as an important member in counseling team, plays a vital role in genetic counseling. She must use genetic knowledge in their clinical practice to know when and how to refer patients and families to experts in genetic health care (Mckussick, 2008).

Significance of the study:

Many studies have shown that 30% of admission and about 40-50% of deaths occurring in pediatric hospitals are accounted for children with genetic disorders or congenital malformations (Gomaa, 2007). The genetic disorders are chronic in nature and therefore require continuous support and health care. Consequently, the genetic diseases causes formidable economic and psychosocial burden on the family with negative reflection on the community at large. At the present time, the most effective means of preventing genetic diseases remains the provision of genetic counseling for individuals at risk of having a child with genetic disorders, especially spouses with consanguinity marriage.

Aim of the study:

The aim of this study is to evaluate the effect of genetic counseling on knowledge of consanguineous spouses' related to genetic disorders and making decision toward reproductive health.

Hypotheses:

Genetic counseling will improve consanguineous spouses' knowledge related to genetic disorders and help spouses make proper reproductive decision

2. Subjects and methods:

Research design:

This is a quasi-experimental study was conducted to explore the effect of genetic counseling on consanguineous spouses.

Setting

This study was carried out at 5% of maternal and child health (MCH) centers affiliated to Ministry of Health in El-Qualiobia governorate which represent 7 centers in rural areas from the total number of 140 MCH centers were chosen randomly for application of genetic counseling program where a large proportion of marriages are contracted between blood relatives.

Sample:

A purposive sample of one hundred (100) spouses who attended the previously mentioned MCH centers for antenatal follow up or for other MCH services were chosen according to the following inclusion criteria; spouses with 1st , 2nd or 3rd degree of consanguinity relation, at reproductive age from 18 to 49 years and didn't previously attend genetic counseling program.

Tools of data collection:

First tool: An interviewing questionnaire was developed to assess the sociodemographic characteristics and spouses knowledge related to genetic disorders and genetic counseling. It consisted of three parts:

A) Sociodemographic characteristics of spouses which include age, level of education, job, consanguinity degree and income.

B) Past and present health history of spouses as regards family history, obstetric history, consanguinity degree (were documented in the form of pedigree (Load, et al., 2009), first degree: first cousin; second degree: second cousin; third degree: step or distant relative.

C) Spouses knowledge related to genetic disorders and genetic counseling, it was used before and after the counseling program.

Answer of individual knowledge questions were categorized on two-point scale as satisfactory and unsatisfactory. For the total evaluation of knowledge the correct answers was added for every participant and normalized to a value on a 100 point scale .A satisfactory overall knowledge level is considered if the total degree is more than or equal 50; otherwise it was regarded as unsatisfactory knowledge level.

Second tool: Data collection from medical record, it contained results of genetic investigations (karyotype test, ultrasound and biological tests), ante natal care and reproductive decision.

Content validity revised by five expertise group from faculty members of Community Health Nursing and specialized physicians in genetic.

Pilot study:

A pilot study was carried out on seven spouses at El Qualiobia Governorate ;one from each maternal and child health center before embarking on data collection, in order to test the applicability of tools, as well its feasibility. The modification of tools was done to reach to the finalized form. Subjects in the pilot were not included in the main study sample to avoid bias.

Field work:

Official letters was issued to the directors of selected maternal and child health centers for permission of data collection and conducting the study. Oral consent was secured from each spouse after explaining the aim of the study and ensuring that all information will be used only for research purposes.

Data were collected over nine months (September 2010-June 2011)

The Genetic counseling construction has passed through different phases as follow:

The preparatory phase and assessment phase:

In this phase the researchers' revised current local and international related literature which helped in designing the tools.

The researchers attended the maternal and child health centers from 9.00 am to 1.00 pm for two days/week to collect data till the sample size reached the previously determined number. Based on actual educational needs 'assessment of spouses and guided by relevant literature, counseling sessions were

developed. **The general objective of genetic counseling** was to acquire the consanguineous spouses' knowledge related to genetic disorders and help them to make informed decisions toward reproductive health and genetic screening. At the end of counseling sessions, the spouses will:

- Explain the facts contributing to genetic disorders that may affect offspring.
- Comprehend how heredity affecting offspring.
- Take a decision toward their reproductive health.
- Propose the available management.

The sessions included theoretical background about genetic disorders. Every spouse was interviewed for about 45 minutes to fill the tools (pre test). Then the spouses in the study sample were provided by four constructive teaching sessions. Each session took about 45 minutes integrated with teaching points and the researchers before going on to a new topic used questions to check the spouse recall and understanding of the material already covered. Sessions were conducted by the researchers according to **GATHER** approach:

Greet: The investigators established relationship with spouses emphasizing the purposes and benefits of genetic counseling according to their tradition and religion. The investigator reassured spouses that what will be said is confidential.

Ask: The investigators asked spouses about their sociodemographic circumstances, past and present health status, and reproductive options. Assessing spouse's genetic knowledge and their levels of anxiety separately using questions similar to first tool constructed by the investigators.

Tell: The investigators told spouses about nature of genetic disorders and its consequences, why screening, causes of inherited characteristics, risk of recurrence, indications of genetic counseling, genetic investigations, antenatal care, family planning, life style, and places of genetic services in Qualiobeja Governorate.

Help: The investigators helped spouses choose alternatives management as regards antenatal care, family planning and different methods that could be used.

Evaluate: The investigators explained different lines of alternatives of genetic harmful factors in their life style that can be modified to reduce the risk of defects of offspring and suggest appropriate referrals.

Return to follow up visits: The investigators returned for follow up evaluation through home phone and records in maternal and child health centers.

Different methods of counseling as face to face and interactive counseling with laptop. Using effective media as posters, real objects and a model for reproductive system, taking into consideration

using simple and clear Arabic language to suit the level of all spouses. A booklet was constructed for spouses as an educational reference after counseling implementation. This booklet contains items about purpose of genetic counseling, risk of consanguinity marriage, early detection of risk factors, antenatal care, healthful factors in lifestyle, transmission of genetic traits from parent to children, types of genetic screening tests and community services of genetic counseling.

Evaluation:

A post test was conducted immediately at the end of counseling sessions using the aforementioned tools to evaluate the effect of counseling on spouses' knowledge while evaluation of spouses decision making regarding to reproductive health, genetic investigations were conducted three months later post counseling through reviewing spouses records and meeting in maternal and child health centers.

Ethical considerations:

The researchers took into consideration spouses' rights based on their needs, giving complete information, assuring them that confidentiality will be obtained and no harmful effect on them. They had also the right to withdraw from the study at any time.

Statistical Design:

Data entry and analysis were performed using SPSS version 11.5

The quantitative data were presented using the arithmetic mean, standard deviation, and analyzed using t-test and analysis of variance ANOVA. Qualitative data are presented by the number and percentage and analyzed by chi-square test to assess the interrelationship among variables. Statistical significant was set at $p < 0.05$.

3. Results:

Table (1) reveals that the mean age of wives in this study was 24.7 ± 5.13 , 65 % of them in the age category from 20 to less than 30 years and 20% less than 20 years. The result shows also that the husbands' mean age was 29.5 ± 6.08 , about 63% of them in the age category from 20 to less than 30 years and 27% in the age category from 30 to less than 40 years. As regard to educational level, the secondary level had the highest percent (42%, 47%) for wives and husbands respectively. This result shows also that 73% of wives were housewives and all of husbands were working. The result of this study demonstrates that 26% of spouses monthly income was sufficient with a mean $\pm SD$ 358.3 ± 110.06 . As regards consanguinity degree between spouses 59% were first degree, 29% were second degree and 12% were third degree.

Table (2) demonstrates The wives whom their age during first pregnancy less than 20 years were 33.7%, 38.2% were aged between 20 to less than 25 years, while 28.1% were aged 25 or more with a mean age 23.0 ± 3.86 . The result also demonstrates that 25% of wives had history of spontaneous abortion less than 3 times, and 2% of them had history of spontaneous abortion 3 times or more. The result indicates that 57% of wives delivered one to two times and 14% delivered three to four times. In relation to 18 pregnant wives in this study 33.3% were at first trimester, 50% of them at second trimester and 16.7% at third trimester.

Table (3) reveals that 50% of spouses had genetic family history, 39% had family history of diabetes mellitus, and 79.4% of them were relatives of second degree and 27.1% of first degree. Family history of Down syndrome was found among 10%, which 17.2% of them were relatives of second degree and 8.2% of the first degree. Family history of renal diseases was found among 9%, which 11.9% of them were relatives of first degree and 6.9% of the second degree. Family history of cystic fibrosis was 7% prevalence, 13.8% of them relatives of second degree. Blindness was common among 7%, 20.7% of them relatives of second degree. Hearing loss and muscle atrophy were found among 5% of family history followed by Epilepsy 4%. Thalassemia, sickle cell and hemophilia were found among 3% of family history.

Table (4) shows that 24% of children have genetic disorders, 5% of them have Down syndrome and 16.7% of these were third degree between spouses, 3% with cerebral palsy, 3.4% of these from first and second degree between spouses. This table also reveals that 2% an equal percentage of spouses have children suffering from sickle cell anemia, Juvenile D.M, G-6-PD deficiency, color blindness and hydrocephalus. The least equal percentages representing 1% of children were suffered from Thalassemia, PKU, meningocel, imperforated anus, hemophilia and congenital bilateral hip dislocation.

Table (5) indicates that there was improvement in the acquisition of knowledge related to genetic disorders, genetic counseling and investigations, for both wives and husbands post counseling.

Table (6) demonstrates the difference in the mean scores and standard deviation of knowledge pre genetic counseling between husbands and their wives was not significant ($P > 0.05$). However, in relation to post counseling it was statistically significant ($P < 0.05$). The same table also revealed that the mean score and standard deviation of knowledge between

wives and husbands pre-post counseling was statistically significant ($P < 0.05$).

Table (7) shows that 30% of spouses performed genetic investigations. As regards karyotype 16.7% of wives and 10.0% of husbands had abnormal structural aberrations, 6.7% of husbands had abnormal numerical aberrations and 13.3% of wives had sex chromosome abnormality. As for three dimension ultrasound it was performed for 60.0% of pregnant wives, 6.7% of them had intrauterine growth retardation. 3 (10.0%) Of pregnant wives performed amniocentesis which revealed one abnormality representing 3.3%

This table also shows that, the results of HB electrophoresis were 13.3% of wives and 6.7% of husbands had hemolytic anemia. Thalassemia and sickle cell anemia were found only in 3.3% of husbands. As for glucose tolerance test 3.3% of both wives and husbands had diabetes mellitus.

Figure (1) reveals that 62.8% of the spouses didn't perform genetic investigation due to financial causes, followed by 52.8% due to far distance, 37.1% due to fear from discovering disease, 18.6% due to traditions and distrust in lab results, 20.0% due to presence of normal child, 17.1% due to fatalism and 14.3% due to lack of time.

Table (8) demonstrates that 55.6% of pregnant wives decided ante-natal care, and 11.1% decided termination of pregnancy. This table shows also that 9% of wives used family planning methods.

Table (9-a) indicates that the relation between spouses educational level and their knowledge post genetic counseling is highly statistical significant $P < 0.001$.

Table (9-b) reflects statistical significant relation between consanguinity degrees and wives knowledge pre and post genetic counseling. $P < 0.05$. but it was not significant for the husbands.

Table (9-c) shows that there were no statistically significant associations between genetic family histories of the spouses and their knowledge pre or post genetic counseling ($P > 0.05$).

Table (9-d) demonstrates that there were no statistically significant associations between presence of children with genetic disorders and spouses 'knowledge pre or post genetic counseling ($P > 0.05$).

Table (10-a) shows that there were statistical significant relations between spouses genetic investigations and their ages and monthly income at $P < 0.05$.

Table (10-b) reflects that there were no statistically significant associations between spouses genetic investigations and their educational levels ($P > 0.05$).

Table (1): Percentage distribution of spouses according to their sociodemographic characteristics (n=100).

Items	Wives		Husbands	
	No	%	No	%
*Age (Years):				
• <20	20	20	2	2
• 20-	65	65	63	63
• 30-	15	15	27	27
• 40-50	0	0	8	8
Mean ±SD	24.7±5.13		29.5±6.08	
*Educational level:				
• Illiterate	26	26	13	13
• Read and write	19	19	18	18
• Secondary education	42	42	47	47
• University	13	13	22	22
*Job:				
• Not working	73	73	0	0
• Working	27	27	100	100
	No		%	
*Consanguinity degree:				
• First degree	59		59	
• Second degree	29		29	
• Third degree	12		12	
*Family monthly income:				
• 250-	74		74	
• 500+	26		26	
Mean ±SD	358.3±110.06			

Table (2): Percentage distribution of wives according to their reproductive health history (n=100).

Items	No	%
*Age at first pregnancy (Years): n=89		
• < 20	30	33.7
• 20 -	34	38.2
• 25 +	25	28.1
Range	17-32	
Mean ±SD	23.0±3.86	
*Number of spontaneous abortions :		
• 0	73	73
• < 3	25	25
• ≥ 3	2	2
* Number of deliveries:		
• 0	29	29
• 1-2	57	57
• 3-4	14	14
*Current pregnancy gestational age (trimesters) (n= 18)		
• First trimester	6	33.3
• Second trimester	9	50
• Third trimester	3	16.7

Table (3): Percentage distribution of spouses with family history of genetic disorders according to their consanguinity degree (n=100).

	Consanguinity degree						Total 100	
	First (n= 59)		Second (n= 29)		Third (n=12)		No	%
	No	%	No	%	No	%		
Family with genetic disorders							50	50
• Diabetes mellitus.	16	27.1	23	79.3	0	0	39	39
• Down syndrome.	5	8.5	5	17.2	0	0	10	10
• Renal disease.	7	11.9	2	6.9	0	0	9	9
• Cystic fibrosis.	3	5.1	4	13.8	0	0	7	7
• Hearing loss.	2	3.4	3	10.3	0	0	5	5
• Blindness.	1	1.7	6	20.7	0	0	7	7
• Muscle atrophy.	1	1.7	4	13.8	0	0	5	5
• Epilepsy.	0	0.0	4	13.8	0	0	4	4
• Thalassemia.	0	0.0	0	0.0	3	25	3	3
• Sickle cell anemia.	0	0.0	2	6.9	1	8.3	3	3
• Hemophilia.	1	1.7	2	6.9	0	0	3	3

Items are not mutually exclusive.

Table (4): Percentage distribution of spouses according to their children with genetic disorders (n=100).

Items	Consanguinity degree						Total 100	
	First (n= 59)		Second (n= 29)		Third (n=12)		No	%
	No	%	No	%	No	%		
Children with genetic disorders and congenital anomalies							24	24
• Down syndrome	2	3.4	1	3.4	2	16.7	5	5
• Cerebral palsy	2	3.4	1	3.4	0	0	3	3
• Sickle cell anemia.	1	1.7	0	0	1	8.3	2	2
• Juvenile D.M	1	1.7	0	0	1	8.3	2	2
• Thalassemia	0	0	1	3.4	0	0	1	1
• G-6-PD deficiency	1	1.7	0	0	1	8.3	2	2
• Color blindness	0	0	2	6.9	0	0	2	2
• PKU	0	0	1	3.4	0	0	1	1
• Meningocel	0	0	0	0	1	8.3	1	1
• Hydrocephalus	1	1.7	1	3.4	0	0	2	2
• Imperforated anus	0	0	1	3.4	0	0	1	1
• Hemophilia	1	1.7	0	0	0	0	1	1
• Congenital bilateral hip dislocation	0	0	1	3.4	0	0	1	1

Table (5): Percentage distribution of spouses according to their satisfactory knowledge related to genetic disorders, genetic counseling and investigations pre and post counseling (n=100).

Items	Wives				Husbands			
	Pre		Post		Pre		Post	
	No	%	No	%	No	%	No	%
* Genetic disorders:								
• Risk of consanguinity marriage	17	17	98	98	20	20	98	98
• Genetic problems in consanguineous marriage.	19	19	97	97	9	9	99	99
• Warning from consanguinity marriage.	10	10	98	98	12	12	99	99
• Causes of increasing genetic disorders.	16	16	98	98	13	13	99	99
• Early detection of genetic disorders.	14	14	100	100	10	10	100	100
* Genetic counseling & investigations:								
• Meaning of genetic counseling.	12	12	97	97	7	7	100	100
• Community services of genetic counseling.	13	13	99	99	5	5	99	99
• Indication of genetic counseling.	14	14	94	94	2	2	99	99
• Genetic investigation before pregnancy.	14	14	95	95	5	5	99	99
• Genetic investigation during pregnancy.	10	10	99	99	14	14	93	93
• Management of genetic disorders.	22	22	93	93	12	12	98	98

Table (6): Difference between Knowledge of husbands and their wives pre and post genetic counseling. (n=100)

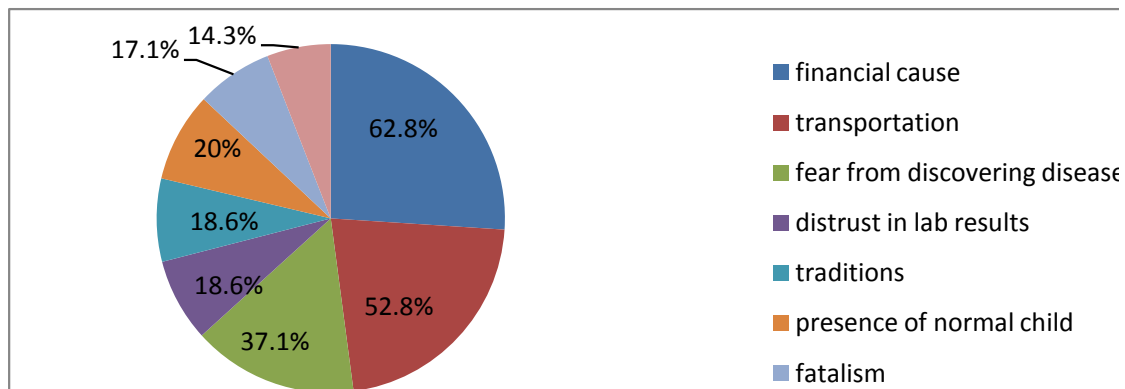
Items	Mean	SD	t-test	P-value
*Pre counseling				
• Wives	14.5	29.5	1.33	.183 P> 0.05 NS
• Husbands	9.7	19.6		
*Post counseling				
• Wives	96.4	9.8	-1.98	0.0487 P< 0.05 S
• Husbands	98.8	7.5		
*Post- Pre				
• Wives	81.9	29.7	-1.99	0.0481 P< 0.05 S
• Husbands	89.9	20.4		

Table (7): Percentage distribution of spouses according to their conducting of genetic investigations post counseling (n=30).

Items	Wives		Husbands	
	No	%	No	%
*Karyotype:				
• Normal	21	70.0	25	83.3
• Abnormal structural aberrations	5	16.7	3	10.0
• Abnormal numerical aberrations	0	0.0	2	6.7
• Sex chromosome abnormality	4	13.3	0	0.0
*Glucose tolerance test:				
• Normal	26	86.7	29	96.7
• Impaired	3	10.0	0	0.0
• Diabetic	1	3.3	1	3.3
*HB electrophoresis:				
• Normal	26	86.7	26	86.7
• Hemolytic anemia	4	13.3	2	6.7
• Sickle cell anemia	0	0.0	1	3.3
• Thalassemia	0	0.0	1	3.3
*Three-Dimension ultrasound of pregnant(n=18)				
• Normal	16	53.3	0	0
• Intrauterine growth retardation	2	6.7	0	0
• *Amniocentesis: (n=3)				
• Normal	2	6.7	0	0
• Abnormal	1	3.3	0	0

Items are not mutually exclusive.

Figure (1): Percentage distribution of spouses according to barriers against conducting genetic investigations post counseling (n=70).



All items are not mutually exclusive.

Table (8): Percentage distribution of spouses according to their decision making toward reproductive health (n=100).

Decision making	No.	%
*Pregnant wives (n=18)		
• Antenatal care	10	55.6
• Pregnancy termination due to growth retardation	2	11.1
*Use of family planning method	9	9.0

Table (9-a): Relation between spouses knowledge post genetic counseling and their educational level (n=100).

Items	Knowledge post genetic counseling		
	Mean	SD	ANOVA
Wife education level			
• Illiterate	88.81	16.52	F = 8.614 P = 0.00004 P<0.001 HS
• Basic education	99.52	2.08	
• Secondary	98.48	3.97	
• University	100.0	0.00	
Husband education level			
• Illiterate	92.31	19.93	F = 4.13 P = 0.008 P<0.001 HS
• Basic education	99.49	2.14	
• Secondary	99.81	1.33	
• university	100	0.00	

Table (9-b): Relation between spouses knowledge pre - post genetic counseling and their consanguinity degree (n=100).

consanguinity degree	Wives Knowledge post-pre genetic counseling		
	Mean	SD	ANOVA
• First	88.81	16.52	F = 4.15 P = 0.0186 < 0.05 S
• Second	99.52	2.08	
• Third	98.48	3.97	
consanguinity degree	Husbands Knowledge post-pre genetic counseling		
	Mean	SD	ANOVA
• First	88.81	16.52	F = 0.739 P = 0.48 > 0.05 NS
• Second	99.52	2.08	
• Third	98.48	3.97	

Table (9-c): Relation between spouses knowledge pre - post genetic counseling and presence of genetic family history (n=100).

Genetic family history	Wife's Knowledge			Husband's Knowledge		
	No.	Mean	SD	No.	Mean	SD
Pre						
• Not present	50	13.64	28.7	50	10.0	20.1
• Present	50	15.27	30.48	50	9.45	19.26
t= -0.28 P=0.783 P>0.05 NS				t=0.14 P = 0.89 P>0.05 NS		
Post						
• Not present	50	96.7	10.09	50	99.64	1.80
• Present	50	99.6	9.68	50	98.00	10.44
t = -0.37 P=0.714 P>0.05 NS				t=1.09 P =0.277 P>0.05 NS		
Post-Pre						
• Not present	50	82.36	28.94	50	89.63	20.03
• Present	50	81.45	30.78	50	88.54	21.00
t = 0.15 P =0.88 P>0.05 NS				t = 0.27 P =0.791 P>0.05 NS		

Table (9-d): Relation between spouses knowledge pre - post genetic counseling and presence of children with genetic disorders (n=100).

Children with generic disorder	Wife's Knowledge			Husband's Knowledge		
	No.	Mean	SD	No.	Mean	SD
Pre						
• Not present	24	17.05	32.75	24	9.85	19.50
• Present	76	13.64	28.53	76	9.69	19.77
$t = 0.49$ $P = 0.624$ $P > 0.05$ NS			$t = 0.03$ $P = 0.972$ $P > 0.05$ NS			
Post						
• Not present	24	94.70	12.26	24	99.62	1.86
• Present	76	96.89	8.98	76	98.56	8.53
$t = -0.95$ $P = 0.344$ $P > 0.05$ NS			$t = 0.6$ $P = 0.55$ $P > 0.05$ NS			
Post-Pre						
• Not present	24	77.65	32.16	24	89.77	19.38
• Present	76	83.25	29.02	76	88.87	20.86
$t = -0.8$ $P = 0.424$ $P > 0.05$ NS			$t = 0.19$ $P = 0.852$ $P > 0.05$ NS			

Table (10-a): Relation between spouse's performance genetic investigations and their age and family income post counseling (n=100)

Items	Performance of genetic investigations			
	Yes(n=30)		No(n=70)	
	No.	%	No.	%
Wife' age (Years):		33.3		
• <20	10		10	14.2
• 20-	14	46.7	51	46.7
• 30-50	6	20.0	9	20.0
Pearson $\chi^2 = 6.74$ $df = 2$ $P = 0.034$ $P < 0.05$ S				
Husband' age (Years):				
• <30	22	73.3	43	61.4
• 30-50	8	26.7	27	38.6
Pearson $\chi^2 = 1.32$ $df = 1$ $P = 0.253$ $P < 0.05$ S				
*Family monthly income (LE):				
• Sufficient	18	60.0	56	80.0
• Not sufficient	12	40.0	14	20.0
Pearson $\chi^2 = 4.37$ $df = 1$ $P = 0.0367$ $P < 0.05$ S				

Table (10-b): Relation between spouse's performance genetic investigations and their education level post counseling. (n=100)

Items	Performance of genetic investigations			
	Yes(n=30)		No(n=70)	
	No.	%	No.	%
Wife education level				
• Illiterate	6	20.0	20	28.6
• Basic education	5	16.7	14	20.0
• Secondary	16	53.3	26	37.1
• University	3	10.0	10	14.3
Pearson $\chi^2 = 2.32$ $df = 3$ $P = 0.508$ $P > 0.05$ NS				
Husband education level				
• Illiterate	3	10.0	10	14.3
• Basic education	4	13.3	14	20.0
• Secondary	17	56.7	30	42.9
• University	6	20.0	16	22.9
Pearson $\chi^2 = 1.75$ $df = 3$ $P = 0.6269$ $P > 0.05$ NS				

4. Discussion:

The present study encompasses 100 spouses with consanguinity relation. It showed that the mean age of wives was 24.7 ± 5.13 years and the mean age of husbands was 29.5 ± 6.08 . Less than half of husbands and slightly more than two fifths of wives had secondary education. The current study finding demonstrated that all of husband and more than one quarter of wives were working. As regards consanguinity degree, more than half of spouses were first degree. The mean monthly income of spouses was 358.3 ± 110.06 . In accordance with these study findings, (table, 1). **Load et al., (2009)** stressed on importance of collecting data about sociodemographic characteristics because some disorders increase in incidence with mothers' age and the education factor which affect knowledge acquirements. .

The current study findings revealed that, the mean age of wives at first pregnancy was 23.0 ± 3.86 and one quarter of them had a history of spontaneous abortion less than three times. More than half of wives delivered once or twice, and half of pregnant wives were in the second trimester (table, 2). An Egyptian study conducted by **Mokhtar and Abdel-Fattah (2008)**, revealed that, consanguinity among couples with repeated abortion constituted 60% with 44% first cousin. In Egypt chromosomal abnormalities are present in nearly half of all spontaneous miscarriages. In accordance with **Abdel Meguid et al., (2008)**, the aggregation of abortions, stillbirth, neonatal and infant deaths is stronger in consanguineous families than those with unrelated marriage. **Ward et al., (2009)**, stated that the reproductive history includes any type of pregnancy loss, spontaneous abortion, stillbirth and prenatal death. For those couples with three or more miscarriages for which no maternal anatomic or physiologic explanation can be found, cytogenetic analysis should be considered.

These study findings demonstrated that, first consanguinity degree had eight genetic disorders. Diabetes mellitus was the commonest followed by renal diseases, Down syndrome, cystic fibrosis, hearing loss, blindness, and muscle atrophy. Spouses with second degree relation had ten genetic disorders. Diabetes mellitus was also the commonest followed by blindness ,Down syndrome ,cystic fibrosis ,muscle atrophy ,epilepsy ,hearing loss, renal disease, hemophilia and sickle cell anemia. Regarding to third consanguinity degree, thalassemia and sickle cell anemia were the two only genetic diseases found (table 3). These findings were incongruence with **Mokhtar and Abdel-Fattah (2008)**, who found that family history of the previous genetic disease was present in approximately the majority of the couples, while **Albar (2007)**, reported that first cousins have

sixteenth of their genes in common because all individual are carriers of five to seven recessive gene. **Dale et al., (2010)** emphasized that one objective in medical genetic counseling is to identify the family genetic risk. Family tree is a powerful diagnostic tool for this purpose, taking and interpreting a basic family history to identify reproductive risk as an important element in preconception and early antenatal care.

The present study findings showed that about one quarter of the spouses had children with thirteen types of genetic disorders and congenital defects. The most common were Down syndrome representing five percent, followed by cerebral palsy accounting for three percent and equal percentage of two percent for sickle cell anemia, juvenile diabetes, G6-PD deficiency, color blindness and hydrocephalus. The least equal percentages representing 1% of children were suffered from Thalassemia, PKU, meningocel, imperforated anus, hemophilia and congenital bilateral hip dislocation (table, 4).

In accordance with this study results of **Hamame et al.,(2008)**, stated that the rate of children with Down syndrome in some Arab countries exceeds the 1.2 to 1.7 per 1000 typical for industrial countries. This may be related to the relatively high proportion of births to older mothers in the region. Up to 50% of children with Down syndrome in the region are estimated to be born to mothers aged 40 or over. In study conducted by **Reynold et al., (2010)**, spouses had family history of different genetic disorders, genetic investigations revealed chromosomal abnormalities in 15%.

The finding of pre counseling showed that, unsatisfactory knowledge among approximately all spouses even the university educated. On the other hand, post counseling, there was a highly significant increase in spouses' knowledge (table, 5). In a study carried out by **Abo-Baker (2008)**, Three quarters of parents had deficit knowledge about genetic disorders; the majority did not know the meaning of genetic disorders and its causes. However, in spite of long term instructions, about one fifth of parents had adequate understanding about nature of the genetic disorders. This could be due to using different methods of counseling as face to face, interactive laptop, discussion and demonstration supported by using real objects, posters, models and handouts which are effective approaches for conveying information.

The study results emphasized a great improvement in the mean score knowledge post counseling for both husbands and their wives (table, 6).

In order to achieve screening tests, spouses under study were provided with adequate information

regarding purpose, types of testing and Place of genetic investigations. However, the present study findings showed that less than one third only of spouses performed genetic investigations (**table, 7**). As regards ultrasound done for pregnant wives in this study, two out of eighteen had intrauterine growth retardation whereas; one out of three had abnormal amniocentesis. Investigation of HB electrophoresis done for spouses were six out of thirty had hemolytic anemia, one out of thirty husbands had sickle cell anemia and thalassemia. This table showed also that about one third of wives and more than one tenth of husbands had abnormality karyotype. The investigators found that spouses faced difficult decision about whether to terminate or to continue the pregnancy. This could be due to religion and cultural perception of rural community which refuse prenatal diagnosis and selective abortion. In accordance with **Abdel Meguid et al., (2008)**, in their study about premarital genetic investigation; effect of genetic counseling found chromosomal analysis of cases revealed about 15% of the studied sample with chromosomal abnormalities, either structural aberrations or numerical aberrations or both. These results indicate the importance of chromosomal analysis as part of genetic investigations in premarital counseling to identify couples who may require post conception amniocentesis.

More than two thirds of spouses in this study did not perform genetic investigations which can be attributed to financial causes, transportation, fear from discovering diseases, tradition, distrust in laboratory results, presence of normal child, fatalism and lack of time (**figure,1**). These results were consistent with those of **Saleem et al., (2009)**, who reported that parental attitude to antenatal diagnosis and pregnancy termination is a consequence of a balance between parental understanding of the disease, its mode of inheritance and the prenatal diagnostic options available on the one hand; and traditional belief in fate, religious, social value and economic factors on the other hand. Genetic services are focused on those who are most able to pay for services.

The present study findings demonstrated that ten of the pregnant wives who received antenatal care, minority terminated their pregnancy due to intrauterine growth retardation (**table,8**) In accordance with this study findings, **Reynold et al., (2010)**, indicated that good antenatal care is essential to anticipate difficulties and complications of labour and to ensure the birth of healthy baby. Results in this table showed also that a very little percent of the studied sample used family planning methods. This could be due to some of spouses had no children or other problems as spontaneous abortion or still births or desire of large family size.

The present study finding revealed that the relation between spouses educational level and their satisfactory knowledge post genetic counseling was highly significant (**table 9-a**). Incongruent to this results, **Tiller et al., (2009)**, reported that women who reported lower level of education may be most likely to benefit from educational strategies designed to supplement genetic counseling to improve their knowledge level.

Concerning the consanguinity degree, the present study finding demonstrated that there was statistically significant correlation between first degree consanguinity and wives' knowledge pre and post genetic counseling (**table, 9-b**). This may be attributed to first degree consanguinity associated with many genetic abnormalities which lead to increasing spouses' interest and experiences.

The current study finding showed insignificant associations between genetic family history of the spouses, and their knowledge pre and post genetic counseling (**table, 9-c**).

This study showed statistically insignificant associations between presence of children with genetic disorders and spouses' knowledge pre and post counseling (**table, 9-d**). In a similar study, **Antley and Hartlage (2010)**, found that mothers of children with Down syndrome had a considerable amount of information regarding the nature of condition before counseling that was related to their educational background, but they lacked knowledge on recurrence risks. As for the post counseling results of the mothers, it was revealed that they understood the nature of the condition, understood the recurrence risk, and had a good understanding of both topics.

The finding of this study showed that there were no statistical significant correlation between spouses performance of genetic investigations and their age, or education, (**table 10 a ,b**). These results could be due to that more than quarter of wives were illiterate ,and the highest percent that performed investigations were among secondary level of education. But there was statistical significant correlation with monthly income where the mean of the income was 358 ± 110.06 L.E. as it puts them beyond their capabilities to conduct genetic investigations which are more than 500 L.E.

5. Conclusion:

In conclusion, this study proved that genetic counseling helps in increasing spouses' knowledge regarding purpose of genetic counseling, genetic disorders, how it will be inherited and the risk of having an affected child. Also, it helped to have decision for their reproductive health related to antenatal care and family planning. In addition, the study showed significant statistical association

between spouses' performances of genetic investigations and their monthly income.

Recommendations:

The finding of this study projected the need for: Genetic clinics should be accessible in all maternal and child health centers especially in rural areas due to high incidence of consanguineous marriage-supplied with necessary facilities and coordinated team work for conducting genetic investigations and genetic counseling program about:

- Risk of consanguineous marriage.
- Children with genetic disorders.
- Early detection of genetic disorders.
- Management of genetic disorders.
- Reproductive health, antenatal care and termination of pregnancy.
- Family planning.

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An investigation into the Impacts of Performance Auditing Components on the Promotion of the Productivity of Iran's State Sectors' Organizational and Structural Resources (Organizational Climate) (Case Study : Iran's Supreme Audit Court)

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Abstract: This research evaluates the impacts of performance auditing components on the promotion of the productivity of state sectors' structural resources. It is a survey research and the survey tool is two researcher-made five-point likert scale questionnaires which have been defined to audit productivity and performance. Both questionnaires have high validity and reliability. The time scope of the research is the duration of data collection which was between January, 2012 and July, 2012. Also, research case is *Iran's Supreme Audit Court* and its offices across provinces. () persons were selected as the statistical population through Cochran formula representing whole society as much as possible. The research contains three hypotheses. To examine them, T-student test was used in SPSS software. Since the questionnaires contain qualitative data, non parametric tests like Pearson Correlation Coefficient were used as well. To examine the hypotheses, multivariate regression and binomial test were used. To prove the hypotheses, "very high", "high" and "somewhat" items were considered as indices. Other employed statistics are: T, R and F regression as well as *Path Analysis Equations*. The results of the research revealed that: 1) performance auditing leads to a profitable, effective and efficient use of structural and organizational resources. 2) The profitable, effective and efficient use of structural and organizational resources promotes productivity and 3) performance auditing results in the promotion of the productivity of state sectors' structural and organizational resources (organizational climate).

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Introduction

Since the promotion of productivity is an essential condition of the survival and continuation of any organization in current turbulent and chaotic environment and regarding the fact that the parameter of organizational structure more likely plays significant role in the promotion of productivity, it is clear that the structure with respect to its content, dimensional and environmental properties greatly affects the development of an organization. Indeed, it is the structural characteristics distinguishing creative and productive organizations from others. This parameter is proportional with the position and place of an organization. Any attempt to promote the productivity of an organization, with respect to its structure, could unveil its uncovered shortages and prepare employees to do their tasks more effectively in order to better deal with daily tasks. Thus, creating an appropriate structure with respect to current situation, in which environment is continuously changing, could have a great influence on productivity promotion. As a result, there is a direct relation between productivity, coordination, accurate distribution of labor, exact classification of organizational duties and proportional structures with current condition which ultimately will result in the use of actual and potential abilities of employees and

individuals. The more percentages of the abilities could be put into practice by a proper and right organizational structure, the more improvement would be expected [Karimi and others 2008].

On the other hand, although performance auditing is not an unknown issue, but only a few of audits have been resulted in supportive actions affecting productivity. Performance auditing could be considered as one of them. As a result, the auditing and responsibility of the state sector is established provided that executive systems are audited based on planning and performance and according to the clear statement of their objectives and expected outcomes. Therefore, performance auditing is a clear statement of observing economy, efficiency and effectiveness of all performances of all big and small organizations. To this end, by conducting performance auditing, auditors could significantly affect governmental decisions and play a great and valuable role in improving and strengthening the systems as well as the promotion of their productivity. Thus, productivity and its continuous improvement have a special place in organizations. In this way, it would be apparent that growth and development demand more attentions to productivity and its continuous improvement in organizations. Investigations show that different

organizations have different tools for improving productivity and performance auditing is one of them.

To this end, in addition to pointing the main concepts of the productivity of structural resources, this paper tries to explain the methods and approaches promoting this kind of productivity through performance auditing components. Now a question:

Do performance auditing components affect the indices and the promotion of the productivity of state sectors' organizational and structural resources (organizational climate)?

To answer this question and regarding the importance of the problem and considering that no comprehensive research has been done about it in our country, the purpose of this study is to investigate the impacts of performance auditing components on the promotion of the productivity of state sectors' organizational and structural resources (organizational climate).

1- Statement of Problem (subject)

1-1 Concepts and Definitions of Structural Resources (Organizational Climate)

According to French, W.L. (1986), organizational climate is an almost sustainable set of the understandings of the members of an organization of the organizational culture features. This understanding affects feeling, vision and behavior of the members in work place. Boulden, G.P. (1992) believes that organizational climate is an environment where employees work and it reflects employees' vision and the management style of that organization. Organizational climate contains a value system. This means that it determines that how works should be done and which behaviors would be confirmed. Schneider, B. (1990) believes that organizational climate is a wide definition of the common understandings of organizational policies and procedures which are visible to employees whether they are official or unofficial. According to Ownes, R. G. (1991) both organizational culture and organizational climate concepts are the structures dealing with only one reality. He believes that the behavior of employees in an organization is not a product of their interaction with direct and sensible events rather it is a product of interaction with indirect and insensible ones. Denison, Daniel (1997) believes that organizational climate has two separate concepts. The first one is the common understanding or common response of individuals to a special situation. Thus, the creation of satisfaction, resistance and engagement atmosphere and so on is probable. The second one is the set of criteria affecting individuals' behavior.

By studying the opinions of different experts in organization and management knowledge, it could be argued that factors like strategy, organization size or scale, technology, environment, power and control

determine structure type while complexity, formality and concentricity represent main structural columns which could get different shapes [Schuller, S. Randall & Jacson E., 2008]. If organizational structure be divided into mechanic and organic classes, in the mechanic class complexity, formality and centralized decision making process are available in high levels while in the organic one, they are low. General columns of structure have not essentially homogenous impacts on employees' or labors' performance or job satisfaction. Personal style of employees as well as their mental interpretation of objective features reduces the impacts of objective features on structure and members. An organization with higher levels of complexity, formality and centralized decision making process generally more reduces the job satisfaction of most employees which in turn reduces productivity [Hamilton- Attwell, Amanda, 1998; Scaller 2008]. Litwin and Stringer [Litwin, G. H., and Stringer, Robert A., 1968] believe that organizational climate addresses the understandings of organizations' members of the formal system, informal method of managers and other important environmental factors. Such an understanding affects visions, beliefs, values and motives of individuals in a work place.

The organizational structure not only directly influences productivity, which affects responding to needs by benefiting from services, but also causes information to follow inside an organization and help managers to allocate the resources and properties of it. In addition to informing, an organization which is about to develop a productivity process, should make immediate actions in defining clear responsibilities and definite responses against the improvement of productivity among its managers and employees [Yusefi and others 2002].

1-2 Concepts, Definitions and Fundamentals of Performance Auditing

The state sector of every country depends to a large extent on the management decisions of the state sector. Obviously, such decisions have a determinative role in the amount of economic income as well as the effectiveness of determined activities and optimal use of production and service facilities. Basically, people and their representative always wish to know whether executive managers have made right decisions or not and whether they could maximally benefit from available facilities. Do state sectors consider total objectives of promoting efficiency and effectiveness, continuous improvement of works and economy? Performance auditing is a beneficial tool for evaluating and improving the systems and directing an organization towards its objectives. In our country, vast majority of economic resources are being managed by the state sector and the quality of management has

critical impacts on people's fate. The managers of this sector should be answerable to people and their representatives and they should prepare responsibility tool based on confirmed information. The nature of the state sector demands the obligatory of performance auditing in addition to estimating financial statements and statement in the framework of the principles and standards of financial auditing. Thus, in addition to use of specialists' services, it is necessary for auditors to evaluate the quality of management decision in different fields and to present their conclusion as well as improvement suggestions to improve management more and more [Nokhbefallah, Afshin, 2005].

However, in a world where human's unlimited wishes stand against limited economic resources, the emergence and fall of any phenomenon originates from the actual and legal requirements of human society. Companies and other economic corporations could not continue their life in the free market economic environment, where the commercial obstacles are continuously removed and firms are merged with together and competition becomes more tight and cruel, unless they have an ideal level of effectiveness in achieving targets, efficiency, economy and resources of the optimal management [Saffar, 2010].

Officials, legislators and citizens need and require that information confirming that governmental funds are spent in a right manner according to rules. People and authors of every country wish to know whether state organizations, plans and services have achieved the predicted target and whether plans and services are controlled economically in organizations. The Supreme Audit Court has the authority to answer the questions [Sajjadi, Jamei, 2003].

The limitation of resources and facilities in one hand and medium-term and long-term economical and social programs for growth and development on the other hand, make it necessary to ensure that the programs and activities of Iran's state sector, as the greatest and the most effective economical sector, have been directed towards determined targets. This makes effective, efficient and economical achievement of them and as a result the establishing of operational auditing would be inevitable.

1-3 the Necessity of Implementing Operational Auditing for Promoting the Productivity of Structural Resources

The article 218 of the 5th development plan of I.R. Iran obliges the implementation of performance (operational) auditing. Thus, paying serious attention to the perspectives of the establishment of the new auditing system especially the productivity of state sectors' structural resources is necessary. According to its legal duties, Iran's Supreme Audit Court has officially started the implementation of performance

auditing system since 2009. The most important outcome is the responsibility of the state sectors for productivity. The employed measures in the main components of performance auditing could have significantly impacts on the continuous improvement of works as well as the productivity of the structural resources of the executor systems. Therefore, it is necessary to evaluate the impacts of the implementation of performance auditing on state sectors' productivity. In addition to measuring the productivity of state sectors' structural resources, this research tries to assess the influence of performance auditing on the promotion of this productivity in order to prepare necessary structures to deepen the implementation of performance auditing. In this way, in addition to the productivity promotion of the structural resources, the infrastructures of economical growth and development of country would be prepared as well.

1-4 Under Evaluation Indices of Organizational and Structural Resources (Organizational Climate)

1-4-1 no frequent shifts or stability of human resource (employees and managers): the stability of human resource in organizational positions improves works and promotes productivity due to generating no confuse as well as more familiarity of workers with the allocated duties.

1-4-2 required time for performing tasks is minimized and unnecessary works and bottlenecks are eliminated: The more a work is done in a shorter time, the more quickly the considered targets are achieved resulting in the promotion of productivity.

1-4-3 the quality of design, performing works and realization of qualitative standards: As it was noted in previous mentioned researches, performing high quality works will increase economy and consequently will promote the productivity.

1-4-4 flexibility in responding to continuous changes of works and systems: for organizations, change is a way by which they promote productivity and preserve their competitive advantage. So, it could be said that the change is an inevitable item for the growth of organizations and organizations members should adopt themselves with changes [Ahadinia, 2005].

1-4-5 structurizing economizing and optimization of energy consumption: a legal connection is available between productivity and correction of consumption pattern concepts. Indeed, obtaining a correct consumption patten requires proper and optimize use of society resources [Mirzaei, 2009]. To this end, the optimization of energy consumption is the most important change occurring in an organization structure which would accompany with outcomes like economic growth, increase of Gross National Product (GNP) along with reduction of costs [Seghti and others, 1998]. Paying attention to the concept of economizing is one

of the ways establishing the improvement of productivity management cycle in an organization. Continuous productivity through economizing would not be achieved by mere slogan and proper structures should be designed as well. Generally, economizing is engaged in an organization through two mechanisms: structure building and encouragement:

- to structurize economizing by considering consumption rate in production bonus
- establishing a good relation between consumption and awards
- establishing a relation between the quality of use of materials and rewards
- paying directly a fracture of the money saved due to energy save to employees
- written encouragement of the save star employees

1-4-6 concentrating duties, authorities, operations and activities on successful and critical targets: generally organizations have no choice to concentrate on their important and critical targets to achieve higher productivity because they should be answerable about the predicted targets. Critical targets are those one for which an organization is made.

1-4-7 increasing of renovation, development and equipping of information technology: information and communication revolution is quickly progressing aiming at reforming the financial fundamentals of societies [Mutula, S., 2006]. In the age of information and communication, information has special value as well [Mc, Leod, R., 1998]. To this end, some systems should be established in order to generate and manage information. Information systems which are a valuable resource, promote managers' and employees' abilities and make the effective realization of organizations targets possible, through higher levels of productivity [Momeni, 1993].

1-4-8 work environment and organizational culture should become favorable and clients should be respected: Talor Bruce (2005) believes that many works could be done to promote productivity. Beyond obvious techniques there are methods we could improve them. Improvement of organizational culture in work groups is one of the most important one. Wright/ P. C/ Perrell/ M./ Gloet/ M. (2008) carried out a research to evaluate the influence of culture on motivating behavior for the promotion of productivity in china. The results revealed that the culture significantly increases employees' motives in work places and results in productivity improvement. The findings of Spence Spence/ Heather K (2002) indicate that however, the improvement of work place condition has a positive impact on employees and commits them to try more to perform their organizational duties. Also, the results of Coulson/ Thomas/ C (1993) revealed that

organizational culture is in relation with productivity and is one of the most effective parameters affecting it.

1-4-9- Establishment of Continuous Improvement Strategy in All Affairs: The continuous improvement of whole affairs of an organization is the key of achieving higher rates of quality and productivity and this will not take effect unless by the participation of all employees. Suggestion system is the most known system attracting the participation of all employees and other related individuals and by accurate implementation of it the first and the most important step in the path of achieving supreme quality and productivity is taken [Batman Ghelich, 2009].

1-4-10 Establishment of Technologic Structures and Modern Technologies: employing advanced technologies in production process is a very important factor in the promotion of productivity. A machine which produces goods quicker, more accurate, with lower losses and more homogenous is surely a high productive machine. Although due to consuming capital the denominator of the ratio (as a data) increases, which results in the increase of investment cost, but the use of technology reduces costs in long term and increases the added value of products. The match between the employed technology and organizational needs however, is one of the items to be considered by organizations in the process of selection and use of technology. In its real meaning and the mentioned dimensions, technologies should be studied accurately and be employed coordinately. If a technology is considered as a single item in an organization and its relation with technologic knowledge of employees as well as the technology level of that organization is not studied, not only it does not increase productivity but also increases costs, reduces employees' satisfaction and eventually reduces productivity [Nasrollah pour, 2005].

Many researchers have found that investment in human capital through making technologic changes and its development, significantly affects productivity. The theories of Human Capital and Economic Growth have been founded on this assumption that sturcuturized knowledge and skills in human capital, directly increases productivity [Becker, G, 1962; Scholtz, T. 1961] and in this way increases economic capacities of attracting new technologies purposes [Nelson, R; Phelps, E,1966]. New growth models know innovation as an important definitive factor of productivity. Recently, it has been fully verified that a new technology is a factor directing the growth of productivity in long term [Coe, D.T., Helpman, E. and Hoffmaister,A., 1995]. The improvement of production technology reduces the production cost per unit product by reducing the price of capital equipments as well as decreased need to workforce. This means the promotion of productivity.

This is why the developed countries and successful multinational corporations spend annually enormous amounts of moneys for R&D activities to achieve superior technologies in order to increase their profits by developing their markets [Kargar and Farajpour, 2009]. Ghalbraith believes that after passing the initial obstacles in the way of economic growth, promotion of technology is the most important condition of development as well as the best way of employing invests to achieve the maximum productivity and economic efficiency as well as supplying and promotion of technology [A group of professors in management field, 2001].

2- Research Background

2-1 Organizational and Structural Resources (Organizational Climate)

According to the opinions of scientists and experts in the fields of management and organizational and industrial psychology (for example, Frech et al, 1986; Schneider, 1990, Owns and Glanovsky, A.R. 1991; Denison (1996); Bulden (1992); Strutton-D, Toma-A and Pelton-LE,1993; Davis,Keith and Newstron, John. W., 1985; Litwin and Stringer, 1968; Abdullah Mahlok, 1992, Burns, T., & Stalker, G. M, 1961; DeMeritt, E. G. (2005), Jackson. Malik. Pamela, J.,(2005); Sofianos, T. J., (2005); Wilson, C. L., 2005; Durcikova, A., 2004) this variable plays a significant role in organizations especially in productivity. Therefore, creating an appropriate organizational climate could have significant impact on increasing an organization's productivity and efficiency. On the other hand, establishment of productivity in an organization is a result of optimum and effective use of resources, reduction of losses, reduction of cost price, improvement of quality and so on which will in turn result in organizational growth and development [Shanam, 2004].

By conducting a research Barari (2004) found a relation between organizational climate and the productivity of the managers of East Tehran municipality. Among the different aspects of organizational climate, structure, risk tolerance, conflict and responsibility are those organizational climate factors predicting productivity. However, Mohsen Sheikhi (2007) found a relation between organizational climate and the productivity of the employees of Tehran Tax Affairs Office and among the different aspects of organizational climate, reward system, risk tolerance, sincerity, support, principles, conflict and identity, predict productivity.

Rahmati (2005) conducted a research and found a relation between organizational climate and the productivity of the employees of Tehran education offices. Among different components of organizational climate, the element of procedures has a significant correlation with productivity. Zare (2007) found a

relation between organizational climate and the productivity of the employees of public-educational hospitals of Iran Medical Science University. In his research with the title of "organizational climate for productivity, a promising of organizational productivity", Witt L.A. (1985) however, found a relation between organizational climate and productivity. In the research he used Litwin-Stringer organizational climate questionnaire as well.

Nazem and Parsi (2010) conducted a research with the title of "the relation between organizational climate and the productivity of Imam Khomeini's Relief Committee; presenting a proper management model". The statistical population of the research consisted of all managers and employees of Imam Khomeini's Relief committee who were working in Tehran province. According to Morgan table, 154 managers and an employee per three managers were selected by multistage random sampling method (total number of employees is 420). Research tools were Litwin, G. H., and Stringer, Robert A., (1968) organizational climate and Smith, JR. Et al (1988) productivity questionnaires. The results of multivariate regression revealed that there is a relation between organizational climate and managers' productivity.

Farajpour (2010), concentrated on the structural factors of organizations and investigated and analyzed double ambition double endeavor role in the improvement of organizational productivity. In his opinion, there is a direct relation between productivity, coordination, accurate division of labor, correct classification of duties and appropriate organizational structure. On the other hand, he believes that delegation of power, time management, distinguishing between activities, compatibility of personal capacities with job features, establishing motivation systems and making infrastructures for team works are six strategic ways for improving productivity via double ambition, double endeavor.

A positive relation was derived between organizational culture and employees' productivity in the study of Nasiripour et al (2007). The study of Seyyed Ameri (2008) confirmed however, a positive significant relation between organizational culture & its components and managers' productivity. In another study Alvani and Ghasemi (2000), showed that there is a positive significant relation between the quality of work life and human resource productivity. Sabokroo et al (2010) have presented an article with the title of "productivity of insurance companies' employees thanks to their emotional intelligent as well as the quality of work life." They showed that there is a positive significant correlation between the quality of work life and its dimensions and employees' productivity. A significant co directionality was seen between many researches including the studies of the

following researches: Shikdar, A & Aa Sawaqed, NM 2003, Gordom, J 1993, Fatemi, N 2002, Lee, Plits and Tangen, S. 2005.

Bordbar et al (2009) carried out a research with the title of "investigating the relation between organizational culture and human resource productivity in insurance industry." It is a descriptive correlation research in which data was collected by desk-field method. The results of this study indicate that there is a positive significant relation between organizational culture and the productivity of the companies' manager as well as between creativity, support, integrity, control, identity, reward system, conflict tolerance, communication models and productivity. Talor (2005), states that so many works could be done for the promotion of productivity. Beyond apparent techniques there are methods which could be improved in order to obtain more productivity. Organizational culture in work groups is one of the most important items. The studies and researches of Hersy/ P./ Blanchard/ K (1983), show that a powerful organizational culture increases employees' organizational commitment and coordinates employees' objectives and organizational ones. This is an effective factor in the promotion of productivity.

The researches of Hersy/ P./ Blanchard/ K (1983), indicate that a strong culture creates a better sense in employees and causes them to do their duties better. Also, such a culture promotes the organizational commitment of employees and coordinates employees' objectives and organizational ones. This is an important factor promoting productivity. In their studies in China, Wright P, Perrell ,Gloet M (2008) however, investigated the role of organizational culture components in the promotion of employees' motivation as well as effective improvement of productivity. Robbins S. (1995) believes that as the members of an organization more understand the principle values and show more commitment to them, the organization would have more powerful culture.

In a study on the recognition and comparison of the promotion of human resource's productivity carried out in Medical Faculty and Health and Sanitary Services of Semnan, Alaolmaleki et al (2002) conducted a descriptive-inferential study on 200 employees of financial-official departments and recognized the role of monetary factors of motivations, training and organizational structure on the promotion of productivity. The influence of organizational structure on the improvement of productivity has been found by the study of Henry et al (2006) as well. According to the visions of the managers working in different levels of the selected hospitals of the Faculty of Medical Science of Mazandaran, the variables of organizational culture and medical equipments have great influence on the productivity of hospitals.

Mahmoudzadeh and Asadi (2005) investigated the impacts of information and communication technology on the productivity growth of workforce in Iran economy using the time series data of 2005 and typical minimum square root and concluded that the productivity of workforce in Iran economy is mostly affected by the total productivity as well as non information and communication technology based capitals. The impacts of human capital as well as information and communication technology on workforce productivity are positive and significant. In a study carried out to investigate the impacts of information and communication technology on the growth of workforce productivity in Iran economy, it was concluded that the capital of information and communication technology as well as human capital have positive impacts on workforce productivity in Iran economy [Mahmoudzadeh and Asadi 2007]. According to the researches of Kim J. (2001), information and communication technology have positive and significant impacts on workforce productivity.

Ansari Ranani and Sabzi Aliabadi (2009) carried out a research with the title of "ranking effective organizational factors in the promotion of workforce productivity in small industries" and concluded that : 1) there is a significant difference between organizational factors including the improvement of life quality, employees' empowerment and motivation for promoting workforce productivity, 2) there is a significant difference between effective factors of work life quality including administration method, engineering of human factors and communication with employees in the promotion of workforce productivity, 3) there is a significant difference between sufficient and available resources, context for the emergence of creativity, employees training and employees participation in the promotion of workforce productivity and 4) there is a significant difference between feedback, work essence, performance evaluation and employees' needs in the promotion of workforce productivity.

The only method for eliminating superfluous until obtaining a productive and high quality production system is nothing but continuous improvement with the participation of whole employees in executing this system. This reality is apparent in the descriptions of Robinson and Schroeder (2004) [Batman Ghelich, 2009].

Jacobs, B., Nahuis, R., & Tang, P.J.G. (2000), analyzed in a paper the technological changes across the economical sectors of Netherlands. Their results show that R&D variables have positive impacts on the promotion of productivity and R&D based growth theories describe growth process better than human capital based ones.

Vaziri et al (2009) carried out a research with the title of "cognition and ranking of effective parameters in human resource productivity (a case study: employees of education organization of Hormozghan Province) using MADM method. The research was a descriptive-survey one and data was collected by desk-field method. The results of employing MADM methods like TOPSIS indicate that among the mentioned factors, structural/managerial parameters (no discrimination and organizational justice, existence of participative management system, establishment of a proper suggestion system and establishment of a proper performance based payment system) are respectively the most effective factors in the promotion of human resource productivity between the employees of the education organization of Hormozghan Province.

Next, the components of occupational parameters were ranked. The results indicate that the quality of work life has the maximum impact on human resource productivity compared with other occupational parameters. Among the components of physical and psychological parameters, mental health at work, existence of supportive atmosphere between employees in an organization and effective and update equipments are the most important factors affecting the productivity of the employees of the education organization of Hormozghan Province. Among the components of personal factors, mental and physical health of employees was the most effective parameters in the promotion of human resource productivity. Finally, the components of the factors of cooperation and sincerity were ranked. Being respected at work has the maximum influence on human resource productivity compared with other components in this category and the second rank belongs to creative communication of managers with employees.

2-2 Performance Auditing

In his M.A. thesis Ahmad Dehghan Naiieri (2005), (the student of industry engineering of Islamic Azad University of Najafabad) investigated the impact of interaction between value engineering and performance auditing on constructive plans productivity. In this research, the impact of the implementation of value engineering on facilitating the implementation of performance auditing and vice versa, as a tool ensuring the implementation of the suggestions of value engineering, was evaluated. He collected required hypotheses and questionnaires out of the opinions of consultants, contractors, and authorities and so on and in addition to approving the hypotheses (the interaction of value engineering and performance auditing in the productivity of constructive plans), he eventually proposed methods for improving value management and cost reduction.

Palyt (2003) studied operational auditing methods in five top auditing corporations in Finland,

France, Netherlands, Switzerland and England. The purpose of the study was to explain the strategic and important selections of the corporations. The concentration of the researcher was on the employed methods, application criteria, operational auditors' skills and operational audit reports. He found that the role of operational auditing is not only beyond observing the internal and external rules and legislations but also plays the role of management consultant in progressing works [Dahanayaki, 2007].

A research was carried out by Jooypa (2010) with the title of "the pathology of the implementation of performance auditing by Iran's Supreme Audit Court and offering improvement suggestions". He recognized that the following factors are respectively the most important obstacles in the implementation of performance auditing by the court: untrained and insufficient skilled auditors of the court, inappropriate budget system, lack of proper measures for investigating the performance of executive systems, unclear responses of executive managers to the court auditors, inappropriate system of collecting and maintaining data and financial-operational information and lack of legal authority (in the law related to the court) for executing performance auditing.

3- Research Hypotheses:

Based on studies background as well as exploratory studies, basic questions of this research could be referred as follows:

- ❖ Performance auditing leads to a profitable, efficient and effective use of structural and organizational resources (organizational climate) of state sectors.
- ❖ Profitable, effective and efficient use of structural and organizational resources (organizational climate) of state sectors promotes productivity.
- ❖ Performance auditing promotes the productivity of state sectors' structural and organizational resources (organizational climate).

4- Research Methodology

The subject of this research is the evaluation of the impacts of the implementation of performance auditing on the promotion of the productivity of state sectors' structural and organizational resources (organizational climate). Performance auditing provides managers with a tool by which they identify problems and eliminate bottlenecks and it has no criticism and caviling vision at all. Its purpose is not to criticize the current functions. Instead, it checks current functions by the cooperation of managers and employees and prepares a program for functional progressing purposes. Therefore, in order to extract more results from performance auditing it should be considered as a revisionary program for economy

which makes current functions more efficient [Reid, Milke, 2005].

This research is about to present to some extent the theoretical fundamentals of performance auditing and the productivity of state sectors' structural and organizational resources (organizational climate). Then, it states and investigates the factors which could promote the productivity of structural resources in state sectors provided that performance auditing is implemented accurately. To know connoisseurs' visions, this research uses questionnaire for data collection purposes.

4-1 Research Method in Collecting Information and Data: the research is a descriptive-analytical research in terms of conclusion and is a survey research in terms of research design and the questionnaire is the survey tool of it. In terms of study method it is an inductive-analogical research as well. In other words, the hypotheses of the research have been made based on inductive arguments and analogical data collection. To approve or reject the hypotheses, required data were collected from selected samples through questionnaires and the hypotheses were approved or rejected by analyzing the obtained information.

On the other hand, it is a correlation research. This method is about to evaluate the effects of the changes of one or more factors in one or more other factors [Khalatbari, 2008]. In this research, researcher selects some predictor variables without manipulating them and evaluates the relation of the selected predictor variables and the index variable and tries to define the relationship between the former and the latter. Therefore, in this research in which researcher has evaluated the relationship between performance auditing components and the productivity of state sectors' structural and organizational resources (organizational climate), the selected approach is appropriate.

It is an applied research objectively which is classified in the group of case studies in terms of investigation type. To collect information for theoretical studies and the research history, desk method, valid articles, journals and sites were used. To collect data for approving or rejecting the hypotheses tests, field study and five-point likert scale questionnaire were used. Following the distribution of the five-point likert scale questionnaire between the members of statistical population and collecting the answers, the obtained data was classified and summarized and their validity were examined. Then, statistical analysis was applied on the data and the final results were compared and discussed with the findings of previous studies.

4-2- Research Scope

❖ The time scope of the research is the duration of data collection which was between January, 2012 and July, 2012.

❖ Research location is the offices of Iran's Supreme Audit Court in Tehran and other Provinces.

❖ The subject of the research is the investigation of the impacts of performance auditing components on the promotion of the productivity of state sectors' structural resources.

5- Statistical Population and Research Sample

5-1 Statistical Population of Research

The statistical population of the research consists of all managers, assistances, auditors, experts and connoisseurs of Iran's Supreme Audit Court across 31 provinces as well as the central committee of Iran's Supreme Audit Court. A total of 2000 individuals were selected through a method which would be explained later. The statistical population of the research consists of those individuals who work in auditing, inspection and administration fields with the university field of accounting, economy, law, civil engineering and IT and so on who continuously deal with professional legislations and rules, standards and so on. For the following reason, the Supreme Audit Court was selected as the statistical population:

- Iran's Supreme Audit Court, as the administrative arm of Iran Islamic parliament, directly deals with financial and operational activities of the state sectors and it is aware of the situation of executive systems.
- Initially, it was the Supreme Audit Court that implemented performance auditing as a modern auditing system and it increasingly became more applicable so that most of the reports of performance auditing in previous years have been/are being executed. For this reason, it is more familiar with and is very professional in the system compared with other units involving state auditing especially performance auditing.
- In the Supreme Audit Court, research activities and subjects are prepared more easily and more professionally under the administration of education and approval of the committee of preparing standards and instructions. Therefore, such researches benefit from high technical and expertise advantages as well as scientific-research level.
- The vast majority of scientific-research activities which are done over the Supreme Audit Court are implemented in national level due to the higher supportive role of the organization and releasing required information and even presenting them to the considered researcher in some cases. Of course, it is possible only for the

auditors and other responsible people of the court.

5-2 Statistical Sample of Research

5-2-1 sampling and the method of determining sample volume: this research used multistage clustered as well as random sampling methods. Data was collected from the statistical population by sampling via Cochran’s formula [Ventiling, Tim, 1997]. The different sub sections of the research were determined and in each section, considered sample was selected using Krejcie and Morgan table. Obviously, the number of the samples of each sub section was proportional with the total members of that sub section. In the definition of sample volume, since analyzing small sample groups could result in instable and misleading solutions, a relatively large sample volume with a total number of 357 persons who were selected randomly was considered. To calculate the required number of individuals who could be representative of society, Cochran’s formula (relation 1) was used as follows:

$$N = \frac{t^2 pq}{D^2(n-1) + t^2 pq}$$

Allowable error $D = \%d$ confidence level $t = 95$
 $1/96 = t$

Sample volume = n
 Statistical population = N
 existence of feature = p
 q = non existence of feature statistics

$$D^2(n-1) + t^2 pq$$

5-2-2 Descriptive Features of Statistical Sample:

Among selected 357 individuals, 329 people were auditors and 28 were specialists. 310 of them were male

and 47 of them were female. Also, educational level of them was as follows: 10 people Junior College, 251 B.S, 91 M.A and 5 PhD. The average of their experience background was 15 years ranged from 1 to more than 30.

6- Data Collection and Measurement Tool, Validity and Reliability of the Tool

In this research data was collected through a researcher-made questionnaire. In making the questionnaire, valid standard questionnaires were used and their questions and items which were proportional with the hypotheses of the research were used as well. To evaluate and analyze the variables of the research, which were discussed in the research literature section, and finally to measure the components and indices of performance auditing and structural resource productivity, two questionnaires were prepared; one for performance auditing, and the other for the productivity of state sectors’ structural resources. A total of 357 questionnaires were distributed between the supreme audit court auditors. After validation of validity and reliability, the questionnaires were introduced to the research statistical sample.

Likert scale was used to measure data [Ganji, 1001] in the meaning that by this scale qualitative features are converted to quantitative ones in order let statistical analysis be done based on the obtained quantitative features. To do this, at first a number is allocated to each item of the questionnaires according to table 1. After collecting the questionnaires the scores of each questionnaire are calculated. Then, statistical analysis be done and the result is derived.

Table 1 questionnaires items numerical values

Questionnaire Name	Question No.	very low	Low	Moderate	High	Very High
impacts of performance auditing on organizational climate micro indices (b1)	1-10	1	2	2	4	5
Impact of organizational climate micro indices on productivity (b2)	1-10	1	2	3	4	5

7- Data Analysis

When data was collected, it was analyzed by SPSS ver. 18. At first data was coded and introduced to the soft ware. Then, it was analyzed by two descriptive and inferential methods in three separate parts. In parts 1 and 2, to describe the opinions of the statistical sample about the questions, frequency distribution, percentage, average and variance tables were used. The procedure was carried out in two significance levels of p-value. (sig.=0 to sig.=0.05). In the third part, the research hypotheses were examined based on the results obtained from studying the questions using exploratory statistics and ANOVA test. Path analysis was carried out by multivariate regression test and curves were drawn in Excel.

7-1 Descriptive Analysis of Data

In the process of investigating the research questions, descriptive statistics were used to prepare statistical frequency distribution tables (tables and graphs representing the frequency distribution of the statistical population) and to estimate the central indices, arithmetic mean, dispersion indices, and standard deviation and so on were employed. The descriptive statistics of the research including average, mean, maximum, minimum and standard deviation of data have been calculated and shown in table 2. The values only represent a general view of the distribution status of data. The descriptive indices indicate mean, variance and standard deviation of age, experience background, frequency and frequency percentage of males and females and their graduation status as well as the

frequency and frequency percentage of the items of each question which have been replied. In this section, demographic features are described using the tables. Tables are from the most important tools for measuring the data of a human-social research. The ultimate purpose of tables is to make quantitative and measurable data and show an accurate image of data as much as possible..

Table2 frequency distribution of responders in terms of central indices

Employment	background	position	education level	marital status	age	gender	central indices	
344	347	329	354	342	352	349	N	Valid
13	10	28	3	15	5	8		Missing
4.00	3.00	3.00	3.00	2.00	2.00	1.00	Median	
4	3	3	3	2	2	1	Mode	

7-2 Exploratory Analysis of Data

7-2-1 Examination of Research Hypotheses

7-2-1-1 Hypothesis No. (1):

There is a significant relation between the implementation of performance auditing and the improvement & development of state sectors' structural and organizational resources (organizational climate):

The independent variable i.e. the implementation of performance auditing has been designed in interval scale. However, the subsidiary

dependent variable (mediator or meditating variable), i.e. state sectors' structural and organizational resources has been measured in interval scale as well. Therefore, Pearson statistical technique was used to examine the hypothesis. Statistical hypotheses are written as follows: H:P=0 hypothesis 0 and H:P>0 hypothesis 1. The hypothesis 0 assumes that there is no relation between the implementation of performance auditing and the improvement of state sectors' structural and organizational resources of while the other hypothesis assumes a relation.

Table 3 Examination of Hypothesis No. 1

Variable	Mean	Standard Deviation	Pearson Coefficient	Sig.
implementation of performance auditing	3.69	0.655	0.583	0.000
improvement of structural & organizational resources	3.78	0.619		

Table (3-1): Descriptive Statistics

variables	Mean	Std. Deviation	N
structural resources	3.78	.619	357
performance auditing	3.69	.655	357

Table (3-2): Correlations

variables	Correlation	structural resources	performance auditing
structural resources	Pearson Correlation	1	.583**
	Sig. (2-tailed)		.000
	N	357	357
performance auditing	Pearson Correlation	.583**	1
	Sig. (2-tailed)	.000	
	N	357	357

Table (3-3): Model Summary

Model	R	R Square	Adjusted R Square	Std. Error of the Estimate
1	.924a	.854	.854	.255

Table (3-4): ANOVA^b

Model		Sum of Squares	df	Mean Square	F	Sig.
1	Regression	134.588	1	134.588	2075.094	.000a
	Residual	23.025	355	.065		
	Total	157.613	356			

Table (3-5): Coefficients^a

Model		Unstandardized Coefficients		Standardized Coefficients	T	Sig.
		B	Std. Error	Beta		
1	(Constant)	.231	.077		3.001	.003
	performance auditing	.938	.021	.924	45.553	.000

In the above tables Pearson statistical technique is employed to examine that whether

relationship between the implementation of performance auditing and effective and efficient use

of state sectors' structural and organizational resources is significant. According to the results, the mean value of the improvement of state sectors' structural and organizational resources is (3.78) while the mean value of the implementation of performance auditing is (3.69). Pearson coefficient is derived (r=0.583) indicating a high correlation between the variables. The coefficient is a positive number with direct orientation implying that as the implementation

Model No. 1: the model of the hypothesis (1)

rate of performance auditing increase, the improvement rate of state sectors' structural and organizational resources increases as well. Since the level of significance is sig=0.000 which is below 0.05, the relation is confirmed with 99% confidence. Thus, the hypothesis No. 0 is rejected. According to tables 3-1 to 5, path equation for confirming the hypothesis is as follows:

$$\alpha 1V1 \text{ (improvement index of structural resources)} = .231 + .938 \times (\text{performance auditing}) + .098$$

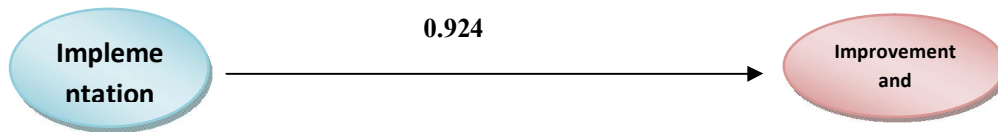


Fig. 1 path analysis for the hypothesis No. 1
The results of this hypothesis could be used in future studies by researchers.

7-2-1-2 Hypothesis No. 2

There is a significant relation between improvement and development of structural and organizational resources (organizational climate) and the productivity of state sectors:

The independent variable of the improvement and development of structural and organizational resources has been designed in interval scale. Also, the dependent variable of the productivity of state sectors has been measured in interval scale as well. Therefore,

Pearson statistical technique has been used to examine the hypothesis. Statistical hypotheses are written as follows, respectively: H:P=0 hypothesis 0 and H:P>0 hypothesis 1

In the hypothesis No. 0 it is assumed that there is no relation between improvement & development of structural and organizational resources and productivity of state sectors while the other hypothesis assumes a relation.

Table 4: Examination of hypothesis No. 2

Variable	mean	standard deviation	Pearson coefficient	Sig.
improvement & development of organizational and structural resources	3.69	0.665	0.581	0.000
productivity of state sectors	3.9	0.567		

Table (4-1): Descriptive Statistics

	Mean	Std. Deviation	N
Productivity of state sectors	3.90	.567	357
Structural & organizational resources	3.69	.665	357

Table (4-2): Correlations

		Productivity of state sectors	Structural & organizational resources
Productivity of state sectors	Pearson Correlation	1	.581**
	Sig. (2-tailed)		.000
	N	357	357
Structural & organizational resources	Pearson Correlation	.581**	1
	Sig. (2-tailed)	.000	
	N	357	357

According to the above tables, to examine that whether the relation between the improvement and development of structural & organizational resources and the productivity of state sectors is

significant, Pearson statistical technique is employed. According to the results of the tables, the mean value of the improvement and development of structural and organizational resources is (3.69) while the mean

value of the productivity of state sectors is (3.9). Also, the value of Pearson coefficient is derived ($r=0.581$) implying a high correlation between the mentioned variables. This is a positive variable with direct orientation indicating that as the productivity of state

sectors increases the improvement and development of structural and organizational resources increases as well. Since the significance level is ($sig.=0.000$) which is below 0.05, the relation is confirmed with 99% confidence. So, the hypothesis No. 0 is rejected.

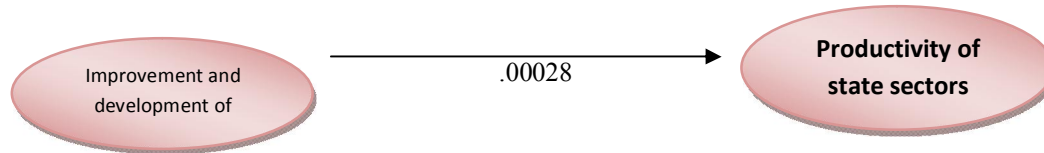


Fig. 2: path analysis of the hypothesis No.2

The obtained results agree with the results of French et al (1986). Schneider (1990), Ownes and Glanovsky, A. R (1991), Denison (1996), Bulden (1992), Strutton-D, Toma-A, and Pelton-LE, (1993), Davis, Keith and Newstrom, John W. (1985), Litwin and Stringer (1968), Abdullah, Mahlok, (1992), Burns, T., & Stalker, G. M (1961), DeMeritt, E. G. (2005), Jackson. Malik. Pamela, J. (2005), Sofianos, T. J. (2005), Wilson, C. L. (2005), Durcikova, A. (2004), Shahnam (2004), Barari (2005), Mohsen Sheikhi (2007), Rahmati 92005), Witt, L.A (1985), Zare (2007), Nazem and Parsi (2010), Farajpour (2010), Nasiripour et al (2007), SeyyeD Ameri (2008), Alvani and Ghasemi (2000), Sabokroo et al (2010), Shikdar, A & Aa Sawaqed, NM (2003), Gordom, J (1993), Fatemi, N (2002), Lee, Politz and Tangan (2005), Bordbar et al (2009), Taylor (2005), Hersy/ P./ Blanchard/ K (1983), Wright P, Perrell ,Gloet M (2008), Robbins S (1995), alaolmaleki et al (2002),

Henry et al (2006), Maleki et al (2005), Mahmoodzade and Asadi (2007), Kim J, (2001), Ansari Renani and sabzi Aliabadi (2009), Robinson and Schroeder (2004), Jacobs, B., Nahuis, R., & Tang, P.J.G (2000), Vaziri et al (2009) and many other researches.

7-2-1-3- Hypothesis No. 3: Research Subject

There is a significant relation between performance auditing components and the promotion of the productivity of state sectors’ structural and organizational resources (organizational climate).

The independent variable of performance auditing has been designed in interval scale and the dependent variable of the productivity of state sectors’ structural and organizational resources has been measured in interval scale as well. Therefore, path analysis technique is employed as per the following table:

Table 5- path analysis of hypothesis No. (3)

Variable name	Direct effect	Indirect effect	Total effect
Implementation of performance auditing-organizational and structural resources productivity		0.00028 *0.924	0.0002

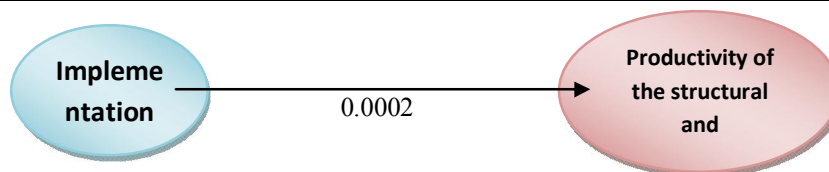


Fig. 3 path analysis of hypothesis No. 3

According to the data shown in table 5, after calculating the direct and indirect effects of independent variables on the productivity of structural and organizational resources, it was concluded that by considering all direct and indirect paths the implementation of performance auditing has an increasing influence on the productivity of state sectors’ structural and organizational resources. This means that wherever the performance auditing has been implemented more, the productivity of state sectors’ structural and organizational resources o has

been increased as well; of course, the increased amount was negligib.

Conclusion

Based on the results obtained form the hypotheses 1 to 3, the following items could be concluded:

- 1) The implementation of performance auditing improves state sectors’ structural and organizational resources (organizational climate).
- 2) The improvement and development of structural and organizational resources (organizational climate) promotes productivity in state sectors.

3) The implementation of performance auditing promotes the productivity of state sectors' structural and organizational resources (organizational climate)

8- Research Suggestions

The following suggestions are presented based on the results of the research:

- It is suggested to use other variables besides the employed variables to measure productive management systems in order to let the influence of performance auditing on them be estimated.
- It is suggested to repeat this research in another statistical population in order the obtained results be analyzed and compared with the current results.

9- Research Limitations

The conducting of the research could face with the following limitations regarding its dimensions and due to the fact that it is a national research:

- Since there was no global standard questionnaire for productivity and performance auditing fields, recognition of elements especially productivity indices took many time and reduced the speed of the research.
- Since it was a national research carried out across Iran, the process of collecting questionnaires proceeds very slowly and imposed great costs.

10- Implications for Future Researches

- It is suggested that another research be carried out about the impacts of performance auditing on the profitability and productivity of the companies listed in TSE.
- It is suggested that in future researches, researches concentrate on the quality of the implementation of performance auditing and its relation with state auditing standards.
- It is suggested that future researches consider the impacts of implementing compliance audit on the promotion of the answerability of state sectors.

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Expression of the Chemokine MCP-1 and Chemokine Receptors CXCR4 and CCR2 in Egyptian Acute Myeloid Leukemia Patients

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Abstract: Background: AML blasts of different FAB subsets express specific chemokines and chemokine receptors depending on their degree of maturation which might account for some aspects in their pattern of extramedullary invasion (EMI) and accumulation of leukemic cells. **Objectives:** We aimed to define the pattern of chemokine MCP-1 and chemokine receptors CXCR4 and CCR2 expression by AML blasts in two AML FAB subgroups, myeloid M0/M1/ M2 and monocytic M4/M5 groups to determine their impact on tumor load and EMI. **Patients and Methods:** The study was performed on 50 de novo AML patients. Expression of CXCR4 and CCR2 was measured by flow cytometry while MCP-1 expression was detected by reverse transcriptase polymerase chain reaction (RT-PCR). **Results:** Median TLC was $65.6 \times 10^9/L$ in MCP1 positive patients versus $37.2 \times 10^9/L$ in MCP1 negative cases ($p = 0.07$). MCP1 was positive in 14/20 (70%) patients with EMI versus 6/20 (30%) patients only without EMI ($p = 0.05$). CXCR4 was positive in most AML patients (38/50, 76%) with no significant difference between AML FAB subgroups ($p = 0.9$). However, median CXCR4 percent positivity by flow cytometry was 79% (0.3-98) in the M4/M5 group versus 57.5% (1.9-89) in the M0/M1/ M2 ($p = 0.08$). CXCR4 was positive in 35/43 patients (81%) with hypercellular bone marrow (BM) at diagnosis ($p = 0.02$). CCR2 positivity was higher in M4/M5 group (8/21, 38%) than M0/M1/M2 group (2/29, 7%) ($p = 0.006$). Meanwhile, MCP-1 expression was positive in 20/48 (41.7%) of our AML cohort and was insignificantly higher in M4/M5 group (10/21, 48%) than M0/M1/M2 group (10/29, 34%) ($p = 0.2$). Regarding EMI, lymphadenopathy was found in 90% of patients in M4/M5 group versus 30% in M0/M1/M2 group ($p = 0.001$). **Conclusion:** Data suggest that MCP-1 and CXCR4 have major impact on tumor load in AML at time of diagnosis. In addition, MCP1 have a striking role in EMI irrespective of the FAB subtype. Its ligand CCR2 seems to be restricted to monocytic group (M4/M5) which showed significant lymphadenopathy when compared to M0/M1/M2 group.

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Keywords: AML, CXCR4, CCR2, MCP-1, Extramedullary invasion.

1. Introduction

AML is an aggressive disease characterized by accumulation of immature malignant cells in the bone marrow (BM) which may later invade the blood stream and localize in extramedullary sites [1]. The 5 years overall survival (OS) for patients less than 60 years of age receiving the most intensive conventional chemotherapy is less than 50% [2]. AML is considered a very heterogenous disorder, and the recently published WHO classification was therefore based on a combination of clinical history, morphology, cytogenetic and molecular abnormalities [3].

The mechanisms regulating the trafficking of leukemic myeloid blasts are still poorly understood. Chemokines are a family of soluble proteins that are involved in wide range of biological processes with relevance for hematological malignancies including cell trafficking, regulation of cell proliferation and apoptosis, immunoregulation, normal hematopoiesis and angiogenesis [4]. A substantial evidence of AML

blasts migration requires the sequential engagement of specific cytokines and their receptors [1]. Monocyte chemoattractant protein (MCP1) and its ligand CCR2 are chemokines that could be involved in this process [1, 5]. The local chemokine network in human AML is probably further modulated by the hypoxic BM microenvironment and the local release of chemokines by non leukemic BM stromal cells [6]. The accumulation of malignant cells can be indeed favored by the production of chemokines by tumor cells themselves and/or surrounding non-tumoral cells [7]. Furthermore, CXCR4 expression was widely described and proved to have a prognostic impact in AML [8].

In this study, we aimed to define the pattern of chemokine (MCP-1) and chemokine receptors (CXCR4 and CCR2) expression by AML blasts in two AML FAB subgroups, myeloid M0/M1/ M2 group and monocytic M4/M5 group. Chemokines expression was correlated to tumor load manifested

by high total leucocytic count (TLC), degree of bone marrow cellularity and infiltration by blasts and extramedullary invasion (EMI) as represented by organomegaly and lymphadenopathy.

2. Patients and Methods

The present study was carried in the Clinical Pathology Department, National Cancer Institute (NCI), Cairo University during the period between July 2007 and December 2009.

Patients: Fifty de novo AML patients (28 males and 22 females) presented to the Hemato-Oncology department prior to any treatment. Patients were evaluated for expression of CXCR4 and CCR2 by flow cytometry and for expression of MCP-1 by RT-PCR. Written informed consent was obtained from every patient. Study was carried after approval of the institutional review board according to declaration of Helsinki.

All patients were subjected to complete history and physical examination with particular attention to age, gender, presenting symptoms, performance status, presence of fever, signs of infections, bleeding manifestations, hepatomegaly, splenomegaly, lymphadenopathy and symptoms of central nervous system (CNS) infiltration (headache, vomiting, blurring of vision). Tumor load was defined as high TLC at diagnosis, degree of bone marrow (BM) infiltration (cellularity and bone marrow blast % at diagnosis) and EMI in spleen, lymph nodes (LN), gum, CSF and skin [9]. Hepatomegaly as a parameter of EMI was excluded due to the high incidence of bilharziasis and viral hepatitis in Egypt.

Methods: Laboratory investigations done included complete blood count (CBC) with TLC, blasts percentage, hemoglobin level and platelet count. Biochemical analysis included serum urea, creatinine, uric acid, liver profile [serum bilirubin, alkaline phosphatase, AST, ALT, serum albumin], fasting blood sugar and 2 hrs postprandial and serum LDH.

Bone marrow aspirate smears were examined for assessment of cellularity and blasts percentage.

Cytochemistry (myeloperoxidase [or Sudan Black] supplemented by Periodic acid Schiff, acid phosphatase, specific esterase and non-specific esterase) were performed whenever necessary. All patients were classified according to the French-American-British [FAB] classification.

CSF examination was performed to patients with symptoms of CNS involvement, AML M4 and M5 and patients with TLC $>100 \times 10^9/L$.

Immunophenotypic analysis on peripheral blood (PB) or BM blasts was performed at diagnosis using multicolor flow cytometry (Coulter Epics, XL, Hialeh) [10]. A wide panel of FITC (fluorescein) or PE (phycoerythrin) conjugated monoclonal antibodies (MoAb) was used including pan leucocytic

marker (CD45), myeloid markers (MPO, CD33, CD13, and CD14), B-lymphoid markers (CD 19, CD 10, and CD22), T-lymphoid markers (CD3, CD4, CD5, CD7, and CD8), stem cell marker CD34 and HLA-DR in addition to anti **CXCR4** Mo Ab, FITC (**DAKO**) and anti **CCR2** PE (**R & D systems**).

Detection of surface markers: The whole blood staining method was performed. In short, 10 ul labeled MoAb was added to 100 ul blood, incubated in the dark for 20 minutes then processed by Q system (Coulter Corp, Hialeh, FL) where immunoprep reagent A for lysing, B as stabilizer and C as fixative were consecutively added.

Detection of intracellular markers: Hundred ul of whole blood was lysed using lysis solution (Becton and Dickenson) for 10 minutes. Cells were washed once and resuspended in 1 ml PBS. A mixture of 500 ul 4% paraformaldehyde as fixative, 500 ul PBS and 5 ul tween 20 as detergent was added to the cells and incubated for 10 min. The cells were washed and 10 ul Mo Ab was added and incubated for 3 min at 4°C. Cells were washed, suspended in 500ul PBS and analyzed.

Interpretation: Any antigen was considered positive when $\geq 20\%$ of blast cells were stained above the negative control except for CD34, MPO and CD10 where $\geq 10\%$ was considered positive [8]. Cell surface expression of CXCR4 and CCR2 was considered positive above 20%.

MCP-1 detection by RT-PCR:

RNA Extraction: Total RNA was extracted from 300 ul PB or BM samples using a salting out procedure (*Purescript, Gentra, Minneapolis, MN, USA*) according to manufacturer's instructions. Samples were stored at $-70^\circ C$ till used. RNA quality was assayed by gel electrophoreses on ethidium bromide stained 1% agarose containing 2.2 mol/L formaldehyde.

Reverse Transcription: cDNA synthesis was performed by reverse transcriptase using Gene Amp Gold RNA PCR Reagent Kit (*Applied Biosystems, USA*), 1ug RNA was used in 20 uL volume including 1x RT-PCR buffer, 2.5 mM MgCL₂, 1 mM dNTPS blend, 10 U/20 ul RNase inhibitor, 10 mM DTT, 1.25 um Random Hexamer and 15 U/ 20 ul Multiscribe Reverse Transcriptase enzyme. Cyclic conditions consisted of 25°C for 10 min and 42°C for 1 hour.

PCR reaction for MCP-1 detection consisted of 5x RT PCR buffer, 1.75 mM MgCL₂, 0.8 uL 200uM of each dNTPs, 2-5 U of Ampli Taq Gold DNA polymerase enzyme (5 units/ ul), 1 uL of 7.5 pmol of each primer and 2-3 ul cDNA. DEPC water was added to a total reaction volume of 50 ul. MCP-1 primer sequence was sense: 5-CTC ATA GCA GCC ACC TTC AT-3 and antisense: 5- GCT TTT CCT

CTT GAA CCA CA-3 (R & D systems, US Biological, USA).

Cycling conditions: Initial denaturation at 95°C for 5 min was performed in a thermocycler (*biometra, Germany*) followed by 35 cycles of amplification consisting of denaturation at 95°C for 45 sec, annealing at 65°C for 45 sec and extension at 72°C for 45 sec. A final extension step of 10 min at 72°C was added. A housekeeping gene, B-actin was run with every PCR reaction to check cDNA integrity and exclude any PCR failure. Each run included positive control cell line supplied from R & D, negative control cell line, HL 60 and non template control (NTC). All PCR products obtained through individualized RT-PCR reactions were separated on 2% agarose gel electrophoresis. Positive sample reaction appeared at 198 bp. Positive control appeared at 320 bp.

Statistical Methods:

Data was analyzed using SPSS win statistical package version 15 (SPSS Inc., Chicago, IL). Numerical data were expressed as mean and standard deviation (SD) or median and range as appropriate. Qualitative data were expressed as frequency and percentage. Chi-square test was used to examine the relation between qualitative variables. Comparison between two groups regarding quantitative variables was done using non-parametric t-test. Survival analysis was done using Kaplan-Meier method and Cox-regression method. All tests used

were two-tailed. P -value ≤ 0.05 was considered significant [11].

3. Results

This work was carried out on 50 de novo AML patients: 28 males (56%) and 22 females (44%) with a median age of 37.5 years (1 month - 82 years). According to FAB classification, one patient (2%) was classified as M0, 14 (28%) as M1, 14 (28%) as M2, 18 (36%) as M4 and 3 patients (6%) as M5. M0/M1/ M2 patients were classified together as one group and constituted 58% (29/50) of all cases while M4/ M5 group constituted 42% (21/50). Median follow up period of patients was 18 months (3- 28.6) Table 1 represents major laboratory parameters and table 2 shows clinical data of 50 AML patients.

Table (1): Laboratory data of 50 AML patients

Parameters	Median (range)
TLC ($10^9/L$)	55.7 (1-351)
Hb (g/dL)	7 (3.9-13)
Platelets ($10^9/L$)	41.5 (4-187)
BM blast % at diagnosis	66 (12-98)
BM blast % at complete remission (CR)	1 (0-5)

Table (2): Clinical data of 50 AML patients

Parameter	Number	Percent
Hepatomegaly	25	50%
Splenomegaly	25	50%
Hepatosplenoegaly	17	34%
Lymphadenopathy	27	54%
Spleen + Lymphadenopathy	12	24%
Gum involvement	2	4%
CSF infiltration	0	0%
Skin involvement	0	0%
Extramedullary infiltration (involvement of spleen, LN, gum, CSF and/or skin)	28	56%
BM cellularity at time of diagnosis		
Hypercellular	43	86%
Normocellular	7	14%

Median age of M0/ M1/ M2 group was 45 years (18-70) while median age was 24 years (1 month -82 years) in the M4/ M5 group ($P = 0.01$). Median Bone marrow blast percent (%) at time of diagnosis in M0/ M1/ M2 group was 75% (12-98%) versus 61% (15-87%) in M4/ M5 group ($P = 0.08$). None of other clinical or laboratory parameters as gender, TLC, Hb, platelet count, splenomegaly, lymph node (LN) involvement or BM cellularity

carried a statistically significant difference between both studied FAB groups.

Expression of CXCR4 by flow cytometry: CXCR4 was positive in 38/50 patient (76%) and was negative in 12 (24%) patients. Median percentage expression was 68% (0.3-98%). Twenty two /28 patients (78%) were positive for CXCR4 in the M0/M1/M2 group and 16/21 (76%) patients in the M4/ M5 group ($P = 0.9$).

Median CXCR4 % positivity was 57.5% (1.9-89) in the M0/ M1/ M2 group versus 79% (0.3-98) in the

M4/ M5 group ($P = 0.08$).

(F1)[A] Z0007396.lmd : FL2 LOG

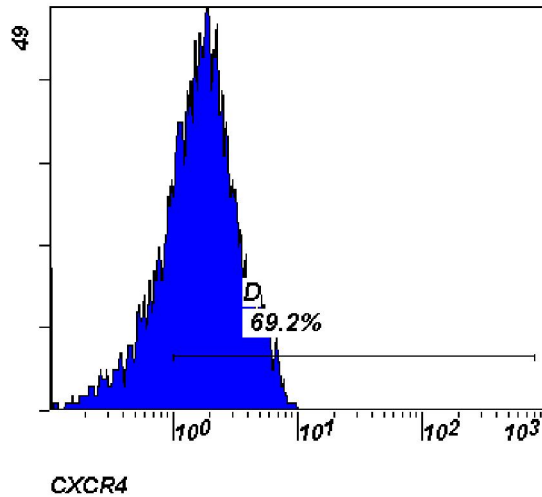


Figure (1): Flow cytometric histogram of an M5 case positive for CXCR4.

Expression of CCR2 by flow cytometry: CCR2 was positive in 10/50 (20%) and was negative in 40/50 patients (80%) in the whole AML cohort. Two

patients were positive for CCR2 (2/29, 7%) in the M0/M1/ M2 group while 8/21 (38%) patients in the M4/M5 group were positive ($P = 0.006$, Figure 2).

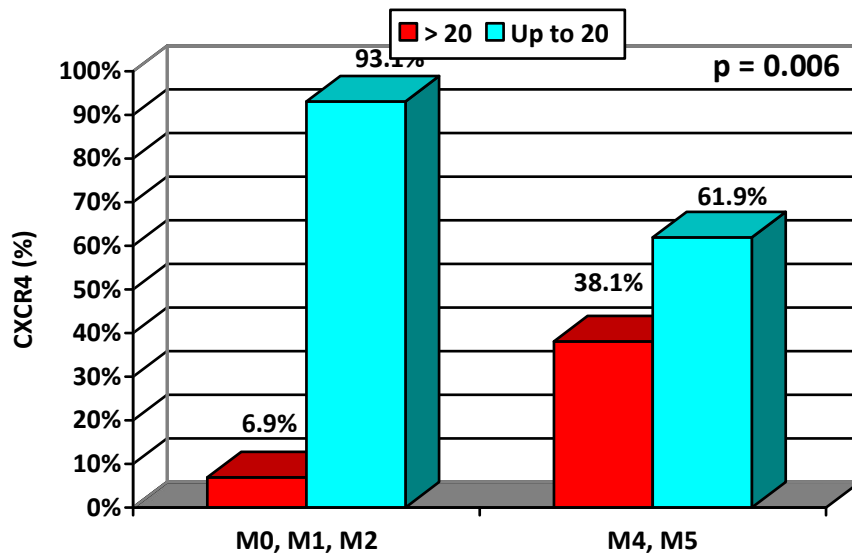


Figure (2): CCR2 positive patients in different phenotypic groups of AML patients

Median CCR2 MFI ratio expression was 1.5 (0.5-11) in the whole AML group. Median was 1.1 (0.49-11) in M0/M1/M2 group while in the M4/M5 group, median was 3.5 (1.5-9.4) ($P = 0.01$).

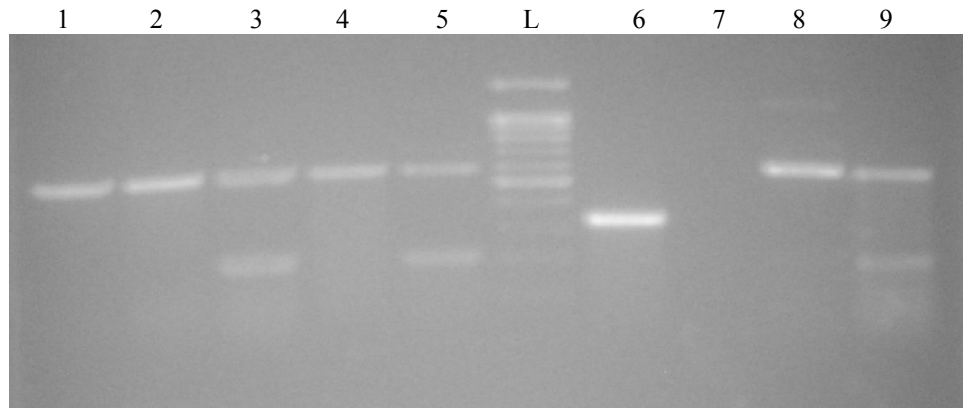


Fig. (3): MCP-1 expression by RT-PCR: L= Molecular weight marker (Ladder) Lanes 1, 2, 4 and 8= Negative MCP-1 samples. Lanes 3, 5 and 9= Positive MCP-1 samples (198bp). Lane 7= Non Template Control. Lane 6= Positive Control (320bp).

MCP-1 EXPRESSION BY RT-PCR: Forty-eight cases were tested: 20 patients (41.7%) were positive while 28 patients (58.3%) were negative (Figure 3). Ten out of 29 patients (34%) in M0/M1/M2 group were positive versus 10/21 (48%) in M4/M5 group ($P = 0.2$).

Relation between the level of expressions of CXCR4, CCR2 and MCP-1 and tumor load:

EMI was present in 15/28 (54%) of patients in the M0/M1/M2 group versus 13/28 (46%) of patients in the M4/ M5 group ($P = 0.4$).

Lymphadenopathy was found in 19/21 (90%) of patients in the M4/M5 group versus 8/29 (30%) in the M0/ M1/ M2 group ($P=0.001$).

Regarding CXCR4 and CCR2 expression levels, no statistic significant relation to tumor load was detected. However in MCP-1 positive patients, median TLC was $65.6 \times 10^9/L$ ($1-351.0 \times 10^9/L$) versus $37.2 \times 10^9/L$ ($3-267 \times 10^9/L$) in MCP-1 negative cases ($P = 0.07$). In addition, 14/20 (70%) patients with EMI had positive MCP1 expression versus 6/20 (30%) patients only with no EMI ($P = 0.05$).

BM cellularity: 35/43 of patients (81%) with hypercellular BM were positive for CXCR4 versus 3/7 patients (43%) with normocellular marrow ($p=0.02$). However, BM hypercellularity did not show any statistically significant relation with CCR2 or MCP1 positivity ($P=0.6$).

Relation of chemokines expression to BM blast % at time of diagnosis: No statistically significant association was encountered between BM blast % at diagnosis and CXCR4, CCR2 or MPC1 positivity ($P = 0.7$, $P=0.2$ and $P=0.5$ respectively).

Overall Survival was higher in M0/M1/ M2 group than the M4/M5 group, however the relation did not

reach statistical significance ($P = 0.3$). CXCR4, CCR2 and MCP1 did not show any impact on survival ($P=0.2$, $P=0.3$ and $P=0.6$, respectively).

4. Discussion

AML is a very heterogeneous disorder. Besides cytogenetic and molecular abnormalities, interactions of stromal cells and extracellular matrix with leukemic blasts can also generate antiapoptotic signals that contribute to neoplastic progression and persistence of treatment related minimal residual disease [12]. Cytokine induced, receptor-mediated phosphorylation patterns of intracellular mediators can identify subsets of patients with different prognosis [8].

In this study, median age range was 37.5 years and male to female ratio was 1.2:1. In similar studies, male to female ratio was comparable however median age was higher (64yrs) [8, 13]. The different FAB subsets in our patients were also comparable to western value [14]. Fifty six % (28/50) of our patients had EMI in spleen, LN, gum, CSF and/or skin. Another study detected EMI in 40% of patients and nearly all fell in the M4/ M5 group. This group also excluded liver involvement from their study because of endemic hepatitis [1]. In our study, 90% of cases associated with LN enlargement fell in the M4/M5 versus 30% only in M0/M1/M2 group ($p=0.001$). However, no significant difference between the two groups regarding EMI as a whole was observed. One group found that 40% of AML patients with EMI were mostly M4/M5 [15] while EMI was reported in 30% of patients in another series [16].

CXCR4 was positive in most of our AML patients (38/50, 76%) regardless the FAB subtype confirming previous published results [1, 17]. Mean CXCR4 expression in patients with no EMI was $62.7 \pm 30.7\%$ which was significantly higher than that

of patients with EMI (49.4±31.9%) ($P=0.04$). An explanation stated is that CXCR4 allows tumor cells to access cellular niches in the BM that favor tumor cell survival and growth [17]. In support of this evidence was the significant relation between CXCR4 expression and BM cellularity at time of diagnosis. The majority of our patients with hypercellular BM (81%) were CXCR4 positive while 57% of normocellular marrows were CXCR4 negative ($P=0.02$). However no significant difference in CXCR4 expression between the 2 FAB subgroups studied was found. This goes hand in hand with another report that found CXCR4 widely expressed in 84% of AML patients [1].

MCP-1 expression was positive in 34% of M0/M1/M2 group versus 48% in the M4/M5 group in our patient cohort. Although higher in monocytic group, no statistically significant difference was detected between the 2 groups ($p=0.2$). In contrast, others found MCP-1 positive in 37.5% of M0/M1 group, 60% in M2 group and 100% in M4/M5 group, with a significant difference between the 3 groups [1]. One group explained this variability of results by measuring MCP-1 during AML blasts culture and showing that the time at which maximal amounts of MCP-1 was produced differed between AML samples [19].

Regarding CCR2 expression, 7% of patients in the M0/M1/M2 group were positive versus 38% of patients in the M4/M5 group ($p=0.006$). It was stated that CCR2 is uniquely expressed by all M4/M5 subsets and not other AML FAB subsets [1]. From 20 positive patients for MCP-1 expression, five were positive for its ligand CCR2 while from 28 MCP1 negative patients; only four were positive for CCR2 giving a concordance of 60% (29/48) and discordance of 40% (19/48) between both markers. Our data agree with others who stated that production of chemokines and their specific receptors such as MCP-1/CCR2 allows functional cross talks within the malignant clone that helps its accumulation. This was significant in finding that 90% of patients with lymphadenopathy fell in the M4/M5 group as both markers were higher than in the M0/M1/M2 group. In addition, median TLC was higher in the MCP-1 positive than negative group and CXCR4 was positive in nearly all patients with hypercellular BM underscoring the effect of these 2 cytokines on tumor load at time of diagnosis. However, our results are not in complete agreement with studies that reported MCP-1 expression to be responsible for EMI as a whole in monocytic leukemia as EMI was found higher in our M0/M1/M2 group. It is the chemokine itself that seems to be responsible for EMI whenever expressed by AML blasts. As a proof of different biological behavior in our patient cohort, the frequency of MCP-1 positivity

was comparable in both AML subgroups but positive MCP1 was significantly associated with patients showing signs of EMI.

In conclusion, MCP-1 is associated with higher TLC at diagnosis and seems to play a significant role in EMI. It has a higher expression in monocytic leukemias, although insignificant however, its ligand CCR2 is nearly restricted to M4/M5 FAB AML subtypes suggesting that chemokine/receptor interactions orchestrate EMI in AML. CXCR4 showed unrestricted positivity in most AML FAB subtypes and was significantly associated with tumor load at diagnosis especially hypercellular BM and was inversely associated with EMI. In AML, chemokine expression is one of many variable factors that modulate this very heterogeneous disease. Other exogenous growth factors which are cytokine dependent in proliferation like GM-CSF, SCF and Flt3L should be investigated concomitantly. A larger scale of patients needs to be included for accurate characterization of the function played by these specific cytokines in different AML FAB subtypes.

Competing interest: The authors declare no competing financial interests.

Author Contribution: MA designed and performed research and analyzed data. YN and NE performed research, carried out molecular genetic studies and flow cytometry and analyzed laboratory data. FE performed research, analyzed molecular genetic data and wrote the paper. HR and YM designed and facilitated the research. All authors read and approved the final manuscript.

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Prospective Study for CMV Detection in Cancer Patients: Comparison between PCR, Antigenemia, and Serological Assays

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Abstract: Background. Human cytomegalovirus (HCMV) is a persistent pathogen, can cause life threatening infection in immunocompromised patients. Therefore, sensitive and reliable diagnostic test is essential for choice line of antiviral therapy and patients' management. **Methods.** HCMV detection was investigated by serological assay, PCR assay in both WBC's and plasma samples, antigenemia assay in PMBLs in 32 leukemia patients, 20 bladder cancer patients and 20 apparently healthy controls. **Results.** HCMV IgG was detected in 100% of our cancer patients. High HCMV IgG Ab titer was found to be less frequent in leukemia patients than solid tumor patients. In other words, low HCMV Ab titer was most common in leukemia patients. Antigenemia assay was positive in 8/32 (25%) of leukemia patients but viremia was positive in only 2/32 (6%) of leukemia patients. High level of antigenemia was associated with development of severe HCMV disease in leukemia patients. **Conclusion.** Antigenemia test is a reliable diagnostic tool in diagnosing active HCMV infection and progression. Therefore it can be helpful in guiding therapy in leukemia patients.

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Keywords: HCMV, Immunocompromised hosts, HCMV IgG, Antigenemia, PCR

1. Introduction

Human cytomegalovirus (HCMV) is a widespread pathogen responsible for asymptomatic and persistent infections in healthy individuals. In developing countries where poor hygiene and overcrowdings, children acquire infection early and seroprevalence approaches 100% by early adulthood. HCMV like all herpes viruses establishes latency and reactivates under condition of immunocompromised, like those with human immunodeficiency virus (HIV) infection, patients following allogeneic stem cell transplantation (SCT) or organ transplantation and patients with hematological malignancies^(1,2). In immunocompromised hosts, CMV infection can causes various life-threatening diseases like; pneumonitis, hepatitis, gastrointestinal diseases, retinitis, etc. Also, it can increase incidence of other opportunistic infections and decrease survival of patients. In addition, they have reported that mortality rate due to CMV pneumonia was higher among lymphopenic patients highlights the important role of lymphocytes in controlling CMV infection⁽³⁾.

Since, the choice of suitable strategy of antiviral line of therapy to prevent development of CMV infections and significant disease management in immunocompromised hosts depends on sensitive, accurate, reliable diagnostic test. Several reports demonstrated relevant methods are preferred for

diagnosis of HCMV infection such as; detection of pp65 antigen from peripheral blood leukocytes (antigenemia assay) and CMV DNA⁽⁴⁾. But such reports presented many discrepancies between these methods. Also their results were not obtained from patients with hematological malignancies. Therefore, the present study aimed at comparing results of different methods that can be helpful in diagnosing active HCMV infection. Consequently, accurate methods for determination of CMV infection will help in management of CMV infection and disease, and preventing development of drug resistant CMV mutant strains and in turn advanced line of treatment.

2. Patients and Methods

Patients

This study was conducted on 89 adult participants divided into three groups. The first group comprised 32 leukemia patients (9ALL, 9 AML, 12 CML, and 2 CLL) FAB classification was applied to ALL patients categorizing them into L1, L2 and L3 according to bone marrow morphology⁽⁵⁾. The second group comprised 30 patients with bladder cancer diagnosed and treated at the Medical Oncology Department, National Cancer Institute (NCI), Cairo University between September 2010 and October 2011. The third group 27 apparently healthy adults, as normal controls. The Institutional Review board (IRB) of the NCI approved the

protocol. Informed written consent was obtained from guardians of all adults enrolled in the study.

Disease extent and staging were established after a detailed history and physical assessment. Other baseline and prognostic investigations were carried out; Complete blood count (CBC), liver and renal function tests. Individuals among bladder cancer and normal groups were subjected only to routine hematological investigations.

Specimen collection

Blood specimens were collected into tubes with EDTA (Ethylenediaminetetraacetic acid) anticoagulant, left clot for 15 min. at 37°C followed by refrigeration at 2-8°C for another 30 min. Blood was then centrifuged at 400xg for 10 min. Serum was collected and stored in small aliquots at -20°C until examined. The plasma was separated and centrifuged at 800xg for 10min. Samples of plasma were collected in EDTA coated tube, left at room temperature for 1-2 hours for sedimentation. The upper cloudy layer was transferred into clean sterile tube, centrifuged at 800xg for 10 min. and the supernatant fluid (plasma) was stored at -20°C. The pellet was suspended in 0.8% ammonium chloride at 4°C for 3 min. to lyse residual RBCs, followed by rising in PBS. This last step was repeated and the sedimented peripheral blood leukocytes were harvested and stored at -20°C for DNA extraction, and CMV-DNA amplification.

Serological detection of HCMV-IgM by ELISA

Analysis of serum samples for IgM antibodies to CMV was performed using CMV EIAGEN-M kit (clone systems, Italy). Assay procedure was done according to manufacturer's instructions kit. The concentration of antibodies in the sample was estimated using a calibration curve. The unknown samples whose absorbance value were greater than of the cut-off values were considered reactive to IgM to CMV. The unknown samples whose absorbance values were less than cut-off values were considered non-reactive.

Serological detection of HCMV-IgG by ELISA

Analysis of serum samples for IgG antibodies to CMV was performed using CMV ELISA kit (Diamedix-Florida) Assay procedure was done according to manufacturer's instructions kit. The CMV value of the negative control should be less than 18. The CMV value of the positive control should be greater than 23. The unknown samples whose CMV values were greater than 23 were considered positive to CMV-IgG.

Determination and quantitation of HCMV-antigenemia assay:

Antigenemia assay was performed using immunostaining technique. The quantitative detection of HCMV antigen in polymorphonuclear leukocytes

(PMNLs) cytopins were stained using mouse monoclonal antibody (supersensitive antibody, Biogenex, USA) directed against pp68 kD early nonstructural antigen. DAB kits was used for visualization of immunostaining technique⁽⁶⁾.

Positive and negative control slides were included in each staining run. Controls and specimen slides were examined under light microscope using 400x magnification. Positive slide demonstrate CMV-Ag+ leukocytes characterized by a distinct brown perinuclear or nuclear staining. The +ve cells were counted and recorded.

Antigenemia is expressed by CMV antigen positive PMNL in aliquot of 200,000 cells. Low level of antigenemia expressed as presence of fewer than 10 positive cells/200,000cells. High level of antigenemia expressed as presence of more than 10 positive cells/200,000cells.

Molecular detection

1. Nucleic acid extraction:

Viral DNA was extracted from PMNLs and plasma of both leukemia and bladder cancer patients according to Zipeto *et al.*⁽⁷⁾.

2. Amplification of HCMV- DNA

HCMV DNA was selectively amplified by PCR using sequence-specific primers form (shuttle Biotech, Italy). This primer set shown to be specific for CMV and not to amplify DNA from other members of the herpesvirus family. 10 µl of DNA extract was subjected to DNA amplification in 90 µl of reaction buffer containing 10 mM Tris-HCL (pH 8.3), 1.5 mM MgCl₂, 20 nmol of each deoxynucleotide triphosphate, 50 pmol of each primer, and 2.2 units of Amplitaq (Perkin-Elmer Cetus, Norwalk, CT). The reaction was performed in a DNA thermal cycler (Perkin Elmer- Cetus): (i) an initial denaturation step of 5 min at 95°C; (ii) 50 cycles, with 1 cycle consisting of 40 sec of denaturation at 95°C, 50s of annealing at 62°C, and 40sec of extension at 72°C; and (iii) After the cycling program, the samples were incubated for 10 min. at 72°C. PCR was performed in a Perkin Elmer-Cetus thermo cycler⁽⁸⁾.

3- Detection of Amplified products by agarose gel electrophoresis:

15 µl of PCR product was subjected to electrophoresis on a 2% agarose gel (Sigma) in Tris-Acetate buffer (TAE) pH 7.5-7.8, stained with 0.5ug/ml ethidium bromide and examined under UV transillumination and photographed, the expected CMV PCR band was at the level of 326 bp fragment.

Statistical methods

SPSS version 17 statistical software package for windows was used for analyzing the correlation between different immunological parameters in the study groups. Mean/Median were used for

quantitative data description. Mann Whitney test was used for comparison of 2 independent groups and non-parametric ANOVA was used for >2 independent groups. Chi square (χ^2) test or Fisher exact test were used for comparison of proportions. *P* value is significant at 0.05 levels.

3. Results

Demographic features of the studied groups

Distribution of age and sex in the 89 studied individuals was shown in Table 1. Preponderance of males was observed among bladder cancer patients and apparently healthy control group.

Detection of HCMV antibody titer in the studied groups.

All the 32 leukemic and the 30 bladder cancer patients had IgG Ab titer (100%) in comparison to 96% of the control group (Table 2). Twofold of low titer was taken as an indication of viral activity among studied groups (140 EA). Regarding antibody titer and its distribution, our results showed that number of leukemia patients with high HCMV Ab titer was 9/32 (28%) compared with 18/30 (60%) and 23/27 (85%) in both bladder cancer patients and control group. Whereas number of leukemia patients with low HCMV Ab titer (<81 EA) was 5/32 (15.6%) compared with 2/30 (6.6%) and 2/27 (7%) in both bladder cancer patients and control group. Results are shown in table 2.

Regarding HCMV antibody titer in the different age groups, low HCMV Ab titer (<81EA) was found to be more common (33%) in young leukemia patients (<25Y) compared to a frequency of 0% in the old age group (>50 Y). Whereas, high HCMV Ab titer (>81EA) was detected in the all (100%) old age leukemia patients (>50Y), compared with 67% of the young age group (Table 3).

Detection of HCMV DNA and pp-68 antigenemia in leukemia patients

Of the 32 leukemic patients 6 (18.8%) were found to be positive by PCR in leukocytes. Out of those 6, two cases (33%) were viremic as detected in plasma by PCR assay. Results are shown in Fig. 2. Regarding antigenemia results, 8 out of 32 leukemic patients (25%) were positive for pp65 in their PMNLs. Quantitative results were available for those 8 positive patients: 4 (12.5%) patients had fewer than 10 positive cells/200,000 cells examined (low level), 4 (12.5%) patients had 10 or more positive cells/200,000 cells examined (high level) (Table 2). Moreover, when comparing HCMV results obtained by PCR with that obtained by antigenemias assay. Our results showed that out of 8 positive cases for antigenemia assay, 2 (25%) patients showed negative results by PCR assay (in both cells and plasma) (Fig.2)

In addition, out of 8 positive cases for antigenemia assay, 3 (37.5%) cases had high Ab titer (>140EA) and only one case (12.5%) had low Ab titer (<80EA).

Correlation of HCMV Ab titer and antigenemia with the severity of HCMV disease

Leukemic patients were divided into 2 groups according to the severity of CMV disease into: Patients with mild HCMV disease (clinical score <7), and those with severe HCMV disease (clinical score ≥ 7). Results showed that there was no difference in distribution of low and high Ab titer among patients with mild or severe HCMV disease. But the number of leukemia patients with high antigenemia level (>10Ag $\times 10^5$ cells) was more among leukemic patients with severe HCMV disease (Fig. 3).

Table 1. Demographic features of the studied groups

Group	No. of cases	Age (years)		Sex		
		Median	Range	Male	Female	M:F Ratio
Leukemias	32	40	18-80	17	15	1.1:1
Bladder ca.	30	55	24-72	21	9	2.3:1
Controls	27	34	20-65	21	6	3.5:1
Total	89	43	18-80	59	30	2:1

Table 2. Detection of HCMV infection by 3 different methods in the studied groups

Parameter	Leukemia group N=32		Bladder cancer group N=30		Normal control group N=27	
	No of +ve cases	%	No of +ve cases	%	No of +ve cases	%
-ELISA (IgG) assay:	32	100	30	100	26	96
Low titer (<80 EA)	5	15.6	2	6.6	2	7
High titer (>140 EA)	9	28	18	60	23	85
-PP-65 antigenemia assay:	8	25	1	3	0	0
Low level (<10Ag+/2x10 ⁵ cells)	4	12.5	0	0	0	0
High level (<10Ag+/2x10 ⁵ cells)	4	12.5	0	0	0	0
-PCR assay:						
In Leukocytes	6	19	3	10	0	0
In Plasma	2	6	0	0	0	0

EA: ELISA arbitrary unit.

High Ab titer >140 was taken as an indication of active viral infection or reactivation

Table 3. Presence of low and high CMV IgG Ab titer among certain age groups (<25Y, <50Y) in all subject groups

Age groups CMV titre Group	Total no.	<25 Y		>50 Y		
		<81 EA	>81 EA	Total no.	<81 EA	>81 EA
		No.(%)	No.(%)		No.(%)	No.(%)
Leukemia	9	3 (33%)	6 (67%)	11	0 (0%)	11 (100%)
Bladder Ca.	1	0 (0%)	1 (100%)	19	0 (0%)	19 (100%)
Normal	9	0 (0%)	9 (100%)	4	0 (0%)	4 (100%)

EA: ELISA arbitrary unit.

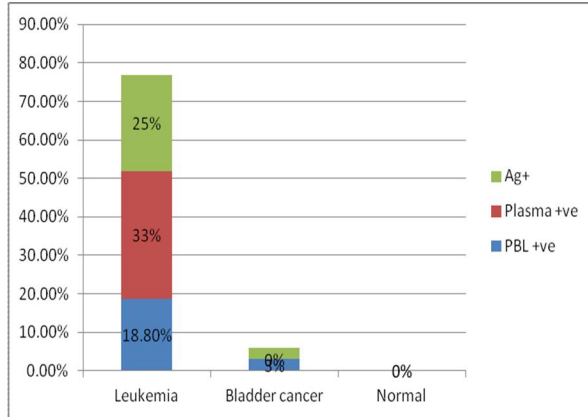


Fig. 2. Detection of HCMV by antigenemia and PCR assays in all subject groups

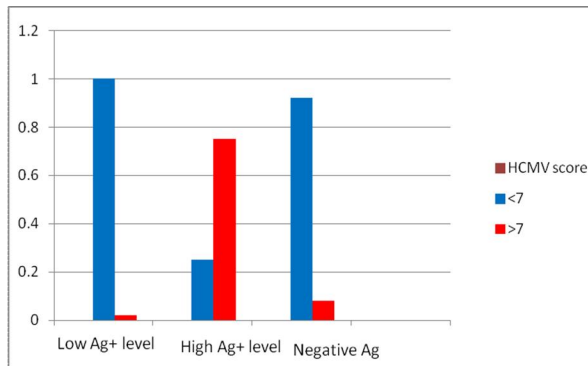


Fig 3. Correlation between severity of CMV disease and antigenemia level in leukemia patients

4. Discussion

Early and accurate diagnosis and reliable methods for monitoring CMV infection are essential not only for patients' managing (9), but also for epidemiological studies to understand host-virus relationship (10). The conventional methods for the diagnosis of CMV infection/disease are viral isolation by viral culture, serology which includes CMV specific antigen and antibody detection, molecular method for detection of viral DNA from blood and clinical specimens. Viral isolation in tissue culture is the gold standard method but, it is labor intensive and takes time (24-48hrs) till the results are

available. Hence, other rapid methods such as detection of pp65 antigen from peripheral blood leukocytes (antigenemia assay) and CMV DNA are preferred for diagnosis (4).

In accordance with previous Egyptian reports, the seropositive reactions to HCMV was 100% in Egyptian cancer patients, compared to >90 % among apparently healthy controls. Whereas, other study stated that HCMV seropositivity was 83% in immunocompromised patients with malignant and non malignant blood disorders (11). Moreover, our results showed that the lowest percentage of high Ab titer (>140 EA) (28%) and the highest percentage of low Ab titer (<80 EA) was among leukemia patients. This may reflect imbalance present in immune defense mechanism present in leukemia patients whose cell mediated immunity is impaired and favoring development of CMV infection and disease. These results were further confirmed by our observation which showed that only 37% (3/8) of leukemia patients positive for antigenemia had high HCMV Ab titer. Several previous studies supported our results which demonstrated that no serologic response in severely immunocompromised patients who suffered fatal disseminated CMV infection, since ability of patients to respond immunologically is obviously impaired (12, 13). Also, in sensitive test used for detection of specific CMV-IgG, as concluded by Greijer et al., (14) who suggested the use of a combination of peptides from pp150, gB, and pp28 to give optimal and specific reactivity with CMV IgG.

Molecular methods considered to be the relevant diagnostic methods for detection of CMV DNA in various samples. In the present study, HCMV DNAemia (HCMV DNA in PBL) was detected in 18.8 % (6/32) of leukemia patients, only 33% out of those patients had active HCMV infection and then they are at higher risk of developing CMV disease (15). However, PCR test has the ability to detect minute amounts of nucleic acid in various clinical samples, and can detect the onset of CMV viremia 1 to 2 week prior to culture and antigenemia tests, its inherent sensitivity poses a problem because

latent CMV genomes, which are present in leukocytes of practically all seropositive individuals, may be amplified⁽¹⁶⁾. In this context, Quantitation of CMV DNA in plasma and other biological samples is very useful for rapid diagnosis of infection and effective monitoring clinical course of disease and response to therapy.

The current study lack quantitation of HCMV DNA by real time PCR, but quantitation was performed by antigenemia assay. A valuable feature of the CMV antigenemia assay is that, it is rapid (2-4 hrs), quantitative, doesn't require special equipments, antigenemia became positive 8+ 7 days before serologic signs of active infection. Therefore, antigenemia test is useful in early diagnosis, monitoring infection and antiviral treatment in immunocompromised patients⁽¹⁷⁾. Our results showed that 8 out of 32 leukemia patients (25%) were positive for HCMV by antigenemia assay. The quantitative nature of the antigenemia assay may give an estimate of viral load, and this may be useful for monitoring patients before, during, and after therapy.

When comparing results of our PBL-PCR and plasma PCR with antigenemia assay, sensitivity and specificity were found to be 75% and 100% for our PBL-PCR and 25% and 100% for our plasma PCR. False negative results obtained by PBL-PCR could be due to several reasons. First, sensitivity of primers used for amplifying CMV was low⁽¹⁸⁾. Second, Genetic variations and variability of clinical strains of HCMV may affect performance of PCR. Third, Presence of inhibitory factors in tested specimens. In addition, the six leukemia patients who were positive for antigenemia and were not viremic can be explained by early infection (new strain) or reactivation of HCMV has been detected. This was consistent with explanation of Boeckh et al.⁽¹⁹⁾ who found that in the early stage of reactivation detection of DNA and pp65 likely represents mainly phagocytosis of virus DNA originating from replicating CMV-infected cells such as endothelial cells, which can be detected in peripheral blood in patients with progressive infection. That CMV DNA often cannot be detected in plasma during this phagocytosis process. This also was demonstrated by Lübeck et al⁽²⁰⁾ who observed that antigenemia preceded viremia by 3-9 days. Therefore, early positive or rising antigenemia levels may signal the onset of active CMV disease and allow early preemptive therapy to be initiated, particularly in transplant recipients⁽²¹⁾.

Moreover, when comparing level of antigenemia with severity of HCMV disease, our results showed that 75% of leukemia patients with high antigenemia level had severe CMV disease as estimated by plotkin's scoring system. This was in

consistent with previous report which showed that antigenemia rate which is one of the risk factors for development of fatal outcome of CMV disease in lymphoma patients (median number of CMV infected cells per 1000,000 WBCs was higher in patients with CMV-disease compared to those with antigenemia (median 18 vs 5 cells). But our results need to be repeated using monoclonal antibody directed against CMV pp65 as we may get better results. Also, future research will need to focus on the implementation of real time PCR to achieve standardized, reproducible results on larger samples of cancer patients hoping to reach, to a cut off for diagnosing active HCMV infection. Also, antigenemia assay using monoclonal antibody

Conclusion

Prevalence of HCMV IgG was 100% among immunocompromised cancer patients. Presence of high HCMV Ab titer was lower in leukemia patients than solid tumor patients, but presence of low HCMV Ab titer was higher in leukemia patients than solid tumor patients indicating impairment in cell mediated and humoral immune response as a result of disease. Quantitative Antigenemia assay showed better results than qualitative PCR assay for detection HCMV infection. Also, high level of antigenemia pp68 was correlated with severity of HCMV disease. Treatment decisions in the clinic should therefore be taken with caution, considering trends in viral load and the sensitivity of the methods used in individual laboratories, clinical manifestations, and not just absolute values recorded in a single test.

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Association of Interleukin-18 with Sustained Virological Response (SVR) To Interferon Therapy in Patients with Chronic Liver Diseases

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Abstract: Background: Pegylated interferon plus ribavirin is the standard therapy for treatment of Chronic hepatitis C (CHC) patients, this therapy is only effective in 50–60% of infected individuals. Pretreatment predictors associated with sustained virological response (SVR) to interferon treatment have not yet been fully investigated. Several factors have been shown to influence response to antiviral treatment, one of them is interleukin – 18 (IL-18). There are few data on IL-18 in relation to infectious diseases, but it plays a prominent role in chronic HCV infection. Thus, the current study is designated to assess serum Interleukin – 18 levels in CHC genotype 4 patients and its association with treatment response. **Patients and Methods:** This study was performed on fifty Egyptian chronic hepatitis C patients, who received combined pegylated interferon alpha and ribavirin therapy and twenty healthy blood donors as a control group. Quantitative hepatitis C virus RNA was done by real time RT-PCR technique. Serum IL-18 level was assayed using quantitative ELISA plate method. **Results:** The mean level of IL-18 was significantly higher in CHC patients (212.15 Pg/ml) compared to the controls (48.95 Pg/ml). IL-18 level in responders was significantly reduced after 6 months from the end of treatment compared to those at baseline level ($P=0.001$), but such decrease was lower than that in non responders ($P=0.058$). IL-18 level was positively correlated with high and moderate viral load in non responders. **Conclusions:** Serum IL- 18 level has the potential to be used as a biological marker to predict outcome of antiviral therapy among CHC genotype 4 patients.

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1. Introduction

Hepatitis C virus (HCV) has been estimated by the World Health Organization to infect 170-200 million patients worldwide, with the highest prevalence rate about 22% among Egyptian population⁽¹⁾. Characteristic features of HCV infection include its persistence in the host and progression to chronic hepatitis, leading to cirrhosis, which is a strong risk factor for the development of hepatocellular carcinoma (HCC)⁽²⁾. Interferon based therapy can reduce HCV to undetectable levels and improve prognosis. The primary aim of antiviral therapy in HCV patients is a sustained virological response (SVR), which is defined as undetectable serum HCV RNA 24 weeks after completion of therapy. Combined pegylated interferon- α and ribavirin therapy has sustained virological response rates reaching in different clinical trials from 54% to 61%^(3,4).

Cytokines play an important role in the pathogenesis, progression, and treatment outcome of HCV infection. Because the control of cytokine production is highly complex and the effects of cytokines are widespread throughout multiple

regulatory networks, it would seem that screening for multiple biomarkers could clarify the immunopathogenesis of the disease and predict antiviral therapy response⁽⁵⁾. IL-18 previously has been known as interferon-gamma-inducing factor, is a pleiotropic proinflammatory cytokine that is expressed mainly by peripheral blood mononuclear cells and macrophages. In the liver, besides its expression in Kupffer cells, IL-18 can also be synthesized by injured hepatocytes^(6,7). The fundamental function of IL-18 is an enhancement of T helper type 1 (T_H1) cytokine production⁽⁸⁾. The dynamics of TH1/TH2 response determine the outcome of antiviral therapy to chronic hepatitis C (CHC) and that IL- 18 is an important mediator of the TH1/TH2 balance⁽⁴⁾. The balance of TH1 and TH2 CD4+ responses has proven relevant to HCV infection. Accumulating evidence has shown that an early TH1 immune response leads to viral clearance, whereas a TH2 response favors chronic evolution⁽²³⁾. IFN- α treatment has a negative influence on IL- 18 concentration, independently of viral effects⁽²¹⁾. Therefore, TH1 decreased, TH2 increased and incidence defect in dynamics of TH1 / TH2 balance occurred. Studies in murine models and cell lines

indicate that IL-18 has potent antitumor effects that are mediated by enhancement of cytotoxic T lymphocyte and NK activity, induction of apoptosis and reduction of tumor development. Hence, it has been hypothesized its role in prevention of HCC⁽⁹⁾. Moreover, there is a dearth of data on the nature of the involvement of IL-18 in HCV pathogenesis and host defense⁽⁹⁾. However, the effect of IL-18 on antiviral therapy for chronic hepatitis C is still unclear⁽⁴⁾. There are few data on IL-18 in relation to infectious diseases, but it plays a prominent role in chronic HCV infection. In this context, the aim of the present study is to investigate role of IL-18 and its association with outcome of PEG-IFN and ribavirin therapy hoping to find a non invasive marker can be used to predict response to antiviral therapy in chronic hepatitis C genotype 4.

2. Patients and Methods

Patients

This prospective study was conducted with 70 participants divided into two groups. The first group comprised 50 patients with CHC-4 patients diagnosed and treated at Ain Shams University Specialized Hospital, Cairo, between October 2010 and January 2012. The second group included 20 apparently healthy participants who had donated blood at the National Cancer Institute, Cairo University. The Ethical Committee of Ain Shams University Specialized Hospital approved the study protocol, which was prepared in accordance with the ethical guidelines of the 1975 Declaration of Helsinki and later revisions.

Written consent was obtained from all participants prior to enrollment in the study and all were mentally and physically capable of answering a questionnaire. Inclusion criteria: adult patients of both sexes (18-46 years old), diagnosis within the previous 12 months, positive for HCV RNA in serum (by RT-PCR assay), with evidence of chronic hepatitis supported by liver biopsy. The control group was made from adults negative for HCV RNA and HBV DNA. Patients were not receiving hepatitis treatment at the time of sampling. The presence of HBV infection or co-infection was excluded by serum ELISA for anti-HBc and HBsAg. In addition to investigations needed to fulfill the selection criteria, all individuals included in this study were subjected to the following:

A. Medical History

Full history was taken with special reference to risk factors for liver diseases such as previous HCV exposure in surgical wards, blood transfusions, dental therapy, needlestick injury, history of HCV in the spouse and iv. injection.

B. Physical Examination

Complete medical examination with particular focus upon the manifestations of hepatitis such as jaundice, hepatomegaly, and tenderness in the right hypochondrium. BMI was calculated as body weight in kilograms divided by the square of height in meters (kg/m²). Abdominal ultrasonography was performed for all patients.

C. Histopathological investigations

Liver biopsy specimens were formalin-fixed and paraffin embedded then sectioned and stained (hematoxylin and eosin) for routine histopathological examination. Grading and staging of chronic hepatitis was performed according to Modified Knodell's Score⁽¹²⁾.

D. Laboratory investigations

Venous blood samples were taken in the morning after 12-h overnight fast. Plasma glucose, serum alanine aminotransferase (ALT), aspartate aminotransferase (AST), albumin (Alb), total bilirubin levels (Bil) and cholesterol (Chol) were measured by using Synchron CX4 clinical system (standard clinical laboratory methods) at the Clinical Laboratory Department, Ain Shams Specialized Hospital. Serum alpha-fetoprotein levels were estimated by serological techniques (Axyam System, Abbott Laboratories). Prothrombin Time (PT) measurements were performed for all patients; normal PT was 13 seconds (100% concentration and International Normalization Ratio (INR) of 1). Interleukin (IL- 18) was calculated on Quantitative determination of IL- 18 by ELISA technique. ELISA was performed according to the manufacturer's instructions. The Human IL-18 ELISA Kit measures human IL-18 by using third generation kits (DiaSorin, Italy) according to the manufacturer's instructions. The concentration of IL18 in the samples is then determined by comparing the O.D. of the samples to the standard curve.

E. Viral Markers

ELISA assays

Sera of all patients and controls were tested for HBsAg, anti-HBc and anti-HCV antibodies by ELISA, using third generation kits (DiaSorin, Italy) according to the manufacturer's instructions.

Polymerase chain reaction (PCR) for detection of hepatitis C virus

RT-PCR was performed as previously described⁽¹³⁾ and 10 µl samples of the amplicons were analyzed by electrophoresis (1.2% agarose gel, ethidium bromide staining).

HCV genotyping

HCV genotype was determined using INNO LiPAII and III versant Kit (Innogenetics, Ghent, Belgium) according to manufacturer's directions.

Quantitation of HCV-RNA in serum:

HCV-RNA was quantitated in all patients' serum samples using Real Time PCR (RT-PCR) ⁽¹⁴⁾ (primers and RT-PCR reagents from Stratagene, Qiagen, USA). Low viremia was defined as viral load lower than 100×10^3 IU/L, moderate viremia as viral load $100-1000 \times 10^3$ IU/L, and high viremia when viral load $> 1000 \times 10^3$ IU/L ⁽¹⁵⁾.

Statistical analysis:

Mean \pm standard deviation (\pm SD), frequencies (number of cases) and relative frequencies (percentages) were used where appropriate. Comparison of quantitative variables between the study groups was done using paired-samples T test for dependent samples when comparing 2 groups. For comparing categorical data, Chi square (χ^2) test was performed. Exact test was used instead when the expected frequency is less than 5. A probability value (*p* value) less than 0.05 was considered statistically significant. Pearson Correlation Coefficient - Benesty method was used to test correlation between numerical variables. Receiver-operator characteristic (ROC) curves were calculated the area under the curve (AUC) and 95% confidence interval (CI) were calculated for each plot. In order to select cutoff value that best combined sensitivity and specificity. All tests are two-tailed; a *p*-value < 0.05 was considered significant. Statistical calculations were performed using SPSS (Statistical Package for the Social Science; SPSS Inc., Chicago, IL, USA) version 17 for Microsoft Windows.

3. Results:

Detection and quantification of serum markers in CHC - 4 patients and their controls.

The mean baseline serum concentration of ALT (51.50 vs 35.30 IU/L; *p* = 0.000), AST (65.50 vs 48.35 IU/L; *p* = 0.000), and Hb (12.21 vs 10.35 g/dl; *p* = 0.000) were significantly higher in CHC patients than in healthy control (Table 1).

Of 50 patients receiving PEG-IFN and ribavirin therapy, 29(58%) were responders with accompanying normalization of ALT levels and 21(42%) were non responders. Three (6%) patients out of the 21 non responders had relapsed. For the patients at the baseline (before treatment), the mean AST level in responders group was significantly lower than that in non responder group (47.24 vs 74.81 IU/L; *p* = 0.000). But, mean ALT level in responder group was not significantly lower than that in non responder group (54.71 vs 59.29 IU/L; *p* = 0.381). Results are shown in Table 2.

As regards IL-18 level, the mean baseline level of IL-18 was significantly higher in patients with HCV-4 infection than in healthy controls (212.15 vs

48.95 pg/ml; *p* = 0.000), Table 1. However, mean baseline level of IL-18 was slightly higher though not significant in responders than in non responders (221.19 vs 217.33 pg/ml; *p* = 0.744), it showed a significant reduction after 6 months from end of treatment in responders group (194.57 vs 102.00 pg/ml; *p* = 0.001) compared with non responders (217.33 vs 194.57 pg/ml; *p* = 0.058).

Clinico-pathological findings and serum IL-18 levels.

Several demographic (age and sex) and clinical (AST, ALT, and HCV viral load), pathological (fibrosis and necro-inflammatory activity) finding were examined for their correlation with serum cytokine (IL-18) level in patients infected with CHC genotype 4. No correlation was observed between IL-18 levels and sex, ALT, AST, T. Bil, or AFP (Table 3).

Generally, number of CHC-4 patients who showed minimal scarring of fibrosis (F1) after 6 months of completion of antiviral therapy was higher than those before treatment (12% vs 4%). Also, number of patients who showed milder necro-inflammatory activity (A2) was higher after six months of end treatment than that before treatment (88% vs 34%). Such pathological observations were found to be correlated with HCV viral load, as number of patients with high viral load decreased from 26% before treatment to 2% after end of treatment. Data are shown in Table 1.

Regarding the correlation between clinic-pathological parameters and IL-18 level, mean level of IL-18 showed positive correlation though not significant with advanced stage of fibrosis and was dramatically decreased after 6 months from end of treatment compared to before treatment (Fig. 1).

Similarly, mean level of IL-18 was found to be correlated with necro-inflammatory activity in CHC-4 responders and non responders patients. Patients with higher HAI index (A3) showed higher mean level of IL-18 than those with lower HAI (A1), Fig. 2.

IL-18 and viral load

Mean level of IL-18 was significantly correlated with HCV viral load after 6 months from the end of treatment. Mean IL-18 level in CHC-4 patients with high viral load was significantly higher than those negative for HCV-4 after end of treatment ($r = -0.807$, *p* = 0.001). As regards response to treatment, mean level of IL-18 was significantly higher in non responders with moderate and high viral load than those with low viral load. But significant reduction in IL-18 level was observed in responders after end of treatment (*p* = 0.001), Fig. 3.

Table 1: Demographic characteristics and laboratory parameters of the studied groups

Variable	Control N=20	CHC (Baseline) N=50	CHC (end of follow-up) N=50	P=value
Demographic characters				
Age (yr) mean ± SD	33.10 ± 8.169	41.30 ± 7.928	41.30 ± 7.928	0.005 ^a
Sex				0.258 ^a
Male	9	34	34	
Female	11	16	16	
M:F ratio	1:1.22	2.13:1	2.13:1	
BMI (kg/m ²) mean±SD	24.85 ± 8.054	30 ± 10.407	30 ± 10.407	
Obese > 25 n (%)	7 (35 %)	22 (44 %)	23 (46 %)	0.111 ^a , 0.492 ^b , 0.000 ^c
Non-obese n (%)	13 (65%)	28 (56 %)	27 (54 %)	
Biochemical tests (mean ± SD)				
IL- 18 (Pg/ml)	48.95 ± 11.166	212.15 ± 40.977	153.70 ± 56.552	0.000^a, 0.000^b, 0.000^c
ALT (IU/L)	30 ± 6.00877	51.50 ± 13.930	35.30 ± 10.979	0.000 ^a , 0.036 ^b , 0.000 ^c
AST (IU/L)	32.40 ± 9.064	65.50 ± 21.681	48.35 ± 23.006	0.000 ^a , 0.012 ^b , 0.000 ^c
T.Bil (mg/dl)	0.745 ± 0.2012	1.130 ± 0.4378	0.955 ± 0.4850	0.002 ^a , 0.089 ^b , 0.265 ^c
D.Bil (mg/dl)	0.15 ± 0.0607	0.29 ± 0.1917	0.22 ± 0.1824	0.004 ^a , 0.1 ^b , 0.53 ^c
Albumin (g/dl)	3.85 ± 0.2164	3.790 ± 0.3243	3.585 ± 0.4826	0.466 ^a , 0.043 ^b , 0.079 ^c
PT %	99.625 ± 0.2048	93.50 ± 6.902	91.25 ± 7.926	0.965 ^a , 0.634 ^b , 0.015 ^c
Glucose(mg/dl)	101.85 ± 13.914	102.90 ± 18.148	98.25 ± 9.436	0.856 ^a , 0.405 ^b , 0.132 ^c
HB (g/dl)	11.80 ± 1.735	12.21 ± 1.7177	10.35 ± 1.2258	0.472 ^a , 0.007 ^b , 0.000 ^c
TSH (ng/dl)	2.78 ± 1.1813	3.435 ± 0.7235	4.05 ± 1.2976	0.074 ^a , 0.007 ^b , 0.028 ^c
Serum AFP (ng/ml)	5.86 ± 2.0291	11.85 ± 4.44	11.35 ± 4.069	0.000 ^a , 0.000 ^b , 0.865 ^c
Creatinine (mg/dl)	0.99 ± 0.181	1.385 ± 1.7989	1.13 ± 0.225	0.354 ^a , 0.043 ^b , 0.749 ^c
HCV RNA (Viral load copies/IU/L) N (%)				
High		13(26%)	1(2%)	0.248
Moderate		23(46%)	9(18%)	
Low		14(28%)	11(22%)	
- ve			29(58%)	
Stage of fibrosis N(%)				
F1		2(4%)	6(12%)	
F2		30(60%)	28(56%)	
F3		18(36%)	16(32%)	
F4		0	0	
Necroinflammatory activity index (HAI) N(%)				
A1		5(10%)	24(48%)	
A2		44(88%)	17(34%)	
A3		0	0	
A4		1(2%)	9(18%)	

Data are mean ± SD, frequency (%); obesity defined as BMI>25; ALT, alanine aminotransferase; AST, aspartate aminotransferase; PT%, prothrombine concentration; T. Bil, total bilirubin; D. Bil, direct bilirubin; HB, hemoglobin; IL-18, Interlukin-18; AFP, alpha fetoprotein; p-value comparison between CHC patients at baseline and healthy control ^a, CHC patients after 6 months from end treatment and healthy control ^b, and CHC patients at baseline and CHC patients after 6 months from end treatment ^c.

Table 2: Demographic characteristics and laboratory parameters of responders and non responders (at baseline and end of follow-up):

Variable	At baseline		At end follow-up		P=value
	Responders (n = 29; %58)	Non-responders (n = 21; %42)	Responders (n = 29; %58)	Non-responders (n = 21; %42)	
Demographic characters					
Age (yr) mean ± SD	40.14 ± 8.645	41.24 ± 7.622	40.14 ± 8.645	41.24 ± 7.622	0.651
Sex					0.772
Male	19	15	19	15	
Female	10	6	10	6	
M:F ratio	1.9 : 1	2.5 : 1	1.9 : 1	2.5 : 1	

BMI (kg/m ²) mean ± SD	20.24 ± 4.949	29.86 ± 7.512	20.24 ± 4.949	29.86 ± 7.512	0.001
Obese > 25 n (%)	5(17.2 %)	17(80.9 %)	5(17.2 %)	17(80.9 %)	
Non-obese n (%)	24(82.8 %)	4(19.1 %)	24(82.8 %)	4(19.1 %)	
Biochemical tests mean ± SD					
IL- 18 (Pg/ml)	221.19 ± 51.493	217.33 ± 27.13	102 ± 4.416	194.57 ± 50.246	0.744^a, 0.000^b
ALT (IU/L)	54.71 ± 16.091	59.29 ± 13.517	33.14 ± 6.093	41.29 ± 11.637	0.381 ^a , 0.017 ^b
AST (IU/L)	47.24 ± 12.429	74.81 ± 17.691	32.95 ± 7.131	64.24 ± 24.284	0.000 ^a , 0.000 ^b
T.Bil (mg/dl)	0.981 ± 0.26	1.21 ± 0.53	0.781 ± 0.1504	1.252 ± 0.725	0.093 ^a , 0.009 ^b
D.Bil (mg/dl)	0.219 ± 0.075	0.324 ± 0.2278	0.143 ± 0.0507	0.329 ± 0.2572	0.081 ^a , 0.004 ^b
Albumin (g/dl)	3.924 ± 0.3714	3.757 ± 0.3091	3.919 ± 0.1965	3.376 ± 0.5088	0.126 ^a , 0.000 ^b
PT %	90.95 ± 5.277	90.05 ± 7.940	90.95 ± 5.277	90.05 ± 7.940	0.637 ^a , 0.37 ^b
Glucose(mg/dl)	99.33 ± 16.883	98.57 ± 17.829	95.81 ± 20.629	109.76 ± 18.566	0.885 ^a , 0.041 ^b
HB (g/dl)	12.105 ± 1.6764	12.448 ± 1.7285	10.381 ± 1.244	10.19 ± 1.3274	0.557 ^a , 0.618 ^b
TSH (ng/dl)	3.652 ± 0.6137	3.419 ± 0.6562	4.45 ± 1.459	4.43 ± 1.434	0.235 ^a , 0.966 ^b
Serum AFP (ng/ml)	9.50 ± 4.323	9.90 ± 5.291	9.10 ± 1.998	10.90 ± 4.592	0.742 ^a , 0.084 ^b
Creatinine (mg/dl)	1.333 ± 1.7625	0.995 ± 0.1532	0.938 ± 0.1533	1.229 ± 0.3036	0.393 ^a , 0.001 ^b
HCV RNA (Viral load copies/IU/L) N (%)					
High	7(24.4%)	6(28.6%)	0	1(4.7%)	0.242 ^a , 0.000 ^b
Moderate	12(41.4%)	11(52.4%)	0	9(42.9%)	
Low	10(34.5%)	4(19%)	0	11(52.4%)	
- ve	0	0	29(100%)	0	
Stage of fibrosis N(%)					
F1	2(6.9%)	0	5(17.2%)	1(4.8%)	0.620 ^a , 0.747 ^b
F2	20(69%)	10(47.6%)	24(82.8%)	4(19%)	
F3	7(24.1%)	11(52.4%)	0	16(76.2%)	
F4	0	0	0	0	
Necro-inflammatory activity index (HAI) N(%)					
A1	4(13.8%)	1(4.8%)	22(75.9%)	2(9.5%)	0.099 ^a , 0.586 ^b
A2	25(86.2%)	19(90.4%)	6(20.7%)	11(52.4%)	
A3	0	1(4.8%)	1(3.4%)	8(38.1%)	
A4	0	0	0	0	

p- value comparison between responders and non responders to IFN-treatments at baseline ^a; Responders and non responders after 6 months from end treatment ^b.

Table 3: Correlation between IL-18 and other parameters

Parameters	IL – 18 level							
	Control N=20		CHC N=50		Responders (n = 29; %58)		Non-responders (n = 21; % 42)	
	r	P= value	r	P= value	r	P= value	r	P= value
Demographic characters								
Age (yr)	-0.002	0.992	-0.292	0.040	-0.212	0.269	-0.498	0.022
Sex	-0.290	0.214	0.027	0.854	0.070	0.727	0.299	0.189
BMI (kg/m ²)	-0.145	0.543	-0.053	0.712	0.077	0.692	-0.385	0.085
Biochemical tests								
ALT (IU/L)	0.061	0.798	0.109	0.449	0.037	0.849	0.362	0.107
AST (IU/L)	0.162	0.495	-0.016	0.914	0.115	0.551	-0.098	0.672
T.Bil (mg/dl)	-0.168	0.480	-0.033	0.820	-0.092	0.634	0.069	0.765
D.Bil (mg/dl)	-0.182	0.441	-0.069	0.640	-0.129	0.504	-0.011	0.962
Albumin (g/dl)	-0.008	0.975	0.044	0.759	-0.023	0.904	0.179	0.436
PT %	-0.292	0.212	0.118	0.413	-0.340	0.071	0.568	0.007
Glucose(mg/dl)	0.069	0.771	0.110	0.447	0.112	0.561	0.110	0.635
HB (g/dl)	0.171	0.472	-0.060	0.678	-0.026	0.894	-0.111	0.631
TSH (ng/dl)	-0.182	0.443	0.010	0.944	-0.026	0.894	0.035	0.879
Serum AFP (ng/ml)	0.128	0.592	-0.184	0.202	-0.250	0.191	-0.041	0.859
Creatinine (mg/dl)	-0.014	0.952	-0.034	0.815	0.37	0.850	-0.144	0.534

HCV RNA (Viral load copies/IU/L)	-	-	0.278	0.050	0.295	0.120	0.231	0.314
Stage of fibrosis	-	-	0.146	0.313	0.273	0.153	-0.049	0.832
Necroinflammatory activity index (HAI)	-	-	0.273	0.055	0.320	0.091	0.245	0.285

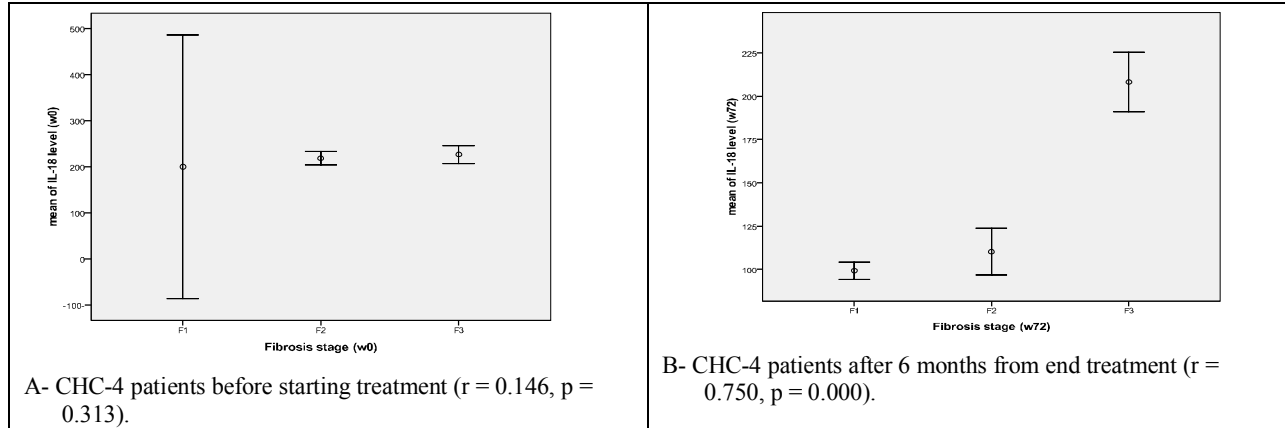


Figure1: Correlation between IL- 18 and Stage of fibrosis in CHC-4 patients

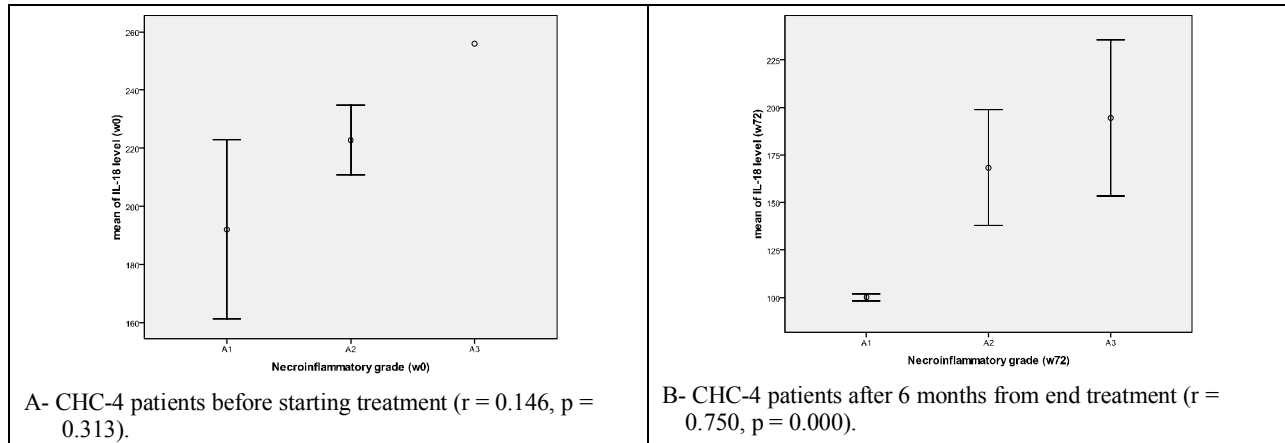


Figure2: Correlation between IL- 18 and Necro-inflammatory activity index in CHC-4 patients

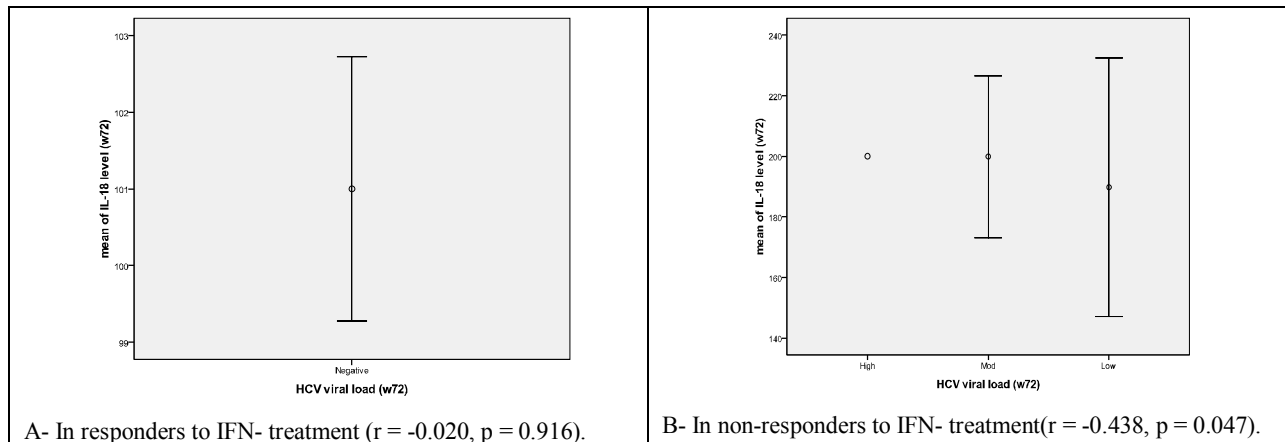


Figure3: Correlation between IL- 18 and HCV viral load and response to antiviral therapy

4. Discussion

IL-18 has been reported by previous studies as a marker in HCC with others cytokines ⁽¹⁶⁾. In the current study, it has been used as a predictor to the

outcome of PEG-IFN and ribavirin therapy in chronic hepatitis C patients, where measuring of IL-18 level has been performed in those patients before treatment and after 6 months from end of treatment (week 72). We analyzed its association with outcome of PEG interferon and ribavirin therapy hoping to find biological marker that might be used in predicting antiviral therapy response.

Our results showed that IL-18 level was higher in patients with HCV infection than in control participants, in accordance with Sharma *et al.*⁽⁹⁾, and Yoneda *et al.*⁽⁴⁾. In addition, IL-18 showed a marked reduction after 6 months from the end of treatment. Previous reports have demonstrated upregulated levels of IL-18 in CHC genotype 1 and 4 infected patients and its correlation with hepatic injury. McGunniess *et al.*⁽¹⁷⁾ have demonstrated chemo-attractant properties of IL-18 (IL-1 β , MIP-1 β), mediating upregulation of TH1 associated IL-2 and IFN γ and down regulation of TH2 cytokine 10. This indicates its proinflammatory role in the course of hepatic impairment in CHC patients and its key role in disease pathogenesis. Ludwiczek *et al.*⁽¹⁸⁾ have reported that plasma level of IL-18 was significantly higher in cirrhotic than non cirrhotic HCV patients.

In accordance with a study performed by Schvoerer *et al.*⁽¹⁹⁾ who observed that IL-18 level was significantly correlated with hepatic histologic activity, our results showed such correlation but without significant difference. This may be due to small sample size which influenced statistical analysis.

As regards response to interferon treatment, it has been demonstrated that IL-18 levels were significantly higher at baseline in CHC genotype 1 infected patients who achieved a SVR than those who did not⁽⁴⁾. This was in agreement with our findings for CHC genotype 4 infected patients, indicating no relationship between HCV genotypes 1 or 4 and IL-18 production. Moreover, it has been reported that high levels of IL-18 is one of the independent factors related to SVR in patients treated with PEG-IFN and ribavirin⁽⁴⁾. This was also confirmed by Abiru and his colleagues⁽¹⁶⁾ who stated that cirrhotic patients with low levels of IL-18 may progress to HCC, suggesting that IL-18 could be tested as a prognostic marker for cirrhotic patients who are likely to develop HCC. Such previous studies may support our results which have shown significant decrease in IL-18 level of responders compared with non-responders, suggesting positive correlation between IL-18 level and response to antiviral therapy.

In addition, Marin-Serrano and his colleagues⁽²⁰⁾ have reported that there was a significant decrease in IL-18 levels in both responders and non responders

after 6 months from end of treatment, with no difference in the decrease of cytokine level between the two groups. In this context, several issues should be mentioned before explaining such contradictory results; first, there is a favorable effect of interferon treatment on reducing this cytokine and its detrimental effect on histologic damage such as necroinflammatory activity and fibrosis index irrespective of viral effect. Thus, IL-18 cytokine should be a target for therapeutic interventions to reduce liver damage in CHC patients. Second, decreased levels of IL-18 could be caused by negative feedback regulation through parallel increase in IL-18BP or receptors resulting in impairment of its bioactivity and then associated with progression of disease. Third, differential production of IL-18 during various stages of HCV infection could also be a result of polymorphism in the regulatory gene of IL-18. These polymorphisms may be associated with protection against or susceptibility to infections. Fourth, precise cellular and molecular mechanisms and mediators underlying the liver damage and also protective antiviral effect may differ. Thus the relationship among genotype, IL-18 production and HCV progression warrants further study. In addition to all previous factors other cytokines like IL-12 synergize the role of IL-18, in promoting Th1-mediated immune response and viral eradication.

Sharma *et al.*⁽⁹⁾ stated that during early and asymptomatic stage of infection, decreased levels of IL-18 may stimulate and maintain high levels of HCV virions, resulting in persistence. During later stage of infection, an increase in IL-18 might result in prevention of progression to end-stage of liver disease. This was explained by ability of IL-18 to modulate the viability of the cells by increasing Fas-mediated apoptosis of infected hepatocytes, supporting HCV replication, favoring their elimination and dissemination of the viral particles. This mechanism is inhibited by core protein of HCV in persistent infection. Therefore, we suggest that our non responders with high and moderate viral load and high level of IL-18 are at higher risk for HCC development.

Regarding liver function tests, our results showed significant decrease in AST levels in responders than in non responders. This goes well with Yoneda *et al.*⁽⁴⁾ who found that AST is one of the independent factors related to SVR. As regards correlation between AST and ALT levels with IL-18 level, our results was consistent with Sharma *et al.*⁽⁹⁾, which didn't show any association between IL-18 level and ALT or AST values in responders and non responders. Also, in accordance with Mohran *et al.*⁽²¹⁾ no correlation was observed between IL-18 level

and T.Bil, D.Bil., and albumin but significant correlation was observed between prothrombin activity and IL-18 in responders and non responders.

Our results showed also significant increase in AFP in CHC patients compared to controls and this was in agreement with previous reports done by Hamouda *et al.* ⁽²²⁾, Tamura, *et al.* ⁽²³⁾, and Mohran *et al.* ⁽²¹⁾

Regarding TSH level, it has been demonstrated that the most common complications of IFN α therapy for chronic hepatitis C infection is interferon induced thyroiditis (IIT) by necrosis not by apoptosis mechanism. Also, HCV infection itself contributes to the initiation of thyroid autoimmunity ⁽²⁴⁾. Therefore, all patients were subjected to routine thyroid screening. Our results showed significant increase in TSH level after 6 months from end of treatment, but no correlation was observed between IL-18 and this variable in responders and non responders. Previous studies have shown a wide variation of thyroid dysfunction incidence in patients with CHC during and after IFN- α based therapy, at a rate of 2.5% to 35% in different countries ^(25,26). This variability can be attributed either to an underestimation of the true prevalence of thyroid dysfunction or to the diverse genetic predisposition of the subjects ⁽²⁷⁾.

Conclusion:

IL-18 level was seen to be elevated in CHC genotype 4 patients than in apparently healthy subjects. IL-18 was correlated with histological stages of the liver injury, but small sample size affect significant correlation. IL-18 level in responders was significantly reduced after 6 months from the end of treatment compared with those at baseline level, but such decrease was not significant in non responders. IL-18 level was positively correlated with high moderate viral load in non responders, indicating its correlation with pathogenesis of liver disease in the course of HCV infection.

Authors' contributions.

AAM developed plan and performed the research; WSM, performed statistical analysis, tabulated data and shared in editing process, SAL evaluated and edited draft manuscript, responsible for publication process, MA gathered clinical data and contributed in practical part and editing process and MMH contributed to analytical tools and supervising work.

All authors have read and approved the final manuscript

Competing interests

The authors declare that they have no competing interests

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Management of non-responder health care workers to hepatitis B routine vaccination

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Abstract: Introdoction: Hepatitis B comprises one of the major health problems worldwide. Health Care Workers (HCW) are a group at risk for Hepatitis B Virus (HBV) infection. The aim of this study is Management of non-responder health care workers to hepatitis B routine vaccination. **Methods:** In a descriptive-analytical study conducted in the Department of infectious diseases in the University Of Medical Sciences Of Tabriz, Non-responder cases of HCWs to HBV vaccination were studied and management. **Results and Conclusions:** 36.8% of HCWs were male and 63.3% of them were female. Mean age of male HCWs was 34.05 ± 8.58 year and in female HCWs was 30.43 ± 6.15 year ($P < 0.001$). Mean of Primary response antibody titer in male HCWs was 340.59 ± 205.15 IU/L and in female HCWs was 282.75 ± 194.22 IU/L ($P = 0.011$). Mean of Secondary response (after one booster dose) antibody titer in male HCWs was 388.52 ± 175.25 IU/L and in female HCWs was 357.81 ± 164.24 IU/L ($P = 0.110$). Non responder rate of HCWs for Routine vaccination (tree dose at 0,1 and 6 months) was 31(9.36%). Non responder rate of HCWs after one booster dose vaccination (after tree dose at 0,1 and 6 months) was 7(2.11%). Non responder rate of HCWs for secondary tree time (with double dose) vaccination (after tree dose at 0,1 and 6 months \pm one booster dose vaccination) was 2(0.6%). This method seems best suited for routine immunization of people who give inappropriate response to routine vaccination. Those who did not respond to this method too, are recommended to be excluded from high risk activities in terms of exposure such as needle stick, and in case of any possible exposure, HBIG should be applied.

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Keywords: Hepatitis B Vaccines; Immunization; Vaccination; Non-responder; Booster Dose; Health Care Workers

1. Introduction

Viral hepatitis is one of the major occupational diseases among health care workers. Therefore, the only way to control the infection is application of necessary conditions to sterilize instruments, use of disposable gloves and needles, and vaccination of hospital staff to prevent the contamination (Hassel Horn, 1997).

Healthcare workers (HCWs) are more at risk of acquiring infection from their patients or transmitting various infections among their patients, or transferring their own infections to the patients. Acquisition of some of these infections causes severe illnesses, chronic diseases or hazardous complications (Jaggar, 2002; Ross, 2002). In order to reduce the mentioned transmission ways, the strict application of standard methods for preventing transmission of infection between patients and staff (HCWs) and their appropriate immunization has been recommended (Beltrami, 2000; Gerberding, 1995; Averhoff, 1998; Mahoney, 1999).

In medical-health centers, transmission of infection occurs through direct contact with blood or body fluids (surgery, laboratory staff, etc.), blood transfusion and hemodialysis (Zanetti, 2001; Koff, 2002; Williams, 2001; Brotherton, 2003).

In case of HCWs, occupational exposure is a constant and real concern, and this risk is higher in the starting years of this profession.

Incidence of new infections of HBV among HCWs has been reported 1% per year (Zimmeraman, 2003). The risk of transmission of HBV is 2,400 cases in every 1,000,000 surgeries, which is a high figure compared to HVC (140 per million) and HIV (24 million) (Koziol and Henderson, 1996). The risk of transmission of HBV from HCWs to the people is high as well (Hasselhorn and Hofmann, 2000).

Unlike HIV and hepatitis C, transmission of HBV can be prevented by vaccination (Roggendorf and Viazov, 2003). This effective and safe vaccine was introduced and approved in 1981 (Williams, 2001) and released in 1982 (Duclos, 2003).

Since 1991, injection of this vaccine in health centers became compulsory by WHO and other international organizations (Kane, 2000). This vaccine injected into the deltoid muscle in three doses and in months 0, 1 and 6 respectively (Kane, 2000), and over 95% of the recipients give a proper response to the vaccine (Roggendorf and Viazov, 2003). With HBV vaccination, percentage of carriers has been reduced from 15-20% to 1% (Duclos, 2003).

Regarding the wide range of HBV infection in the world, its serious complications and the high cost of treatment due to infection, the prevention of disease is inevitable.

As recommended by WHO, the groups at high risk, including HCWs, should be vaccinated against HBV.

After vaccination, antibodies against HBV are produced in the blood. Amount of the secreted antibodies in the blood depends on the number of vaccine doses and the rate of immune response of the body to the vaccine (Alavian, 2006).

When the antibody titer falls below 10 Miu/ml, people get susceptible, and there is a possibility that they get infected by HBV despite previous vaccination. Therefore, serologic examination of HBs Ab and determination of antibody levels at regular intervals is essential in HCWs, and in case of reduction of antibody titer, a booster dose of HBV vaccine should be administered (Marchou, 1995).

In this study, we were to evaluate the response rate of HCWs to HBV vaccination in cases with inappropriate response in terms of response to the booster dose and double dose revaccination.

2. Material and Methods

In a descriptive-analytical study conducted in the Department of infectious diseases in the University Of Medical Sciences Of Tabriz, Non-responder cases of HCWs to HBV vaccination were studied and management.

The studied HCWs are vaccinated by hepatitis B vaccine with following properties (entitled EUVAX B, met the WHO requirements, made in Korea, LG life sciences company) for three doses (0, 1 and 6 months) and antibody was titrated three months after vaccination. All utilized vaccines were from one brand and all tests were performed in one laboratory.

ELISA test was used to evaluate the samples used kit in this study was the Anti-HBs kit, made by ROCHE Company entitled "COBAS". Methods of this kit was ELISA, in which ELISA micro plates in this method ELISA micro plates are covered by antigen S so that after adding serum containing antibodies against antigen S, antigens would bind with antibodies. In the next step, antigen S conjugated with peroxidase enzyme is added which attaches to the part of the antibodies not bound to antigens. Later, adding chromogene and substrate dyes the solution whose color can be read by ELISA reader.

After performing tests and reading the plates by ELISA reader, standard curves were provided using standard samples. Later using these curves, the concentration of antibodies in the tested sample were calculated. Based on the instructions of the kit manufacturer, antibody level less than 10 units per mL

was considered negative and amounts higher as positive.

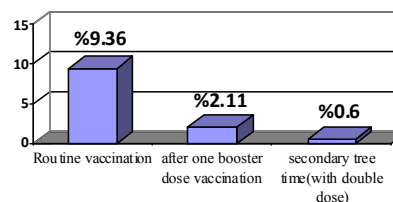
In this study, HCWs vaccinated routinely 3 times during the past 5 years on schedule (6-1-0) with negative HBcAB and HBsAg titers were studied in terms of HBsAB.

In this study, 331 HCWs were studied and those with inadequate HBsAb titers (under 10) were selected. These HCWs received a booster dose of HBV vaccine and were studied again 3 to 6 months later in the same laboratory in terms of HBsAb titers.

In this study, seven HCWs under study still had inadequate HBsAb titers. These people underwent 3-times double dose subcutaneous revaccination and 6 months after vaccination, their HBsAb titers were evaluated.

3. Results

122(36.8%) of HCWs were male and 209(63.3%) of them were female. Mean age of male HCWs was 34.05 ± 8.58 year and in female HCWs was 30.43 ± 6.15 year ($P < 0.001$). Mean of Primary response antibody titer in male HCWs was 340.59 ± 205.15 IU/L and in female HCWs was 282.75 ± 194.22 IU/L. Mean of Primary response antibody titer in male was significantly higher than female HCWs ($P = 0.011$). Mean of Secondary response (after one booster dose) antibody titer in male HCWs was 388.52 ± 175.25 IU/L and in female HCWs was 357.81 ± 164.24 IU/L.



Significant difference was not found in Secondary response (after one booster dose) antibody titer between two gender ($P = 0.110$)

Chart 1. Non Responder Rate of HCWS at tree stage of Vaccination

Non responder rate of HCWs for Routine vaccination (tree dose at 0, 1 and 6 months) was 31(9.36%). Non responder rate of HCWs after one booster dose vaccination (after tree dose at 0, 1 and 6 months) was 7(2.11%). Non responder rate of HCWs for secondary tree time (with double dose) vaccination (after tree dose at 0,1 and 6 months \pm one booster dose vaccination) was 2(0.6%) (Chart 1).

Evaluation of Age, Height and Weight of HCW based on primary response antibody titer were shown in table 1. Evaluation of response to Vaccination based on Gender, Smoking and Hyperlipidemia were shown in table 2.

Table 1. Evaluation of Age, Height and Weight of HCW based on primary response antibody titer.

	Primary Response			P
	Good Responders	Low Responders	Non Responders	
Age(Year)	31.32 ± 7.02	32.65 ± 7.96	33.71 ± 8.51	0.146
Height(m)	1.64 ± .08	1.64 ± .07	1.65 ± .08	0.906
Weight(Kg)	66.28 ± 12.79	67.75 ± 14.02	69.48 ± 11.96	0.365

Table 2. Evaluation of response to Vaccination based on Gender, Smoking and Hyperlipidemia

		Sex		P	Smoking		P	Hyperlipidemia		P
		Male	Female		Yes	No		Yes	No	
		Primary Response	Non Responders		10	21		0.158	4	
	Low Responders	15	37	3	49	6	46			
	Good Responders	97	151		9	239		30	218	
Secondary response (after one booster dose)	Non Responders	3	4	0.123	2	5	<0.001	2	5	0.601
	Low Responders	4	1		2	3		0	5	
	Good Responders	115	204		12	307		38	281	

4. Discussions

In the study of Hofmann et al, 2% of female and 1.5% of male vaccinees did not develop anti Hbs and 4.8% and 7.1% respectively were low responders (anti Hbs <100 <10 IU / l) (Hofmann, 1997).

In our study, out of 31 Non-Responder HCWs in the first stage, 10 patients (32%) were male and 21 (68%) were female, that in this study, non-responsiveness was higher among females.

Ramos et al showed that 2 to 10% of healthy adults do not respond to vaccination by producing protective levels of antibody anti-HBs (assumed as protective, concentrations of ab. Anti-HBs > 10 UI / L) (Ramos, 2000).

It is unclear whether booster vaccination of non-responders offers higher anti-HBs seroconversion, and hepatitis B vaccine prevents the infection of hepatitis B mutants in healthcare workers (Chen and Gluud, 2005).

In the study of Valats et al, Up to 20% of healthcare workers are considered as non-responders to hepatitis B vaccination (anti-HBs <10 m UI/ml in serum) (Valats, 2010).

In our study, 36/9% of the cases under study were Non-Responders, similar to the results of above mentioned study.

Chlíbek et al show that the immune response decreases with increasing age (Chlíbek, 2007).

In the study of Zeeshan et al, the percentage of non responders increased gradually from 9% in participants under 25, 13% in 25-34, 26% in 35-49, and 63% in ≥50 years of age (Zeeshan, 2007).

HBsAb titer in study cases was reduced by increasing weight; however, this relationship was not statistically significant. As well, mean age of the study cases was higher than the others, and this difference was not significant.

Chlíbek et al demonstrated that males achieved lower geometric mean titres (GMT) of

antibodies and lower seroprotectivity rates compared to females (Chlíbek, 2007).

In the study of Zeeshan et al, male non-responders were more frequent (18%) than female ones (8%) (Zeeshan, 2007).

In our study, the rate of non-responsiveness in females was higher than in males, and after administration of the booster dose, this rate in females was higher than in males under study.

Cardell et al demonstrated that the seroconversion rate of protective anti-HBs level was 68% after 3 doses and 89% after 3 or 4 doses (Cardell, 1999).

In our study, the Good Responders after administration of 3 and 4 doses of vaccine were 74.9% and 96.4% respectively.

Factors associated with a lower response rate in the study of Cardell et al were increasing age (p <0.05) and smoking (p <0.001) (Cardell, 1999).

In our study, although the level of antibody titer in smokers was lower than in non-smokers, this difference was not statistically significant.

Alerany et al showed that age is the variable most closely linked to the risk of a poor immunological response (Alerany, 1993).

Yen et al demonstrated that being male, age under 40 years and positive anti-HBc are associated with non-responsiveness to HB vaccination (Yen, 2005).

Immunized workers were more protected against HBV infection than non-immunized workers, indicating that HBV vaccine was a useful measure for protection against the infection (Nagao, 2008).

Conclusions

This method seems best suited for routine immunization of people who give inappropriate response to routine vaccination.

Those who did not respond to this method too, are recommended to be excluded from high risk activities

in terms of exposure such as needle stick, and in case of any possible exposure, HBIG should be applied.

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Thyroid Storm with Rare Cardiac Presentations, 10 Year-Intensive Care Unit Experience: Case SeriesWaleed Albaker¹, Yousef Almubarak¹, Amar H. Khamis²1: Department of Internal Medicine, 2: Department of Family & Community Medicine, College of Medicine, University of Dammam, Saudi Arabia. dr_waleed99@hotmail.com

Abstract: Thyroid storm causes serious alterations in cardiac parameters. These include an increase in resting heart rate, myocardial contractility and a predisposition to arrhythmias. As the result, most patients with thyroid storm experienced cardiovascular manifestations. The most common arrhythmia is atrial fibrillation and supraventricular tachycardia, however, ventricular arrhythmia, pulmonary hypertension and right side heart failure have been rarely reported in the literatures. In this report, we have reviewed 7 cases of thyroid storm patients with rare cardiac manifestations.

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Key words: Thyroid storm, Heart failure, Arrhythmia

INTRODUCTION:

Cardiovascular manifestations of thyroid storm are well known documented facts in literatures. The most common arrhythmia is atrial fibrillation and supraventricular tachycardia; however, ventricular arrhythmia, pulmonary hypertension and right side heart failure have been rarely reported in the literatures. In this report, we have reviewed 7 cases of severe thyroid storm patients who presented to our intensive care unit at university hospital with rare cardiac presentation (Table 1).

Case 1: A previously healthy 37 years old lady presented to King Fahd hospital of university in august 2012 with palpitation and bilateral lower limbs swelling. She also reported weight loss of 15 kg over past 4 months and heat intolerance. On physical examination, she had tachycardia, elevated jugular venous pressure 15+, right exophthalmos, goiter, chest auscultation revealed bilateral basal crepitations up to midzone and bilateral legs swelling up to knees. A Chest X-ray showed cardiomegaly with pulmonary edema. Electrocardiography showed atrial fibrillation at rate of 180/min. 1 hours after presentation, she developed cardiac arrest for 2 minutes with ventricular fibrillation. She was intubated and received electrical cardioversion and regained her A.F rhythm and was started on inotropic support for cardiac failure then transferred to ICU care. Her thyroid stimulating hormone level was suppressed <0.0025 uIU/ml (reference range 0.35-4.94) and free T4 was 3.24 ng/dl (reference range 0.7-1.48) and her free T3 was 9.91pg/ml (reference range 1.71-3.71). her anti thyroglobulin antibody was 105.78 IU/ml (reference positive level >4.1 IU/ml) and anti thyroid peroxidase > 1000 IU/ml (reference positive level >5.6 IU/ml). She was diagnosed with thyroid storm (Burch score was 85)¹ with acute

pulmonary edema and heart failure with fast rate A.F and received hydrocortisone, propranolol, propylthiouracil and logul'siodine.

A transthoracic echocardiogram revealed reduced ejection fraction (45%), septal hypokinesis, severe dilated left atrium, moderate dilated right ventricle and right atrium with severe mitral and tricuspid regurgitations as well as pulmonary hypertension (pulmonary artery pressure >70 mm hg).

By the 2nd day in ICU, she was off from inotropic support and by the 3rd day, she was extubated. She was kept on anti-thyroid medications only, and repeated echocardiogram within 1 week and 3 weeks showed continuous regression and normalization of her cardiac manifestation. By 3rd week, echocardiogram show normal systolic function, normal right ventricle size and normal pulmonary pressure with mild tricuspid and mitral regurgitation.

Case 2: A 40 years old male, who was diagnosed to have grave's disease for 6 months on treatment, presented with shortness of breath on exertion for the last 2 months associated with lower limb swelling. 3 days prior to presentation, his shortness of breath became even at rest associated with orthopnea and paroxysmal nocturnal dyspnea. On physical examination his temperature was 38.2°C and pulse of 110/min. He had elevated jugular venous pressure 16+, chest auscultation revealed bilateral basal crepitations, S3 gallop, distended abdomen with positive shifting dullness and lower limbs swelling. Chest X-ray showed pulmonary congestion. Echocardiogram showed dilated left ventricle with EF 40%, septal hypokinesis and dilated right ventricle with pulmonary artery pressure of >50 mm hg.

His thyroid stimulating hormone level was suppressed <0.0025 uIU/ml and free T4 was 5.23 ng/dl and her free T3 was 9.91pg/ml. He was

diagnosed with thyroid storm (Burch score 55) with acute heart failure and was started on neomercazole, beta blockers and steroid therapy in addition to diuretics. Patient conditions improved and a follow up echocardiogram showed normal left ventricle with EF 55%, normal right ventricle and normal pulmonary artery pressure of 25 mm hg.

Case 3: A 26 years old Indonesian housemaid was admitted to hospital in April 2010 with shortness of breath, palpitations and lower limb swelling for 2 weeks. She also had weight loss and neck swelling for 5 months durations. On admission, her temperature was 39°C, pulse was irregular 150 beats/min. She had jugular venous pressure 15+ with goiter, Variable S1 on heart auscultation with lower limb swelling up to knees. Her thyroid stimulating hormone level was suppressed <0.0025 uIU/ml and free T4 was >6 ng/dl and her free T3 was >30pg/ml. ECG was done and it showed fast rate atrial fibrillation, and her chest X-ray showed pulmonary congestion.

Echocardiogram showed normal left ventricle systolic function, moderate tricuspid regurgitation with dilated right ventricle and severe pulmonary hypertension > 70 mm hg. She was diagnosed with thyroid storm (Burch score 80) with acute isolated right side heart failure. She was admitted to intensive care unit and was started on propylthiouracil, propranolol and steroid therapy with anti heart failure medications. She improved clinically and was discharged home on anti-thyroid therapy.

Case 4: A 49 years old male who was diagnosed to have grave's disease and type 2 diabetes mellitus in June 2004. He was maintained on carbimazole 15mg TID and never achieved eu-thyroidism. He was found to have chronic atrial fibrillation and was maintained on warfarin.

In November 2005, he presented to emergency room with severe shortness of breath even at rest with orthopnea, paroxysmal nocturnal dyspnea and productive cough for one week. On examination, his temperature was 38.8°C, pulse irregular 160 beats/min, blood pressure 170/60, elevated jugular venous pressure 18+, bilateral crepitations of lung up to midzone and lower limb edema up to the middle of thighs. His thyroid stimulating hormone level was suppressed <0.0025 uIU/ml and free T4 was 5.06 ng/dl and her free T3 was 14.5pg/ml. His chest X-ray showed pulmonary edema and his ECG showed atrial fibrillation with rate 160 beats/min.

His echocardiogram showed severe dilated left ventricle with global hypo- hypokinesis, ejection fraction of 25%, moderate mitral regurgitation and moderate tricuspid regurgitation with severe pulmonary hypertension > 70 mm hg.

He was diagnosed thyroid storm with acute heart failure (Burch score 65), patient was started on non-invasive positive airway pressure, carbimazole, propranolol with anti-failure medication and was admitted to intensive care unit. At the same day of presentation, patient developed ventricular fibrillation and died.

Case 5: A previously healthy 42 years old male was brought to emergency room by his brother with severe respiratory distress. His complaint was shortness of breath with fever which started 2 days ago and became worse over the next day associated with cough and chest pain with palpitation. There was no weight loss, sweating other hyperthyroid symptoms.

On examination, he was in respiratory distress with rate of 38 breaths/min and cyanosis, O2 saturation was 80%, blood pressure 160/80, pulse of 145 beats/min and temperature of 38.7°C. His Chest examination revealed bilateral basal crepitations, jugular venous pressure of 18+, normal S1 with loud P2 in cardiac auscultation. His ECG showed sinus tachycardia and CXR show pulmonary edema. His Echocardiogram show moderate systolic dysfunction, severe mitral regurgitation, severe tricuspid regurgitation and pulmonary hypertension more (P.A. pressure > 50 mm hg).

He was intubated in the emergency room because of severe respiratory distress, started on diuretic treatment and anti-biotic with working diagnosis of acute heart failure with possible community acquired pneumonia. 2 days post intubation; his CXR and blood gases were improved but still had persistent tachycardia 140+ beats/min and had a trial of extubation. Post-extubation he became again in respiratory distress with severe tachycardia 160 beats/min and because of his persistent tachycardia, thyroid function test was requested. His thyroid stimulating hormone level was suppressed <0.0025 uIU/ml (reference range 0.35-4.94) and free T4 was 2.23 ng/dl (reference range 0.7-1.48) and her free T3 was 4.81 pg/ml ((reference range 1.71-3.71).

Subsequently, he was diagnosed with thyroid storm (Burch Score 85) with acute biventricular heart failure. He received anti-thyroid treatment with anti-failure management and improved clinically and was discharged home.

Case 6: A 39 years old male presented with history of proximal muscle weakness, palpitation and shortness of breath on mild exertion for 2 weeks durations and diffuse abdominal pain for 2 days. He has positive history of weight loss > 45kg in last 3 months, heat intolerance and profuse sweating for 6 months.

Table 1. Cases

	Case 1	Case 2	Case 3	Case 4	Case 5	Case 6	Case 7
Gender	female	Male	Female	male	Male	Male	Female
Clinical presentation	Cardiac arrest	Heart failure	Right side heart failure	Heart failure	Heart failure	Hyperthyroid symptoms	Hyperthyroid symptoms
Thyroid storm score	85	55	80	65	85	30	45
TSH	< 0.0025	<0.0025	<0.0025	<0.0025	<0.0025	<0.0025	<0.0025
Free T3	9.9	>30	>30	14.5	4.81	>30	>30
Free T4	3.24	5.23	>6	5.06	2.23	4.3	4.7
Management	PTU, Steroid, BB and loguls's	Neomercazole, BB and anti-failure	PTU, Steroid and BB	Neomercazole BB and anti-failure	PTU, Steroid, BB and loguls's	Neomercazole, BB	PTU, Steroid, BB and loguls's
ECG	A.F + V.F	A.F	A.F	A.F + V.F	Sinus tachycardia	Sinus tachycardia	SVT/ P.pulmonale
Echo	EF45%, sever MR+TR	EF45%, dilated LV+RV	EF55% dilated RV with T.R	EF25% global hypokinesia, severe dilated LV	EF 45% sever MR+TR	Normal 70%, dilated RV with severe TR	EF 60% ,dilated RV with TR
P.A. Pressure	>70	>50	>70	>60	>50	40	>60
Euthyroid status	Achieved	Achieved	Achieved	Not achieved	Achieved	Not achieved	Achieved
Repeated Echo	EF65%,mild MR+TR Normal P.A.P	EF 60% normal Pul. pressure					
Outcome	Survive	Survive	Survive	death	Survive	Survive, lost F/U	Survive

On examination, he was agitated, his temperature 38.3°C, pulse regular 130 beats/min, resting tremors, exophthalmos, diffuse enlarged goiter and heart auscultation of normal S1 with loud P2. His thyroid stimulating hormone level was suppressed <0.0025 uIU/ml and free T4 was 4.3 ng/dl and her free T3 was >30pg/ml.

Echocardiogram showed normal systolic function, dilated right ventricle, severe tricuspid regurgitation with pulmonary hypertension > 45 mm hg.

He was diagnosed with thyroid storm with acute isolated right side heart failure. He was started on carbimazole, inderal and steroid with clinical and echocardiographic improvement.

Case 7: A 27 years old office secretary lady with previous diagnosis of grave's disease for 4 years. She presented to our emergency department after 2 weeks of being out of medicine (neomercazole). She was in severe respiratory distress, abdominal pain and palpitation which started 3 days ago and increased in severity. On examination, she was agitated in respiratory distress 30 breaths/min with regular tachycardia 150 beats/min, jugular venous pressure 10+ cm, clear chest auscultation with loud P2 with normal S1 in heart auscultation. Generalized abdominal tenderness with pulsatile hepatomegaly and lower limb edema up to knees.

Her initial ECG show supra-ventricular tachycardia and after 2h of presentation it showed sinus tachycardia with P pulmonale. Echocardiogram showed normal systolic function with dilated right ventricle, severe tricuspid regurgitation and pulmonary hypertension >60 mm hg.

Her thyroid stimulating hormone level was suppressed <0.0025 uIU/ml and free T4 was 4.7 ng/dl and her free T3 was >30 pg/ml. She was diagnosed with thyroid storm (Burch score 45) with evidence of right side heart failure. She was managed with propylthiouracil, Inderal, steroid and loguil's iodine. She was improved clinically and echocardiographically in anti-thyroid medication only.

DISCUSSION:

In this review, 4 out of 7 cases presented with atrial fibrillation and one with SVT. The most common clinical presentation of thyrotoxic heart disease is atrial fibrillation. Case 1 and case 4 presented with ventricular fibrillation which is extremely rare and serious arrhythmic complication of thyroid storm. Up to our knowledge, 3 reported cases in the literatures presented with ventricular arrhythmia as initial presentation of thyroid storm.² Few hypothesis were postulated including thyrotoxic periodic paralysis with severe hypokalemia,^{3,4} coronary spasm⁵, QT interval prolongation,⁶ and systolic dysfunction.

In term of heart failure, 4 out of 7 cases presented with left sided heart failure. Based on clinical and echocardiographic presentation, all patients had complete recovery of systolic function with anti-thyroid medications. High output heart failure is well documented to the literatures, especially in those with severe long standing untreated hyperthyroid.⁷ Isolated right sided heart failure secondary to thyroid storm has been rarely reported in the literatures.^{8,9} In our review case 3,6,7 presented with isolated right sided heart failure.

Pulmonary hypertension secondary to thyroid storm was reported in all our cases. A limited numbers of observational studies have documented the prevalence of pulmonary hypertension to range 41-65%. The largest observational study by Marvisi et al, evaluated 114 patients with hyperthyroidism and found mild pulmonary hypertension in 43% and no cases of pulmonary hypertension in control group.¹⁰ In our review all patients with thyroid storm had severe pulmonary hypertension which reversed completely in 6 cases following anti-thyroid medications. One of the strong hypothesis have been postulated that auto-immunity is a major contributor to pulmonary hypertension and right sided heart failure.¹¹

Conclusion:

The most common presentation of thyrotoxic heart disease is atrial fibrillation and high output heart failure. However, other rare cardiac presentations can occur including ventricular arrhythmias, isolated right side heart failure and pulmonary hypertension. Internist should be aware of this association and reversibility with anti-thyroid medications. We advised to conduct large study of thyroid storm presentations in intensive care units and estimate true prevalence and nature history.

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Social and political concepts in the poetry of female sonneteers in the constitutional era

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Abstract: The sonnet is a poetic form that in the constitutional era not only expressed the feelings and emotions of the poet but was also used to direct their political and social aspirations. Many poets, including women, played a role and achieved fame. Despite the small number of these poets and the minimal effect on constitutional revolution, they spoke about their social goals, fought injustice and for the restoration of lost rights, and made great strides in social movements. The most famous women sonneteers were Fatemeh Soltan Farahani, Nimtaj Salmasi, Shams Kasmaie, and Fakhr Azmi Arghon.

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Keywords: Woman, Socio political poetry, Constitutional era, Sonnet

1. Introduction

Looking at the history of Iranian literature, we can see that the most brilliant and glorious moments are embodied in the Persian sonnet, and the most brilliant minds in the history of our literature have expressed themselves in this form. Needless to say, Sadi, Hafez, and Molavi are the greatest poets in the literary world. They are considered the greatest Persian sonneteers. Let's not forget that poem is the most important and most basic element of Persian culture. The sonnet is the foundation of Persian poetry, which is often known for its pure and beautiful sonnets. The sonnet appears in Ghanaian literature. Its subject is only itself, and it is the best format for this type of literary expression (1). The style and purpose of the sonnet was unchanged until Shahrivar 1281 (1902). Another kind of sonnet was at the service of society and political issues but gradually left with the field of poetry in relative comfort. The effect of the Persian poem can be seen in sonnet. Special words were used in sonnet to express concepts. The sonnet fell from its splendor and elegance. There were no splendors in the sonnets of 13th-century poets, such as Neshat Esfahani, Foroughi Bastami, etc. (2). A constitutional poem reflects social aspirations, including freedom, patriotism and anti-colonial modernity, justice and equality, of the Iranian people suppressed in that period. The poets of this period allowed themselves to utilize words from a small word circle used thousands of years ago (3). During the first constitutional realm, poems were used daily in the press. Humor and lyrics and political sonnets were prevalent during this period. In this period, the shadows of the return poem were not clear, and the modern day was not available. Many scholars and poets were caught in limbo (4). The revealing poetic expression of the constitution brought to mind

language on social issues, through decline and degeneracy. It lacked deep poetic understanding. But it indirectly caused a lesson in awareness and consciousness of social poets of the next decade (4).

Committed poetry is used to protest and criticize. Criticism is rooted in social and political issues, often with suffering thoughts and aspirations of the lower classes. Committed literature claims it can help all or part of the community reach its goals, such as eliminating discrimination, achieving freedom, and even some political goals. For those who know commitment as a principle, beauty that does not bring any benefit to people is a useless beauty. This is exactly the idea that the poets of social symbolism adhered to in 30-50th decades (1330-1350 Hijri Shamsi calendar) (5). Social-political concepts of the sonnet were Iranian love, fight with Hijab, fight against foreign domination, liberalism, republicanism, and sometimes an invitation to a rebellious movement.

2. Criticism in the poetry of sonneteer women

The social-political history of Iran cannot exist without women; their presence in Persian literature has not been obvious. Iranian women have a deep connection to poetry. The image of women portrayed in patriarchal culture is not real. They lived for centuries under the domination of men, but over time, changes were created politically - which had an effect on women. Man's changing vision expedited the movement. Women who were not aware of political-social movements tried to move quickly to be consistent with the new literature. Those who were in solitude and unseen because of their tradition and culture and had limitations because of their beliefs, decided to become aware of everything with the changing political situation in the constitutional era. They looked at the facts surrounding them and tried

to gain new experiences in the constitutional era (6). The ancient literature of Iran is very manly, and the voice is thick. We have thousands of men poets and only a handful of women poets. Women have been so behind that even the two of them had pseudonyms "Mastoor" and "Makhfi." The situation is even worse in humor. We have some women poets such as "Rabea" and "Mahasti," "Jahan Khatoon," "Ghorratol ain" but there are no female humor columnists. In Rabea and Mahasti poems there is humorous lyricism. And there is a social satire in the lyrics, "Zhale Ghaem Maghami" and "Parvin Etesami." All of them are related to poetic literature but not related to prose literature (7).

Fateme sultan Farahani, who was the sister of Adibolmamalek and the descendant of Ghaem Magham Farahani, is one female poet who belongs to the Ghajar period. Etemadossaltane reports in the book Khairat Hesan that she was so prolific in Arabic literature, history, and Persian poems at that were held in the same esteem as famous Arab poets. She tried to introduce the women in public life and show their place in social life. Before the constitutional revolution, women did not have a real identity in the Persian poetry. However, Alamtaj Ghaemmaghami (Zhale) expressed their pain despite the silence of other women poets in those conditions.

She expressed her real emotions, feelings, and imagination. Zhaleh asked for a change in the treatment of women. She asked women to start a revolution and gain their own freedom. Zhaleh, for the first time, spoke about women in all her poems, and her feelings, bad or good, came from her female mind (8). She was young in the constitutional era, and her poems are the most unique in literary history to offer a gender perspective. She is from a turbulent period of social-political history of Iran, and a woman of great self-esteem. She described her feminine self instead of repeating concepts (9).

Shams Kasmaie is another poet of this era. She was a liberated, independent-minded woman. She had a fresh mind and a diverse approach to the classic poem. But she did not follow the new method. She was the first woman to picture her potential in a modern structure (10). In her first poem, the content is not repeated. The poet tries to introduce the poem with a special attitude. She tried to start a literary revolution. Unfortunately, Kasmaie did not follow her own experiences. Because we lost her book, few of her poems exist (10).

Mehrtaaj Rakhshan (Badroddoja) was a pioneer in the women's movement and established schools for girls. She wrote poems about women and freedom (10). Nimtaj Salmasi, the most famous poet, wrote poems on social criticism, and she advocated the most revolutionary ideas. This was the first shout

of the woman who wanted to make government aware of the conditions. There are two social-political sonnets from Nimtaj, and they are critical. They are a reflection of social-political issues of that society. Sonnet "Kaveh" is one of her most famous poems, which she wrote before Reza shah (11).

Fakhr Ozma Arghan is one of the most famous women poets and the mother of Simin Behbahani. She was one of the most successful women in her time. She was the editor of Future of Iran and publisher of the magazine Banovan. She was the most active member of the women's center and a member of the Democratic Party. She established many schools for girls. She had some objections about the two genders and some people said she as an "artist of progressive and critical social issues and political themes." In fact, she had some traditional ideas about women.

Fasl Bahar khaanoom (also known as Jannat) was known as Iran dole and her pseudonym was Jannat. She was a 13th-century poet. She had a literary taste and managed to enter the Poets Gathering with the help of her husband. Her house was a meeting place for the Poets Gathering. The important poets of that period gathered in her house to discuss and negotiate. At these gatherings, her poems became famous, and some of them were published in magazines such as Armaghan and Gol-e-zard.

Badri Tondari was a very educated poet. She knew French and Arabic and traveled to European countries. She knew her country was undeveloped and lost. She thought so much about the fate of women in her country and tried to make women in her country educated and literate (9). By looking at poems of women in earlier centuries, classic or traditional, discrete or free, we can see that now women are moving alongside men and their voice is the voice of all human beings. Those people have suffered (8).

4. Conclusion

Women poets, especially after the constitutional era, wrote poems about social and political issues, and some were critical. Most of these women established schools and magazines and participated in political parties. Although they had some limitations in their lives, they proved they could shout justice, freedom, and equality whenever they wanted. These women created social movements for the following generations.

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Searching Candida species in hands of students Qazvin University of Medical Sciences

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Abstract: Background: Candida species are major pathogenic in immunocompromised patients that can be present on all medical personnel and find it in infect hands that may be transferred to patients and even can cause their death. **Objective:** This study aimed at the isolation of Candida species from different fields were medical students. **Methods:** This descriptive study was performed duration 6 months from October 2010 to March 2011. In total 385 students from different fields were sampled. Samples on Sabouraud dextrose agar medium with Chloramphenicol were cultured. Candida species were identified by Corn meal agar medium, Chromagar absorbing and different carbohydrates were used. **Results:** 116 out of 385 cases (30.2%) of the hand culture (of the candidates) were positive. The most common species isolated Candida albicans was 70 cases (60.3%). Many species of Candida from hands of nursing students, 17 (37.8%) were isolated. **Conclusion:** In different fields, hands of the medical students could be containing of candidate, worthy people before contact with immunocompromised patients, to wash their hands.

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1. Introduction

Candidiasis can occur in chronic, sub-acute or acute forms. It has different clinical signs and symptoms with causative agents including a wide spectrum of endogenous and exogenous species of Candida. Candida species are present in the environment and can colonize on the skin or catheters through contaminated instruments or devices or hand contacts.

Candida species can produce infections in a suitable setting including heat, moisture, burn, immune system deficiency, skin scratches, diabetes, leukemia or immune system suppressing drugs use. Candida species are among the most important causative agents of hospital acquired infections (Rippon, 1988).

Fotadar has conducted a study on probable role of German cockroach as a vector in transmission of fungi, and the most prevalent fungi isolated from cockroaches present in the hospital were Candida (Fotadar and Banerjee, 1992).

Hauer introduces pneumonia, bronchitis, UTI and septicemia as the most common hospital acquired infections in descending order and states that hospital acquired infections are most commonly seen among ICU patients, and this is because most ICU patients have debilitated immune system or use antibiotics (Hauer, 1996).

Alvarez considers long time stay in ICU, over 65 year's age, female gender and antibiotics use as influential in acquiring candiduria (Alvarez-Lerma, 2003).

Conteno has evaluated ICU ward air of Antonio hospital in Venezuela for presence of fungi and has isolated filament fungi like Aspergillus, Fusarium, Candida and ... from ICU ward air, and believes that the number of patients being inflicted with such fungi is on the rise (Conteno and Machado, 2004).

Wisplinghoff has conducted a study and stated that Candida species were an important cause of hematologic nosocomial infections and that had increased mortality rate in these patients significantly. In his investigation, average age of the patients was 52 years, their stay in the hospital before having positive blood culture was 21 days, and 57% of them were in ICU wards (Wisplinghoff, 2006).

Chakrabarti and Kumar conducted another study in Shandigar, India, in search of sources of hospital acquired infections in burn care unit of Nehru hospital. In this study, samples were taken from wounds of the patients and also from surrounding environment and their evaluation showed contaminations with fungi like Aspergillus, penicillium, fusarium, and black fungi and yeasts like Candida albicans, Candida tropicalis, Candida krusei, and Candida parapsilosis (Chakrabarti, 1992).

In the year 2010, Hernandez reported a spread of Candida parapsilosis in NICU of a hospital in Mexico which had caused fungemia in a number of those children. The same species were isolated from palms of therapeutic personnel in that ward, and sameness of both agents was approved through DNA analysis (Hernández-Castro, 2010).

In the year 2010, Gulia stated that candidemia of immune deficient patients developed through the hands of nurses was a non-deniable fact. He evaluated 233 cases of candidemia in a retrospective study and found that one fourth of those patients had got candidemia and hospital acquired infections through their nurses. *Candida glabrata* was the most prevalent agent acquired from their blood cultures (Gulia, 2010).

In the year 2007, Van Asbeck introduced neonatal fungemia as a result of contaminated hands of personnel in NICU ward of the hospital under his surveillance. He reported the *Candida parapsilosis* strains acquired from blood cultures and from hands of personnel to be the same through RFLP method. This study confirms other studies already carried out in this relationship (Van Asbeck, 2007).

In the year 2007, Tamura isolated 23 yeasts from catheters inside vessels and hands of personnel of the hospital under his surveillance and stated that the yeasts isolated from catheters were the same as those isolated from the hands of personnel (Tamura, 2007).

In the year 2005, Bonassoli evaluated the presence of yeasts on the hands of 86 hospital personnel and isolated them from 59.3% those people, *Candida parapsilosis* being the most prevalent species isolated. Colonization of these yeasts on the hands of hospital personnel results in sticking of them on plastic surfaces and increasing their risk of transmission to susceptible people (Bonassoli, 2005).

In the year 2001, Parry reported osteomyelitis with *Candida* after vertebral column surgery which had been developed due to presence of *Candida albicans* under artificial nail of OR technician. Fungi had been transferred to operation field and had caused infection. He proposes that OR personnel refrain from wearing artificial nails during operation (Parry, 2001).

In the year 1995, Pertowski reported some sternal wound infections with *Candida albicans* after open heart surgery due to contaminated hands of a nurse. The nurse in charge of changing dressings of the wounds of these patients had had recurrent vaginal infection with *Candida albicans* and had transmitted the infection to the patients through her contaminated hands (Pertowski, 1995).

Fungi are one of the most important factors in development of nosocomial infections, and always measures should be taken for destroying or reduction of population of them (Fotadar and Banerjee, 1992).

The present study has been carried out in Qazvin city of Iran due to importance of this issue.

2. Material and Methods

This is a cross-sectional study carried out in the last quarter of 2010 and the first quarter of 2011,

for 6 months, on 385 male and female students of different fields and different years of medical sciences university (including 75 nursing, 115 medicines, 130 health care and 65 dentistry students). These numbers are proportionate with the population size in each faculty.

Sampling was done through washing hands in 20 ml of brain heart infusion agar culture media placed in sterile nylon bags.

Then the bags were kept in 37 degree incubator for 5 days and afterwards, they were cultured on solid Sabouraud dextrose Agar containing chloramphenicol at mycology lab of faculty of medicine, and were kept at 25 degrees for 5 days for fungal growth.

Then, the grown fungi were identified through routine mycology procedures like using germ tube test, corn meal agar media plus tween 80, CHROM agar and sugar absorption media (api 20 aux). Data were collected in questionnaires and analyzed using descriptive statistic tools (tables, diagrams).

3. Results

From 385 students evaluated, 116 cases (30.2%) had at least one culture positive of the *Candida* species of their hands. Prevalence of positive cultures for *Candida* yeast from hands of the students of different fields of Qazvin medical sciences university were shown in table 1.

Table 1. Prevalence of positive cultures for *Candida* yeast from hands of the students of different fields of Qazvin medical sciences university

Study field	Number	Percent
Management	30	7.8%
Lab sciences	43	11.2%
Nursing	45	11.7%
Midwifery	33	8.6%
Medicine	68	17.7%
Health care	45	11.7%
Emergency	23	6%
Anesthesiology	24	6.2%
Dentistry	51	13.3%
Operating room	22	5.8%
Total	384	100%

Prevalence of *Candida* species isolated from hands of the students of Qazvin medical sciences university was shown in table 2.

From 145 male students evaluated, 45 cases (31%) had at least one culture positive *Candida* species of their hands, which was 29.7% in female students (table 3).

Table 2. Prevalence of *Candida* species isolated from hands of the students of Qazvin medical sciences university

Study field	Number	Percent
<i>Candida albicans</i>	70	60.3%
<i>Candida parapsilosis</i>	24	20.7%
<i>Candida tropicalis</i>	14	12.1%
<i>Candida krusei</i>	5	4.3%
<i>Candida glabrata</i>	3	2.6%
Total	116	100%

Candida albicans species was the most prevalent species isolated from the hands of male and female students, where 70 cases of the whole 116 positive cases (60.3%) belonged to this species (table 4), 74 cases of the whole 116 positive cases (63.8%) belonged to B.Sc. students (table 5).

Table 3. Distribution of evaluated students in accordance with presence of *Candida* yeast on the hands and gender

Presence of <i>Candida</i>	Yes	No	Total
Female	71(18.5%)	168(43.75%)	239(62.2%)
Male	45(11.72%)	100(26.04%)	145(27.8%)
Total	116(30.2%)	268(68.8%)	384(100%)

Table 4. Prevalence distribution of *Candida* species isolated from hands of the students according to gender

	Candida species					Total
	<i>Candida albicans</i>	<i>Candida parapsilosis</i>	<i>Candida tropicalis</i>	<i>Candida krusei</i>	<i>Candida glabrata</i>	
	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)
Female	43(37.6%)	15(12.9%)	8(6.9%)	3(2.6%)	2(1.7%)	71(61.2)
Male	27(23.3%)	9(7.7%)	6(5.2%)	2(1.7%)	1(0.9%)	45(38.8%)
Total	70(60.35%)	24(20.7%)	14(12.07%)	5(4.3%)	3(2.6%)	116(100%)

Table 5. Prevalence distribution of different *Candida* species isolated from hands of the students according to educational degree level

	Candida species					Total
	<i>Candida albicans</i>	<i>Candida parapsilosis</i>	<i>Candida tropicalis</i>	<i>Candida krusei</i>	<i>Candida glabrata</i>	
	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)
Associate degree	4(5.7%)	2(8.3%)	1(7.1)	0(0%)	0(0%)	7(6%)
B.Sc.	44(62.9%)	15(62%)	9(64.3%)	3(60%)	3(100%)	74(63.8%)
M.Sc.	3(4.3%)	0(0%)	0(0%)	0(0%)	0(0%)	3(2.6%)
Doctorate	19(27.1%)	7(29.2%)	4(28.6%)	2(40%)	0(0%)	32(27.6%)
Total	70(100)	24(100%)	14(100%)	5(100%)	3(100%)	-

Table 6. Prevalence distribution of different *Candida* species isolated from hands of the students according to educational study field

	Candida species					Total
	<i>Candida albicans</i>	<i>Candida parapsilosis</i>	<i>Candida tropicalis</i>	<i>Candida krusei</i>	<i>Candida glabrata</i>	
	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)	Number (%)
Management	5(7.2%)	2(8.3%)	1(7.1%)	0(0%)	0(0%)	8(6.9%)
Lab sciences	9(12.8%)	3(12.5%)	2(14.3%)	1(20%)	0(0%)	15(12.9%)
Nursing	10(14.4%)	4(16.6%)	2(14.3%)	1(20%)	0(0%)	17(14.7%)
Midwifery	7(10%)	3(12.5%)	0(0%)	0(0%)	2(66.7%)	12(10.3%)
Medicine	12(17.1%)	4(16.6%)	2(14.3%)	0(0%)	0(0%)	18(15.6%)
Health care	7(10%)	2(8.3%)	1(7.1%)	1(20%)	1(33.3%)	12(10.3%)
Emergency	4(5.7%)	1(4.2%)	1(7.1%)	1(20%)	0(0%)	7(6%)
Anesthesiology	4(5.7%)	1(4.2%)	2(14.3%)	0(0%)	0(0%)	7(6%)
Dentistry	8(11.4%)	3(12.5%)	2(14.3%)	1(20%)	0(0%)	14(12.1%)
Operating room	4(5.7%)	1(4.2%)	1(7.1%)	0(0%)	0(0%)	6(5%)
Total	70(100%)	24(100%)	14(100%)	5(100%)	3(100%)	-

From the whole 116 positive cases, 18 cases (15.6%) belonged to students of medicine (table 6). The highest rate of contamination belonged to nursing students with 37.8%, followed by midwifery students (36.4%), lab sciences (34.9%), medical emergency (30.4%), anesthesia (29.1%), dentistry (27.4%), operating room (27.2%), health care (26.7%), management (26.7%), and medicine (26.4%).

4. Discussion and conclusion

In this study, many *Candida* species were isolated from hands of the students of different fields, which can produce hospital acquired infections in susceptible people, and the most prevalent species of which was *Candida albicans*. In this study on the hands of nursing students, Bonassoli identified *Candida albicans* as the most prevalent species too (Bonassol and Svidzinski, 2002).

Candida albicans has been introduced as the most prevalent fungal species producing hospital acquired infections in the mentioned articles, which can be easily isolated from hands of ICU and surgery personnel. Presence of yeasts on the hands of these personnel is considered as the most important factor in development of hospital acquired infections.

In the study, 37.7% of nursing students had *Candida* yeasts on their hands; Orozco also stated that 32 percent of nursing students participating in his study had *Candida* yeasts on their hands (Orozco, 2009).

Candida parapsilosis was the second yeast isolated from hands of the students in our study, but Yildirin introduced it as the most prevalent *Candida* species found on the hands of hospital personnel under his surveillance (Yildirin, 2007).

Hernandez-Castro also introduced *Candida parapsilosis* as the most common *Candida* species found on the hands of hospital personnel under his surveillance (Hernandez-Castro, 2010).

Martins states that invasive Candidiasis in immune-deficient patients has been on rise in recent years and *Candida albicans* is still the most prevalent species found in fungemia, but infections caused from other non-*albicans* species in susceptible patients are also on rise. Treatment of infections with other non-*albicans* species is difficult due to their resistance against azoles, and they are associated with higher mortality rates.

Martins-Diniz repeatedly isolated yeasts from room door handles of newborns and adults (Martins-Diniz, 2005). In this study, hand washing in liquid Sabouraud dextrose media method was used, same method as used by Yildirin for detecting *Candida* on hands of hospital personnel under his surveillance (Yildirin, 2007).

Orozco also used the same method for isolation of *Candida* on hands of NICU nurses under his surveillance (Orozco, 2009). In this study, for culturing from liquid to solid media, Sabouraud dextrose Agar was used, as it was used in Orozco's study for appearance of yeast colonies on solid culture media (Orozco, 2009).

In this study, corn meal agar api-20C AUX and corn meal agar with shed kits were used for detecting *Candida* species, again, in the same manner as Yildirin used in his study (Yildirin, 2007).

Sahand also used CHROM agar media for detecting *Candida* species (Sahand, 2009).

In this study, nursing students' hands contained the highest number of *Candida* compared to other students, because of their longer presence in hospital; and the same was true in Yildirin's research too (Yildirin, 2007).

Martins-Diniz found 32 species of fungi from a surgery center and ICU including *Candida*

spp. In 10.6% of cases, he isolated *Candida* from pharynx of OR and ICU personnel (Martins-Diniz, 2005). The isolated candid's included *Candida albicans*, *Candida guilliermondii*, *Candida parapsilosis* and *Candida lusitanae*. Critical hospital wards are in a great need for fungal population reduction, since fungi can cause a wide range of illnesses from respiratory allergies to disseminated infections in susceptible people.

Nosocomial infections with fungal origin have been on the rise in recent years, as is mortality from such infections. Fungi causing systemic fungal infections in human usually grow well at 37 degrees centigrade, *Candida albicans* and *Aspergillus fumigatus* being two typical examples of such fungi (Parry, 2001).

Ahmad, having done an investigation, states that *Candida* infection can be exogenous. He isolated *Candida* from hands of nurses in three occasions which had been isolated from blood cultures of ICU patients (Ahmad, 2003).

Fanello also has stated after having done an investigation, that incidence of hospital acquired yeast infections in hospitalized elderly patients were on the rise, which can be due to predisposing factors like having prosthetic denture, poor oral hygiene, using antibiotics, poor nutrition, long stays in hospital, and endocrine diseases (Fanello, 2006).

Vazquez considers *Candida glabrata* infections in his patients as a result of presence of this yeast in hospital environment and on hands of treating personnel (Vazquez, 1998).

In our study, also, this yeast was isolated from hands of the students. Bonassoli, in his research on nursing students evaluated hands and nasal cavity of the 22 students before and 62 days after starting education in hospital and found significant increase in the number of yeasts after starting education in hospital (Bonassol and Svidzinski, 2002).

Holder also insists on importance of regular repeated hand washing in reduction of hospital acquired infections and states that hand washing education, especially for ICU personnel should be considered as a constant concern. After 4 years of education and continual follow up of ICU personnel hand washing, he found a significant reduction in mortality of ICU in-patients in his research.

Air and environment control of wards where immune-deficient patients are being kept, is also an important issue, because such patients are susceptible to environmental fungi and pathogens transmitted to them through personnel (Munoz, 2004). He also insists on environmental disinfection, but it should be noted that eliminated fungi of critical places are replaced after disinfection, and so, disinfection of the

environment should continue constantly (Helder, 2010).

In general, in order to control fungal infections in ICU, OR, and critical wards, disinfecting rooms and devices, cleaning air conditioning systems, minimizing traffic, personnel hand hygiene and improving knowledge of personnel, and hospital environment hygiene are beneficial.

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Accuracy of pleural effusion cytopathology

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Abstract: Introduction: Pleural effusions are pathological processes defined by the accumulation of fluid in pleural cavity. Different etiology causes this problem and occurred in different degrees of clinical severity. The main aim of present study was to determine the accuracy of cytopathology in the diagnosis of pleural effusions, according to histomorphologic features, in the patients that referred to the Rajaei and Kowsar Hospitals. **Methods and materials:** For this cross-sectional study data were evaluated from 100 patients who underwent pleural tap at the Rajaei and Kowsar Hospitals between April 2008 and April 2011. Each subject underwent general physical and radiologic examinations. The smears prepared from the pleural tap specimens and stained by the Papanicolau and Giemsa methods. We classified the cytopathologic results in five groups as following: Malignant mesothelioma (MM), metastatic malignancy, Malignant cells with unknown origin (primary or secondary), Benign, Suboptimal for further diagnosis. All the cases were confirmed by Immunohistochemistry (IHC) and clinical and histopathological follow-up. Both descriptive and statistical analysis methods were applied. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated. **Results:** The total number of patients was 100. The overall mean age was 60 ± 9.48 (ranging from 39 to 80) years. 57 preparations were benign effusions, 8 of these were malignant mesothelioma and 35 of these were metastatic carcinomas. In our study, sensitivity, specificity, positive predictive value and negative predictive value and efficiency of cytopathology in diagnosis of malignant pleural effusion, were 83%, 100%, 100% 79.7% and 90%, respectively. **Conclusion:** In this study, cytopathology is a safe, useful and reliable procedure in discrimination between malignant and benign pleural effusions, and has not sufficient power for identification between primary and secondary pleural malignancy, based on histomorphologic findings. However in these situation uses of cell blocks, IHC studies is highly mandatory. [Samiee Rad F. Accuracy of pleural effusion cytopathology. *Life Sci J* 2012;9(4):4567-4572] (ISSN:1097-8135). <http://www.lifesciencesite.com>. 686

Keywords: Pleural Effusion Cytology; Malignant Mesothelioma; Metastatic Carcinoma

1. Introduction

Pleural effusions are pathological processes defined by the accumulation of fluid in pleural cavity due to disruption of balance between hydrostatic and oncotic pressures in the visceral and parietal pleural vascular channels and occlusion of lymphatic vessels (Light, 2006). Different etiology causes this problem and occurred in variable degrees and different clinical situations (Light, 2006; Lee and Light, 2004).

In the developed countries, the main cause of pleural effusions are as following: end organ failure including heart, kidney, liver, bacterial and viral infections (parapneumonic effusions), malignant involvements (primary or secondary including: lung, breast, ovary, gastrointestinal tract and lymphoma), collagen vascular diseases and asbestos inhalation. In other part of world, especially in developing countries, tuberculosis infections are popular and prevalent (Light, 2006; Lee and Light, 2004; Marel, 1993; Batungwanayo, 1993).

In the unknown primary site pleural effusions, the discrimination between benign effusions from Malignant Mesothelioma (MM) and metastatic carcinoma, is necessary and this differentiation

should be perform based on a accurate tool for discovery of lesion nature. Because, the correct and exact treatment and prognosis followed by definite diagnosis (Lee and Light, 2004; Barreiro and Katzman, 2006). By using the cytopathology, in the more than 70% of patients, differential or definite diagnoses are confirmed (Fiegl, 2003; Maskell and Butland, 2003).

The cytopathology is a safe, rapid, simple, less invasive procedures and cost effective tool for pleural effusions evaluation and malignancy ruled out.

Neoplastic conditions including about 20% causes of pleural effusions (Ammon, 1993).

The most pathogenesis of malignant pleural effusions are permeation of pleura by malignant cells, angiolymphatic invasion and occlusion of sub mesothelial lymphatic channels by tumoral cell embolism, however in some patients, reactive pleural effusions secondary to mass or immunological mediated form were developed. In these conditions, the cytopathological investigations can't be identify atypical cells. The most important ultimate goal in cytopathologic studies of pleural effusions are

diagnosis of the malignancy-related effusion (Johnston, 1985; Menard, 1993; Salyer, 1975; Escudero Bueno, 1990).

Johnston et al shown that the specificity of cytopathology in evaluation of pleural effusion was sufficient and its sensitivity was less than optimal for diagnosis. They found, in unknown origin pleural effusions, application of cytopathology in the identification benign conditions from Malignant Mesothelioma (MM) and metastatic neoplasms has significant accuracy (Johnston, 1985). In the most pleural effusions cases, before any medical or surgical investigations, for better evaluation, pleural tap and cytopathological examination, was performed. It is important, that precision and accuracy of this tool are challenging diagnostic problems. According to results of Bonito et al study, the sensitivity of the cytopathology in diagnosis of MM varies from 31.9% to 86.3% and for malignancy with unknown origin were 11.7% to 75.3% for an accurate evaluation of primary origin (Di Bonito, 1993).

The study results of Jha et al revealed, serosal fluid cytopathology had sensitivity: 56.7%, specificity: 100%, positive predictive value: 100% and negative predictive value: 63.6%, respectively for malignant cells identification (Jha, 2006).

However, definite diagnosis performed by application of pleural biopsy through thoracoscopy or thoracotomy procedure. Both of tools were invasive, aggressive, high instrument cost and intensive training (Johnston, 1985). Confirmatory method for identification of benign from malignant effusions was histopathologic examination of pleural biopsy specimen (Kuralay, 2000).

The main aim of present study was to evaluation the accuracy of cytopathology in the diagnosis of pleural effusions, according to histomorphologic features, in the patients that referred to the Rajae and Kowsar Hospitals.

2. Material and Methods

For this cross-sectional and descriptive study, data were evaluated from 100 patients who underwent pleural tap at the Rajae and Kowsar Hospitals between April 2008 and April 2011. Each subject underwent taking medical history including patient demographics, general physical and radiologic examination. Pleural fluid obtained during thoracentesis. Pleural fluid samples were centrifuged at 2000 (speed of revolutions) rev /min for 10 min to detect cellular components. The smears prepared from the collected specimens and stained by the Papanicolau and Giemsa methods.

The gold standard and confirmatory method was the pleural biopsy for histopathological study,

perform with Abrams needle in distinguishing malignant from benign pleural fluid.

Cytopathologic features in favor of malignancy are as following: Richly cellular smear, marked pleomorphic and enlarged cells with high nucleo to cytoplasmic (N/C) ratio, hyperchromatic nuclei, occasional multinucleated, prominent nucleoli, vacuolated cytoplasm associated with blebs formation and distinct cell borders, in strongly cohesive cell groups pattern(three- dimensional fragments) including : papillary, tumor ball and tight clusters structures. Mitotic activities were increased including atypical form (Robinson and Lake, 2005; Whitaker, 2000).

We classified the cytopathologic results in five groups as following: Malignant mesothelioma (MM), metastatic malignancy, Malignant cells with unknown origin (primary or secondary), Benign, Suboptimal for further diagnosis (Fassina, 2008). All cytopathologic diagnosis was established by Immunohistochemistry (IHC) studies and also by clinicopathologic correlations. For ruled out of possible malignancy, total false negative results, were re-examined, and in this situation no evidence of malignancy are found.

We were applied both descriptive and statistical analysis methods. The statistical evaluation was performed by computer analysis with SPSS Software. The sensitivity, specificity, positive predictive value, negative predictive value and accuracy were calculated. Also we calculated ROC (Receiver Operating Characteristic) based on recommended formulas (Hanley and McNeil, 1983; Hanley and McNeil, 1982; Park, 2004). The area under the ROC curve (AUC) was calculated with 95% confidence intervals (CIs).

3. Results

The one hundred patients studied had a median age of 60 ± 9.48 (ranging from 39 to 80) years. 74 patients were men, and 24 patients were women. The Most prevalent symptom was dyspnea (81%). The malignancy risks factors including: tobacco abuse in 69 patients, a family history of lung cancer in 5 patients, radiation exposure in 2 patients and asbestos fibers exposure in 4 patients. Unilateral pleural effusions were observed in 78 cases. In the 38 patients, radiologic findings were characteristic of malignancy. Simultaneous ascites was found in 23 patients. Among the participants, 47 were no malignancy patients which included 11 with tuberculosis (TB) pleurisy, 20 with parapneumonic effusion, 5 with liver cirrhosis, 5 with end stage renal disease, and 6 with congestive heart failure.

The most common causes of benign pleural effusion in male and female patients were parapneumonia and tuberculosis, respectively. The

pleural malignancy was diagnosed in 53 patients. Based on histopathologic and IHC studies, the final diagnosis in patients with malignant pleural effusions included: lung adenocarcinoma in 18 patients, squamous cell lung carcinoma in 9 patients, malignant mesothelioma in 8 patients, breast cancer 8 patients, gastrointestinal cancer 6 patients and 4 ovarian cancer patients (figure 1-5). Overall, most common primary source of malignancy associated with pleural effusions was lung 27(51%) followed by breast 8(15.1%). In female patients breast malignancy was the most common and in the male patients lung malignancy.

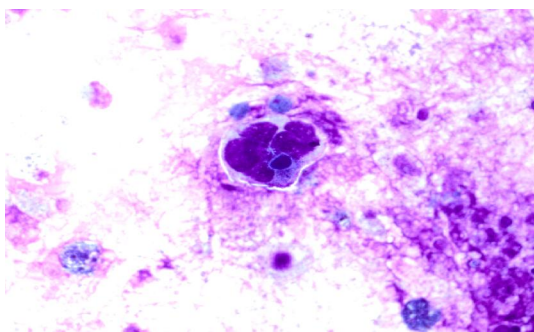


Figure 1. Cytopathology, squamous cell carcinoma, 40. Atypical cell with high N/C ratio, hyperchromatic multi-lobated nuclei, distinct cytoplasm. Pap staining, ×40

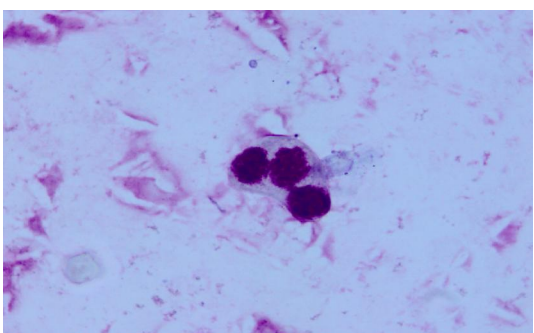


Figure 2. Cytopathology, squamous cell carcinoma. Atypical cell with high N/C ratio, hyperchromatic multi-lobated nuclei, distinct cytoplasm. Pap staining, ×40

Diagnosis comparison between cytopathology and histopathology methods and differential diagnosis of pleural effusions were present in the Table 1. Among the 31 benign effusions that reported by cytopathology tool, malignant cells were observed in 2 cases by histopathology evaluation. Also among the 28 inadequate pleural effusions for further cytopathological diagnosis, in the 10 cases malignancy was confirmed by histopathology method. The overall, in malignant pleural effusion, sensitivity, specificity, positive predictive value and negative predictive value and efficiency were 83%, 100%, 100% 79.7% and 90%, respectively. All of 41 malignant effusion that reported by cytopathology tool, malignancies were confirmed, histopathology. In the evaluation of cytopathology by using of ROC, area under the curve (AUC) of 0.977 (0.940-1.014), the sensitivity and specificity were high in 95% confidence interval (figure 6).

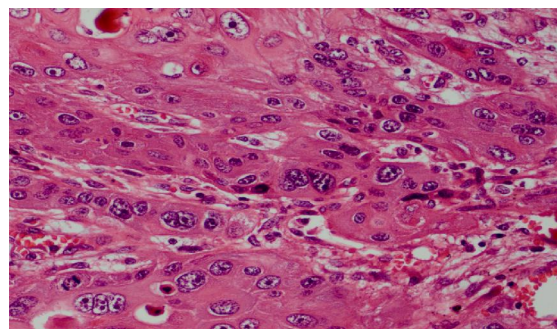


Figure 3. Histopathology of metastatic pleural squamous cell carcinoma. Marked pleomorphic cell with high N/C ratio, vesicular to hyperchromatic mono or multi nuclei, prominent nucleoli, eosinophilic cytoplasm with distinct cell borders. Hematoxylin & Eosin staining ×40

Table 1. Diagnosis comparison between Cytopathology and Histopathology

Cytology \ Pathology	Malignant mesothelioma	metastatic malignancy	malignant cells with unknown origin	Benign	suboptimal for further diagnosis	Total
Malignant mesothelioma	5	0	3	0	0	8
Adenocarcinoma, lung	0	9	4	2	2	18
Squamous cell carcinoma ,lung	0	3	2	0	5	9
Breast cancer	0	3	3	0	2	8
Gastrointestinal cancer	0	4	2	0	0	6
Ovarian cancer	0	2	1	0	1	4
Benign	0	0	0	29	18	47
Total	5	21	15	31	28	100

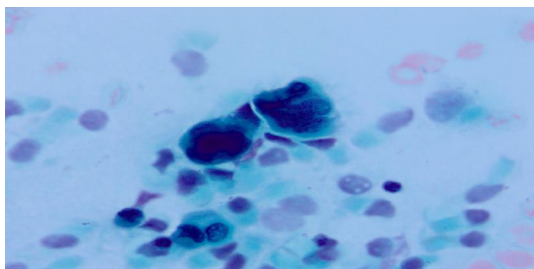


Figure 4. Cytopathology of lung adenocarcinoma. 40. Atypical cell with high N/C ratio, hyperchromatic multi-lobated nuclei, distinct cytoplasm. Pap staining $\times 40$

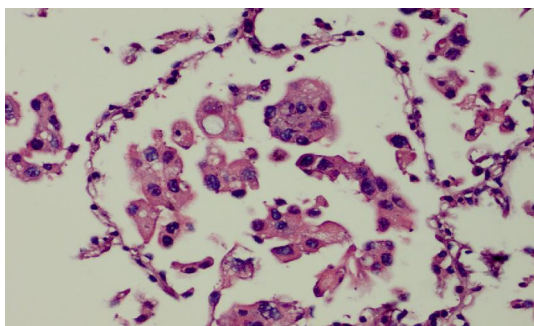


Figure 5. Histopathology of lung adenocarcinoma. The pleomorphic tumoral cells with high N/C ratio, hyperchromatic nuclei, eosinophilic cytoplasm. Hematoxylin & Eosin staining $\times 40$

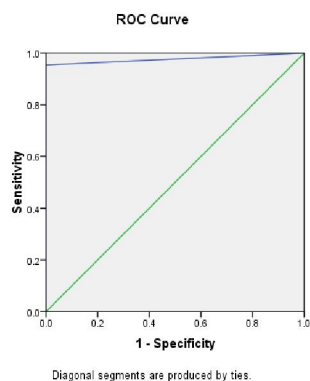


Figure 6. Roc curve for cytopathology tool in evaluation of pleural lesions. AUC: 0.977 (0.940-1.014)

4. Discussions

In the recent study, we found that pleural effusion cytopathology was good accuracy in the discrimination of benign from malignant cases. In pleural effusion cytology, determination of reactive mesothelial cells from metastatic carcinoma and MM is critical. The problem is compounded when neoplastic cells disclose only mild atypia and when

reactive mesothelial cells reveal marked atypical and cellular pleomorphism (Ikeda, 2010).

In many situations, the diagnosis of MM, metastasis, or benign reactive mesothelial proliferation in effusion specimens is based on experienced cytopathologic. The other problems are as following: sampling error, failed tap, few malignant cells shedding, hemorrhagic or inflammatory effusion and interpretative errors (Fassina, 2008). Two other common situations that associated with diagnostic pitfalls are pleural lavage samples and samples from patients having had radiotherapy (Zimmerman, 2005).

By using of cytopathologic features, identification of reactive mesothelial hyperplasia from malignant effusion can be possible, but definite diagnosis of primary or secondary malignancies are not straightforward. Many cellular changes are seen in reactive processes that blurred accurate diagnosis, including: nuclear pleomorphism, macronucleoli and vacuolated cytoplasm (Fassina, 2008; Gupta and Dey, 2003).

Architectural setting also is very critical in definite diagnosis in comparing to cytomorphologic features, because large number of the MMs pertaining to well differentiated categorized, and therefore these features are not significant. The most common growth patterns in MM are three-dimensional tissue fragments including morular structure. However keep minding, for correct diagnosis correlation between cytomorphologic features, architectural growth pattern, tumor necrotic or inflammatory background and clinical data are highly mandatory (Leiman, 2001).

In many conditions in obvious ill and serious individuals with repeated pleural fluid accumulation, only safe route for taking of adequate specimen for appropriate cytopathologic examination is pleural tap (Fassina, 2008).

The sensitivity (range and mean), specificity, positive predictive value and negative predictive value in the previous study of Fassina et al were (65.5% - 90.3% , mean: 81.2%), (64.3% - 100%, - mean: 81.3%), (84.4% - 100%, mean: 91.2%) and (54.5% - 76.9%, mean: 67.4%), respectively (Fassina, 2008).

Our results were agreement with Fassina et al's results in sensitivity and specificity and were higher accuracy in PPV and NPV.

In Fassina study, the further subspecialization of malignant effusions, whether primary or secondary in origin, lead to an obvious decrease in diagnostic accuracy (Fassina, 2008).

The results of previous study shown, the sensitivity of the cytopathology in diagnosis of MM ranged between 31.9% to 86.3% and for metastatic

malignancy 11.7% to 75.3%, in order to accurate finding of primary site (Di Bonito, 1993).

Motherby et al believed that pleural effusion cytopathology has low sensitivity 5.8% to 50% for malignancy detection compared with high specificity power (Motherby, 1999).

The various studies reported different results, especially wide range of difference in sensitivity and specificity. Among them, choose and application of "gold standard" and confirmatory method is important cause. Optimally it should be detailed histopathological review; however some of authors often applied other tool including clinical conception or radiologic investigations (Michael, 1993).

Another cause for these variations was easy availability of expert pulmonary cytopathologist, which is still challengeable concept in many areas of world (James, 2010).

The false negative result in our study was 20.3% and in other research ranged from 23%-42%. Johnsons et al shown, this problem was not resolved by re-examination of slides. He believed main cause of this discrepancy was due to lack of shedding of malignant cells into serosal fluid or due to error in procedure applied to convey the cells to the slides not of inability to recognize the malignant cells (Michael, 1993; Johnson, 1966).

The cellular type of neoplasm that causes a pleural effusion changes false negative rate when pleural effusion is processed by cytology techniques. Squamous cell carcinoma, adenocarcinoma and breast carcinoma were most frequently positive on cytopathologic analysis (Light, 1995; Light, 1973; Prakash and Reiman, 1985; Spriggs and Boddington, 1968; Naylor and Schmidt, 1964).

The application of cell blocks and smears in the evaluation of pleural effusions were associated with better isolation and identification of malignant cells than by either method alone (Sallach, 2002; Dekker and Bupp, 1978).

In the present study, we found satisfactory levels of sensitivity and specificity only in the discrimination of benign from malignant effusions that compared with results of Fassina study (Fassina, 2008).

Due to presence of prominent reparative atypia in reactive hyperplastic mesothelial cells that could mimic malignant conditions, false positive and false negative interpretations are found. With application of ancillary techniques, identification of reactive and malignant processes, and also, MM from unknown origin pleural malignancy was possible for the accurate isolation of reactive processes from malignant forms (Motherby, 1999; Attanoos, 2003).

Generally, Immunohistochemistry (IHC), have greatly enhanced the ability of the cytopathologic to resolve a major difficulty in the categorization of pleural effusions. However, proper interpretations of IHC results are crucial (Leiman, 2001).

We were not added cell blocks to conventional cytopspin (smear) preparation of pleural effusions and it was a limitation in this study.

Conclusion:

In this study, Cytopathology is a useful and reliable tool in discrimination between malignant and benign pleural effusions, and has not sufficient power for identification between primary and secondary pleural malignancy, based on histomorphologic findings. However in this situation use of pertinent clinical history, cell blocks, Immunohistochemistry (IHC) studies are highly mandatory.

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A proposition to apply stem-based model study on the periodic development and destruction of urban textures

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Abstract: The theories on city construction are mainly concerned about studying the city's developmental trends in various periods, verifying the residency areas, occupation and consequently identifying the social trends dominated over the cities. Each theory is extensively focused on organizing a part of city developmental trend but there are some factors resulting in failed developments and predictions including some unpredictable situations which seen in life, different cultures, weather and local conditions and their effects on cities during times, destructions and reconstructions. This paper is mainly concerned about reviewing the available models to provide a development theory based on stem-based model in order to best verify the destruction of old and newly constructed textures. The main approaches to improve such constructions are also mentioned in current paper.

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Keywords: old texture, city construction model, market

1. Introduction

There are many theories on this field such as E.W. Burgess's concentric construction style, Homer Hoyt's crossed construction style, E.U. Ullman's multicore construction style and R. Dikenson's star like construction style. These theories can be used as main courses of study to verify the features of different cities. All these theories have their own features. Besides, all cities don't follow a single model. The formation time, the policies of city constructors, the culture of residents and the city texture are considered being as factors with considerable effects on city development (Figure 1). In the east, in which the cities have thousand years old, the changes seen in people's religion, culture and languages that are quite distinct. Other main factors

to be considered here are the changes seen in people culture and belief, the transformation of churches into mosques, the wars happened and consequence would increase the rate of immigration to city after industrial revolution. Such immigration has caused a special sort of life to be created in cities which is constantly changing. Nowadays, the cities are considered being as places in which different tastes and experiences are met. In traditional society, the number of distinct models is limited but in current society, the number of tastes and experiences are of main features to be highly considered. In most studies performed on city construction, the classification of the same cases in a distinct format may facilitate such studies as most efficient.

2. The stem-based model

The city can not be considered as constructed just through having many buildings juxtaposed to each other [1].

The city as a liable object of variable textures which can be modeled like the stems of a tree could be studied and its developmental trends will be explained and also the destruction and reconstruction of textures would be mapped as best as possible. Through cross-cutting the stem of a tree, it is most likely to study and model the city. The different growth stages of tree can be identified from its stem. As the city represent the developmental trends in different periods, the fall and spring growth rates of tree can be best reflected in their stems. Besides, the rapid growth rate of tree best reflects different environmental conditions. As the conditions are ideal, the growth rate is more considerable but in unpleasant conditions, the growth rate is rather low. Although the cross growth of a stem isn't quite parallel, it is dominated in all directions. The newly constructed cities with low growth rate are of such form which best reminds us to Burgess Theory. It is sometimes supposed the linear cities are exceptional in this case. Although such cities are located near rivers and vales, they most tend to increase in width. That is to mention, the criteria used to define city is not the same in different parts of the world. The theories considering the causes of city formations are mainly concerned on religious, commercial and military causes and even the development of agriculture as well as changing the countries into cities. Like stem, the city has the function of transforming the financial and economical trends because the stem connecting the roots to main branches is considered being as an intermediate among different economical and service-based sectors.

The gatherings of human beings in time and place are mainly affected by their interactions to each other and to all societies [2].

In outer parts, non-compressed textures which best reflect the suburbs could be seen. The residency areas are developed like the way liable creatures are born but with no death [3].

Since the death is inevitable for human beings, any efforts to maintain what constructs are natural. As the growth rate of root is matched with the shadow rate of the tree, the growth rate of city can reflect main branches which direct the city towards developments. The stems aren't located in the center but gradually get away from the center based on city development. Their formation trends are mainly seen in areas around. The stems can be considered being as communications or the ways connecting different

parts of the cities as best. The new activities mainly happen in new and neighboring textures because they will meet the new needs easier. As these stem are cut, the life of city and plants will be in danger. Such vital stems transforming the capital and culture are considered being as the liable part of the city. As they are weakened, the texture of the city will be dead. Like tree, the city most tends to develop in areas around. Such development best reflects the liability and strength of city. The new textures will be gradually formed and cover the formed ones. As the trend and movement are lost in texture, the flexibility will be diminished and the textures may be gradually rough. It consequently leads to decreased chance of life and double roughness. As mentioned, the cells of live creatures will expose to death and consequently be replaced by newly formed cells. Although some parts of the tree or live creature will lose the life, the life still continues. The cells of liable creatures have their own age and are replaced by other parts. The reconstruction can be considered as the continuity of life. So, the attempts made by city planner are mainly concerned about maintaining such continuity.

3. The exhaustion

Following the regressive trends seen in an area, the renting rate of houses will and the value of lands will be gradually decreased to minimum. In case of such condition, the owners will get away their lands to be destructed because they can never obtain the benefits resulting from keeping such lands [4]. The old texture are considered being as those textures in which the life flow is rather dead and no longer can be reconstructed.

The urban areas gradually developed and exposed to some considerable changes during times [5]. Such exhaustion is one of the main issues related to urban areas which cause some forms of disorganization and the lack of balance and compatibility. The exhaustion can be divided in two categories: partial exhaustion and complete exhaustion.

The partial exhaustion: as one of the urban elements either the texture or the activity is exposed to exhaustion. The complete exhaustion: as both mentioned elements are exposed to destruction and exhaustion.

Factors such as the lack of compatibility with current conditions and the vast number of ownerships will make the trends in old textures as weak, for example the limited width of pedestrians in old textures which isn't suitable for transportation systems, the failure of delivering service as needed, the regulations aimed at protecting the old textures. These factors are of considerable effects on the beauties of old textures and cause the trend of

investment and movement to deviate from normal positions. The texture is maintained as most liable when people are actively involved in all different stages of life [6].

4. Repair in old texture

The repair and reconstruction can be considered as a mixture of social, psychological, cultural, economical and political processes [7].

In case of repairing the old textures, it is first required to differentiate between textures with no historical values and the ones with high values because the development of culture and universalism is best reflected in the art and architecture which pave the ways for civilization to be formed. If we consider the civilization being as the expression of culture, it can be concluded the architecture is the factor expressing its nature as best. The old textures best reflect the nature of residents living there. Such textures are of more susceptibility in case of planning. The international brochures are mainly focused on maintaining the heritage as best. The three approaches used to repair the old textures are as follow: The museum-based attitude, the cell-based attitude and the organic attitude or logical thought.

The first attitude is mainly concerned on maintaining the current situations but not helping the life trends to be developed. It won't lead to real reconstructions.

Considering the events seen in times, the richer cities were exposed to more destructions and reconstructions compared with residency areas with limited economics [8].

The cells of a liable creature are refreshed thousand times during life. Such refresh is considered being as essential and vital.

The main structure of a city can be divided in two original and non-original parts. The main or original part constitutes the central structure and best verifies the nature of city. The other parts of the city constitute the non-original part which best reflects the change, variety and option. The main or original part is constituted from communication lines, open spaces and public buildings but the areas people living there are constituted the non-original part [9].

5. Segregation

The places are exposed to changes and modifications to be compatible with behaviors around [3].

The behaviors are also exposed to changes to match with special locations. Such textures are most compatible with those tending to match their own life with situations around. The group-based competitions will lead to ecological segregation of groups involved in [10].

Since the newcomers are in low positions due to low income rate, they are less belonged to it. When the life positions are promoted, they will move to other parts of the city. Any change in the social structure of such textures and the immigrations accomplished will make the people's involvement as less compared with past. The number of single people immigrated to exhausted areas is high which best shows such textures are of temporary residencies and such people send their income to their families in their hometowns. In the other hand, the capital gets away from old texture constantly and the texture will be more exhausted compared with past. Considering the dependency theory, the urban old textures function as periphery role for rich urban textures and the old texture receives no benefits from economic activities of its own residents to reconstruct or repair the areas involved. So, it can be concluded such additional transformations can also be seen in urban locations.

6. The traditional model in the permeability of textures

Since the markets are mainly located in city gates, especially in cities under Iranian civilization effects, the main courses of cities will make the social and economic functions as difficult. The development of architecture elements and city constructions are also other factors with considerable effects. As an example, consider the closed square as religious centers inside the cities which sometimes is considered being as a place to play and entertain. Even mosques will provide the ways to pass through. Besides, the main goal of variety is to increase the option rights. The integration of lands while making the activities as economic may result in improved urban areas. That is t mention; the road is considered being as main aspect of city which paves the ways for all sorts of activities to flow. Besides, the flexibility isn't just in relation with roads because many of such current exhausted textures were flexible and permeable. So, by permeability it is actually meant accomplishing a way as communicational channels to economic, political, cultural and religious functions.



7. Conclusion

The construction style is resulted from the thought style. By finding out the construction process, we can achieve the thought style of its residents and constructors as best. The lack of access to the inside urban textures will lead to weakened connections and failed infrastructure plants and consequently the weakened trends involved in. in cities, the locations isolated aren't considered being in access area and will be gradually exposed to exhaustion. There will be no special trend in goods, services, and the capital and even in transportations and the city vital cycle will be deviated from its normal trend. In such conditions, a special group of people will be attracted by society. Such textures which most accept people with different cultures, especially the locals with economic problems best reflect the culture and life of its residents. So, it is essentially required to consider the networks accomplished and the ones left. We also should consider the permeability factor as most important. The lack of financial sources of the residents living in such textures and the lack of interest to invest on such textures by people with low income will make the

government's intervene as most essential. So, awarding some loans and bank facilities won't be enough in such conditions. Therefore, all decision makers and planners are essentially required to identify the processes involved and develop the permeability of such textures as most efficient.

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The effect of 2% citric acid in control of spontaneous epistaxis in Emergency Department

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Abstract: Introduction: Epistaxis is one of the most common causes of emergency department visits and almost 60% of the public have experienced it at least once in their lifetime. There are different methods for controlling the nasal bleeding. With due attention to the invasive and harmful features of most methods which makes them impossible to use in pre-hospital settings, the aim of this study is to prove that citric acid as a non-synthetic safe agent can be used in controlling the epistaxis. **Methods and materials:** In a randomized clinical trial, we studied 406 patients with chief complaint of epistaxis referring to the emergency department of Imam Reza Hospital of Tabriz from 2010 to 2011 in two groups of case and control. We used 5 drops of 2% citric acid in every nostril for patients in the case group and anterior nasal tampon in the control group. All data were recorded and finally, the appropriate statistical tests were used to compare and analyze them. **Results:** The mean age of patients was 53.94±14 years. 44.8% of patients were female and 55.2% of them were male. There was no significant difference between the controls of bleeding in two studied groups. **Conclusion:** Using both of anterior nasal tampon and 2% citric acid are effective in controlling spontaneous epistaxis and there is no significant difference between them; however, regarding the fact that citric acid or base substance of lemon juice is widely available, its usage is recommended.

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Keywords: Spontaneous Epistaxis; 2% Citric Acid; Emergency Department

1. Introduction

Epistaxis is a common condition as well as a frequent otolaryngology emergency with up to 60% of people experiencing one episode in their lifetime. An estimated 7% to 14% of Americans experience a nosebleed each year. Some 10% of these groups seek medical attention, 10% of whom are ultimately referred to an otolaryngologist for further treatment (Bishop, 2003; Josephson, 1991; Shaw, 1993; Flint, 2010).

The main and most important function of “nose” is to warm up and moisturize the inspiratory airflow. For this purpose, nose has a rich vascular supply of both internal and external carotid arteries, making it vulnerable to episodes of bleeding, either spontaneously or as a result of localized trauma. Most of the time, the bleeding is mild and self-limited; although, it can be profuse and life threatening (Bernius and Perlin, 2006).

Cold and dry weather in autumn and winter is the cause of the high incidence of epistaxis in these seasons. Epistaxis is most common among males and in children, but it is more severe in adults. In previous studies, the age range for incidence of epistaxis has been reported to be below 10 years and above 50 years (Walker, 2007; Hussain, 2006; Nunez, 1999).

In our country, and especially in Tabriz city, HTN crisis is one of the most common causes of emergency visits and of its presentations, epistaxis can be mention. Although HTN is usually considered as a cause of epistaxis, studies have shown that the incidence of epistaxis in patients with HTN is equal to the base population (Theodosios, 2009; Knopffholz, 2009). There are studies that suggest HTN may be the cause of epistaxis (Isezuo, 2008; Hollingsworth, 1952; Charles and Corrigan, 1977).

There is a controversy over treatment of epistaxis in pre-hospital settings. Local application of an ice pack on the forehead or back of the neck, or sucking an ice cube has seen as a widespread practice, but it has been shown to have no statistically significant effects on nasal mucosal blood flow. There are conflicting opinions in the use of ice or nasal packing in the treatment of nose bleeds. Most suggest that using ice or nasal packing is not harmful when initial efforts to pinch the nose fail, while others advise against it (Teymoortash, 2003). The patients may be instructed to pinch the nostrils together for 5 to 30 nonstop minutes and to keep the head elevated but not hyper extended to avoid aspiration of the blood. Usually only 5 to 10 minutes is required to stop the bleeding. A piece of gauze soaked with a nasal decongestant spray, epinephrine at a ratio of 1:10,000, or phenylephrine and placed in

the affected nostril may also be helpful to induce localized vasoconstriction (Bernius and Perlin, 2006). If bleeding cannot be controlled with these simple measures, then transfer to an emergency department is required.

With due attention to the invasive and harmful features of most methods which make them impossible to use in pre-hospital settings, the aim of this study is to prove that citric acid as a non-synthetic safe agent can be used in controlling the epistaxis.

2. Material and Methods

In a randomized clinical trial, we studied 406 patients with chief complaint of epistaxis referring to the emergency department of Imam Reza Hospital of Tabriz from 2010 to 2011 divided randomly in two groups of case and control. Sample size was determined using the formula below:

$$n = \frac{\left(Z_{1-\frac{\alpha}{2}} + Z_{1-\beta} \right)^2 \times [P_1(1 - P_1) + P_2(1 - P_2)]}{(P_1 - P_2)^2}$$

For each patient, a form including demographic data, the cause of epistaxis and the initial vital signs and lab results was filled out.

We used 5 drops of 2% citric acid in every nostril for patients in the case group after cleaning the nostrils with gauze and BP and PR of the patients were checked 5 and 10 minutes after applying the solution. If the nasal bleeding did not stop in 5 minutes, another 5 drops was applied. If bleeding was not stopped after 10 minutes, standard treatment of epistaxis (anterior nasal tampon) was used. Patients were monitored for 24 hours in case rebleeding would occur.

In control group, the standard treatment of anterior nasal tampon was used and as of the case group, the BP and PR of the patients were recorded 5 and 10 minutes after the procedure.

All data were recorded using descriptive analysis (frequency, mean ...), and analyzed using SPSS statistic software to compare the two groups. In every statistical analysis, significance was determined at p value of less than 0.05.

Although 2% citric acid, the base substance of lemon juice, was attenuated, and is thoroughly self-used, a written consent was obtained from each patient and the principles of declaration of Helsinki were met.

3. Results

In this study, 406 patients visiting emergency department of a central hospital with complaint of epistaxis were studied (203 patients in the case group and 203 in the control group). The age

range in the case group was 12-79 years with mean of 53.94 ± 14.00 years of age. Significant difference was not found between mean age of patients in two groups ($P=0.155$) (Chart 1). 42.6% of patients were female and 57.4% were male. In the case group 2 patients had coagulation disorders as well as 4 patients in control group, who were excluded from the study. Mean of age, platelet, PT, PTT and INR of patients based on Diabetes Mellitus, Liver Disease, Hypertension and Cardiovascular Disease are shown in table 1 and 2.

35.8% of patients were hypertensive, and 14% had liver disease without affecting their coagulation tests. Diabetes mellitus had been diagnosed in 33.3% of the patients.

In the group receiving 2% citric acid for the treatment of epistaxis (case group), bleeding stopped in 61.7% of the cases five minutes after using citric acid. In the next 10 minutes, bleeding stopped in all except 6 patients. In the group receiving the standard treatment (anterior nasal tampon), in 63.8% of the patient the bleeding stopped in 5 minutes, and after 10 minutes only in 4 patients rebleeding occurred. Comparison between the two groups in terms of bleeding stoppage in 5 and 10 minutes after treatment, did not show any statistically significant difference ($P=0.25$, $P=0.175$).

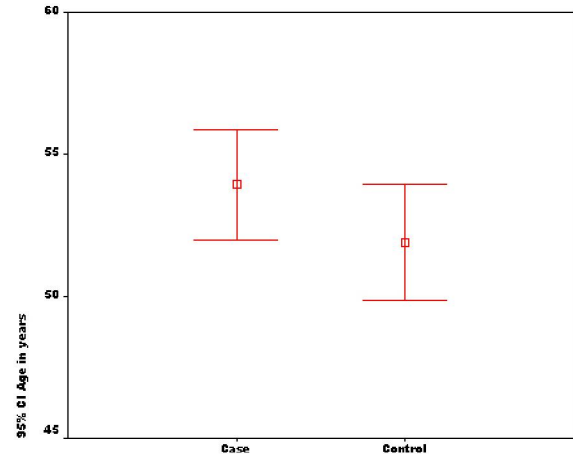


Chart 1. Distribution age of patients between two groups

Minimum platelet count was 150000 and maximum number obtained was 421000 (with the mean of 290630 ± 8450). Lowest PTT was 30 seconds and 98 seconds was the maximum rate with the mean values of 94.8 ± 78.40 seconds. INR range was variable between 1 and 2.5, with mean of 1.3 ± 0.30 . There was no significant difference in platelet count and INR in the two groups ($p=0.367$, $P=0.490$, $P=0.598$).

Mean systolic blood pressure and the mean diastolic blood pressure in our patients was 142.83 ± 25.04 and 81.26 ± 10.54 mmHg respectively. There was no significant differences between case and control groups in terms of systolic and diastolic blood pressure during the first visit ($P=0.990$, $P=0.740$).

Five minutes after applying 2% citric acid, in 3 patients rise of blood pressure was noticed and in 6 patients after 10 minutes. In most patients the blood pressure was either intact or decreased in therapeutic range because of the antihypertensive drugs given to the cases with high blood pressure. There was no significant difference between the change of blood

pressure in the two groups 5 and 10 minutes after the treatment ($P=0.132$, $P=0.136$).

The mean heart rate of 83.16 ± 7.91 bpm was detected in our patients. 5 min after intervention in case group, 143 patients (70.4%) had no change in heart rate and the change in other patients was negligible. Heart rate changes at 5 minutes after intervention in case and control groups were not significantly different from one another ($P=0.102$). After 10 minutes of intervention, 98% of patients had no change in heart rate. Changes in heart rate 10 minutes after the intervention in case and control groups were not significantly different from each other ($P=0.136$).

Table 1. Evaluation of age, platelet, PT, PTT and INR of patients based on Hypertension and Cardiovascular Disease

	Hypertension			Cardiovascular Disease		
	Yes	No	P	Yes	No	P
Age in years	58.46 ± 12.18	48.76 ± 14.56	<0.001	58.77 ± 12.62	51.25 ± 14.46	<0.001
platelet counts	263.78 ± 74.36	310.31 ± 81.07	<0.001	257.18 ± 74.18	299.82 ± 81.12	<0.001
PT	15.07 ± 2.70	14.97 ± 4.27	0.770	16.97 ± 5.52	14.46 ± 2.72	<0.001
PTT	39.97 ± 7.06	41.36 ± 10.03	0.119	45.09 ± 14.32	39.53 ± 6.08	0.001
INR	$1.18 \pm .19$	$1.22 \pm .37$	0.133	$1.42 \pm .54$	$1.14 \pm .15$	<0.001

Table 2. Evaluation of age, platelet, PT, PTT and INR of patients based on Diabetes Mellitus and Liver Disease

	Diabetes Mellitus			Liver Disease		
	Yes	No	P	Yes	No	P
Age in years	56.98 ± 11.48	50.20 ± 15.52	<0.001	58.22 ± 13.04	51.66 ± 14.44	<0.001
platelet counts	295.83 ± 90.67	286.69 ± 74.92	0.289	284.18 ± 87.04	291.84 ± 80.19	0.456
PT	15.27 ± 3.94	14.85 ± 3.50	0.279	15.75 ± 4.25	14.84 ± 3.51	0.082
PTT	42.01 ± 11.93	39.94 ± 6.00	0.043	46.21 ± 12.09	39.47 ± 7.41	<0.001
INR	$1.26 \pm .37$	$1.17 \pm .25$	0.004	$1.38 \pm .47$	$1.16 \pm .24$	<0.001

4. Discussions

To control spontaneous epistaxis, many schemes of therapy have been recommended, such as K and C vitamins, anterior and posterior nasal packing, penicillin, cautery, ice packs, thrombin and fibrin foam, and ligation of the external carotid artery (Menger, 1995). Anterior nasal tampon or packing is a common method for the treatment of epistaxis and is widely used in the Departments of Emergency Medicine. Despite being an effective method of controlling epistaxis, its application demands a skilled person.

To introduce a method that can be efficient and at the same time practicable by non-medical staff, we conducted this study to investigate the effect of 2% citric acid in controlling epistaxis in the emergency medicine department.

In a study conducted by Theodorsis et al, it was noted that the incidence of epistaxis in males is

higher than in females. Also in this study, the mean age for the incidence of epistaxis has been reported 54.76 ± 13.23 years (Theodosis, 2009). Other studies have also revealed greater incidence of epistaxis in male gender, with more severity in adults (Walker, 2007; Hussain, 2006; Nunez, 1999). By comparing our results with these studies, partial consistency is observed.

In various studies, there is controversy over the role of blood pressure in epistaxis; however, as seen in the present study, the mean systolic blood pressure was high in patients visiting ED with complaint of epistaxis. Wang et al. in their study stated the necessity of blood pressure control in prevention of intractable epistaxis (Wang, 2006).

In a study by Isezuo et al., they retrospectively investigated the analysis of 62 adults to find a relationship between blood pressure and epistaxis. And finally, they noted a significant

relationship between increased blood pressure and increased incidence of epistaxis (Isezuo, 2008).

In a study by Herkner et al. at the University of Vienna, studying the relationship between blood pressure and epistaxis, it has been concluded that the increase in arterial blood pressure is an independent cause of bleeding in epistaxis patients (Herkner, 2002). These studies suggest a relationship between elevated blood pressure and increased incidence of epistaxis, which are comparable with findings of our study and confirm our results.

The presence of extremely high systolic blood pressure is said to be a contraindication of using vasoconstrictive drugs, due to the possible danger of cerebral accident (Hollingsworth, 1952).

The results obtained in this study showed that the use of 2% citric acid had no effect on the patient's vital signs and due to its high dilution, it does not affect the lining of nasal epithelium unlike other methods such as chemical cauterization with silver nitrate with negative effects on the mucosa (Bernius and Perlin, 2006; Krempl and Noorily, 1995).

Comparison between the case and control study in the present study did not show any statistically significant difference in treatment success rates. No published studies were found studying the use of citric acid in the treatment of epistaxis; however, there are numerous studies on nasal tampon. In a study by Adornato et al, they noted that the use of nasal tampons could appropriately control the nose-bleeding (Adornato, 2000). In another study carried out by Goddard et al., they noted the anterior nasal tampon as a cost-effective treatment of epistaxis (Goddard and Reiter, 2005). According to a study by Singer et al, anterior nasal packing has been mentioned as a painful procedure both while packing and while taking the pack out after bleeding has stopped (Singer, 2005).

Use of intranasal Oxymetazoline in controlling epistaxis was studied by Kremple and Noorily; sixty-five percent of the patients were successfully managed with Oxymetazoline as their sole therapy. An additional 18% were managed successfully with silver nitrate cautery in combination with Oxymetazoline. These data suggest that pharmacologic management may be adequate in the majority of patients with epistaxis, thus avoiding the need for nasal packing with its associated complications (Krempl and Noorily, 1995).

Menger et al. studied the use of estrogen to control epistaxis. Although effective, it is not accessible, and since possible side effects have not been studied, it cannot be used in ED and in the pre-hospital settings (Menger, 1995).

In our study, both methods of anterior nasal packing and usage of 2% citric acid were effective in controlling the bleeding and there was no significant difference in terms of bleeding control between both interventions. But regarding that the 2% Citric acid or diluted base substance of lemon juice is available in domestic bases and considered to be a safe substance, therefore, it is suitable to control epistaxis.

Conclusion:

This study investigated the effect of 2% citric acid in controlling spontaneous epistaxis in the Department of Emergency Medicine. Finally, we concluded that the impact of this approach in controlling epistaxis is similar to using anterior nasal packing and both of these methods may be effective in controlling epistaxis. However, using the diluted citric acid to control epistaxis is practical in domestic bases. As the results showed, application of 2% citric acid had no effect on patients' vital signs; thus, it can be used by individuals at home. Using this method, owing to its ease and speed of implementation, would be useful in controlling epistaxis in pre-hospital settings.

Observations are being made on the possible side effects of this means of therapy, but not enough data have been accumulated warranting the conclusions. Further investigations should be carried out to resolve this matter.

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The investigation of political aspects of Hajj

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Abstract: Islam is a religion with political and international characteristics in its nature. Beside all these rules, Islam religion in its religious rules kept its political and international nature. This is manifested in Friday prayer and Hajj rituals. Holding Hajj each year is like a congress of the people of various countries and regions in the world with important functions on international relations. One of the functions is preparing the collaboration and international cultural relations and interactions in removing the regional and global problems. The current study aimed to investigate the effect of political aspects of Hajj at international system by Islamic approach.

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Keywords: Hajj; political aspects of Hajj; Historical period; International relations

1. Introduction

In the globalized world and the existing international system directing the relations of the countries to the organizations and regional and transregional conferences and these institutions are effective in forming international collaborations, international relations scientists ignored intentionally the important event as Hajj gathering all people annually. However, due to the lack of awareness of political aspects and its international nature, ignored it in their analyses. The current researcher with his local and Islamic challenges and awareness of international characteristics of Hajj Tamato rituals attempt to take a small step of this part ignored by international and transregional ability of Islam religion. Indeed, from the view of the current researcher, one of the important symbols showing the effective peaceful and justice-based nature of Islam religion in international relations is Religious-political ritual of Hajj. The most important challenge of the author is identification of Hajj issue and its influence in international relations and creating an opportunity at theoretical and academic texts level. In the current study, analysis and description method of information collected from the library and documents is applied.

The investigation of political aspects of Hajj

Any nation adopted various methods in this ritual about Hajj along with the regional thinking and attitudes and founded some centers that gradually by creation of some civil and political communities; Hajj had a special position of power. After the declaration of the prophet hood of the Prophet and from the beginning of Islam propagation to the foundation of Islamic government by the Prophet and even some years after that in Islam history, when infallible Imam were put aside of the power, applied this ritual to influence political aspect of the society

and the participation in political destiny of the society.

A review of political aspects of Hajj at the beginning of Islam

From the beginning of the formation of Islamic government by the Prophet, he used the capacities and potentials of Hajj ritual. Some of the cases with political influence in Islam history and political relations of Islamic society and political interactions of Muslims and Non-Muslims are mentioned as following:

a. Participating in Tawaf as a demonstration of power of Tawhid society/ to maintain and keep the power:

According to some of the theorists, politics means power science (Alam, 2011:34). On the other hand, we can say that one of the dimensions of political interaction means participating in power (Basharieh, 2003:14) to attempt to attain and display power. It means that after volunteer group of participation in power start political action and reaction in the society, they follow some aims. At first, for all members of the group achieving power is of importance and then its increase is on the second priority (Ayver, 1957: 23).

In the prophethood declaration (Be'sat) of the Prophet and explicit propagation of Islam by him in the Arab community, the Muslim group participated in power. One of the extensive examples of the attempt of the Muslims for participation in power and its display is presence in Hajj rituals. The Prophet (pbuh) in year 7th of Hijra (one year before the conquer of Mecca) based on resolution "Hodaybie peach" was permitted to go to Mecca for Hajj and stay there for three days.

In this important condition that was important politically, the Prophet (pbuh) said to the followers that:

Make your shoulders nude and do the rituals as magnificently, that those pagans see your powerful arms”.

We can see that Kaaba Tawaf for the Prophet and his followers was as a power maneuver against the pagans and it was a worship and manifestation of Islamic politics (Leader, 2002:23).

After infallible Imams were put aside from power due to their enemies, they used the annual gathering of HJ as an instrumental tool to state their disagreement and attempted to make the mind of other Muslims prepared.

In year 85 of Hijra, 2 years before the death of Moavieh, Moavieh proudly killed Alavian and Shiie people (followers of Imam Ali (pbuh) and faced them with cruelty.

Imam Hossein (pbuh) in that year participated in Hajj ritual. Beside Hajj rituals, he invited all Bani-Hashem and Shiie people and Ansar for gathering in Mena, more than 1000 people came and some of the followers and children of the Prophet (pbuh) were present. Imam Hossein rose and made a big speech. By expressing the Holy Quran verses and tradition of the Prophet (pbuh) about the superiority of Imam Ali and his qualification and his children for Emamt, each letter he was mentioning, the audience shouted: «اللَّهُمَّ نَعَمْ، قَدْ سَمِعْنَا وَ شَهِدْنَا» : I take Allah witness that I heard this speech from the Prophet and I am sure it is true”, the confirmed Imam Hossein (pbuh) words. At the end, Imam Hossein (pbuh) said to them:” I take oath to transfer my speech to reliable people in your land and make them informed of my invitation”.

Hajj and politics

Hajj performers by religious reasons after returning from Hajj ritual create a new group of society with social identity, and position. This social identity creates a transnational group at all the groups including in Dar El Salam classification. This new identity can interfere in political directions of their countries and lead into the coordinated results with their new classification position. This coordination of the group benefits with the origin of common group lead into the convergence of policies and interactions.

Political economy of Hajj

For a long time, economy and politics in international relations were separated and as all the activities being different qualitatively, were studied by the approaches being different qualitatively (Jackson, Sorenson, 2004:227). Since decade 70, some trends were created showing the complex relation between politics and economy and between the governments and market and international relations should consider them. This relation is the subject of international political economy (Jackson,

Sorenson, 2004:228). Robert Gilpin considered international political economy as the interaction of wealth and power (Hajji Yusefi 2007:103). We can say that international political economy is a political-economical method of the analysis denying the separation of the economy, politics and society and don't remove no form of analysis, political or economical from the beginning (Palan 2007:23).

Thus, international political economy is a structure of international politics economy investigating the role of economical interactions of Hajj between the Hajj performers and their government- host country between the Hajj performers of various countries with each other and economical obligation of Hajj performers against their society and country and the related issues in international relations. The issues of this section are considered from merely economical aspect: Income and costs, merely political: Vulnerability and opportunity and from power and affecting the decisions of other actors as a field of international political economy structure.

Some of the features of political economy of Hajj in Dar El Salam are as following: an economical source in global congress of Hajj is provided via personal costs of one by one of the members. This economical providing is similar to a type of collaboration system in running the affairs. One the other hand, some part of Hajj ritual is paying the religious money and dividing the economical resources among the poor. This method leads into the near relation of social and political groups in the society. Finally, buying and selling souvenirs from the Hajj performers and the host country was common beside this ritual.

The characteristics of Hajj as a transnational parliament in Islam World

Holding Hajj ritual in Islam world is like the parliament of Islam world. The reason of this interpretation is due to the political and sociological features that are observed among the population participating in Hajj rituals. Some of the features are as following:

1- In Hajj gathering, there are some people with special conditions as maturity, wisdom, obedience and power and capability. In this congress, due to the method of holding the ritual and equal level of the participants, social tensions and habits are not appeared.

2- Hajj creates a transnational society that all Muslims from all over the world without considering the geographical features and ethnical traditions and cloth and color participate and they have an integrated appearance.

3- Due to the repetitiveness of this ritual annually, it can provide the basis of a global government based on the values of the Islamic world.

4- The participation of both women and men in Hajj ritual shows the Islam attitude to women as a major part of the society.

This issue can lead to the result that anti-Islam propaganda at global level are faced with a great doubt.

The effect of Hajj and stoning the Devil on taking active foreign policy in Dar El Salam:

The foreign policy of the countries is the set of positions, measurements and decisions that national countries take for each other or to the international organizations and its aim is providing the national benefits of national government as a united group. Foreign policy guarantees the action and reaction at international arena (Basharie, 2003:219). The countries take two types of interaction at international arena based on their abilities, capacities and attitudes of foreign policy system. These approaches can include active foreign policy or internal and passive foreign policy or internal (Boshrie 2003:219).

Hajj pilgrimage is effective in taking active foreign policy from Muslim countries with some reasons. Some of the reasons are as:

1- Hajj congress due to the presence of the people of various countries had close potential of decision makers' view of foreign policy of Dar El Salam countries.

2- In case of taking active foreign policy from Dar El Salam countries to cope with the existing order and using this potential, the time of holding Hajj pilgrimage by political and geostrategic importance can be a good time to state the active positions of foreign policy system of the countries.

3- Stoning the devil ritual has an important role in informing the public opinion of Dar El Salam people against the colonial system of the existing international system and creating public demand from the governments to take active foreign policy against the existing order.

Based on the various population of the Islamic nation in various countries, if they can take unit political positions with focus on active foreign policy and the existing capacities in Hajj political aspects, how it can influence the international policy.

The investigation of Islamic convergence grounds with focus on Hajj pilgrimage

Political sciences and international relations scientists considered special conditions for creating convergence among various countries.

According to them, the communities can take a step to create convergence between themselves and others that historically there is a convergence

history between them (Seifzade 2002, 201). In the theories of political sciences and international relations, there are various kinds of convergence as political, social, and economical and status convergence.

Some of the capacities and political aspects of Hajj:

1- The common ritual between various Islamic religions that is observed well in Hajj pilgrimage shows that all Muslim nations have similar cultural status. These statuses that are observed in personal ritual as Arafe, social ritual as Saei and Tawaf and some rituals with political nature as aversion of cruelty and the existing order can prepare the unity between the Muslims in the world.

2- Hajj pilgrimage due to the possibility of exchanging the beliefs and eliminating cultural and social misunderstandings can prepare the way to make the religions close among the Islamic nations and develop the common identity and increasing the mutual commitment and renovation of convergence between various Islamic countries.

We can say that in encountering with globalization, the Muslim nation inspired by Hajj ritual have two following issues:

1- Sub-national actors in Hajj pilgrimage as pilgrimage performers by creating transnational group of Hajj pilgrims can provide the grounds of Islamic convergence.

3- In Hajj pilgrimage, exchanging the ideas and removing the cultural and social misunderstandings, creating approximate grounds between the religions and various orders between the Islamic nations develop the common identity and increasing the mutual commitment and renovation of convergence between various Islamic countries. By the capacities of globalization for Islamic nation, it makes the Islamic values prevalent and convergence of Islamic nations. It seems that based on the multiple resources of Islamic theory validity, the international relations provide the Muslim theorists and other theorists to use this approach and applying all the existing instruments including globalization to analyze the new reactions in this field and besides analyzing the events, increases the ability of Muslim influence at international level.

4-

Hajj and Islamic global government indices

Thus, the investigation of the global government in western thinking and political attitude of Islam can achieve some indices in terms of Islamic approach of international relations and political sciences and then investigate the indices in consistency with political aspects of Hajj as political aspect of Hajj encountering with international system and some of their ideals.

Active diplomacy

In Islamic global government, active diplomacy instrument is used. Hajj due to the presence of various people and groups of the societies has the capability to behave as diplomacy instrument. As the social class of Hajj pilgrims as defined in other classes' classification, it is possible to be responsible in various national and international organizations and countries. These people after being the member of global class of Hajj pilgrims play the role of non-state diplomats of Islam world regarding the international organizations. According to Islamic sharia, after doing Hajj pilgrimage, it has many common features and these features are reflected in their external behaviors.

On the other hand, the messages in Hajj congress can act as the new and general diplomacy instrument with other nations in the world. If the global structures are changed, the diplomacy is also changed. Underestimation of the sovereignty of the governments, IT, the growth of non-state actors and increasing awareness of people at global level are the main factors playing important role in diplomacy change. It is emphasized that the new diplomacy is a phenomenon in a global civil society in which the new IT and communication, new state and non-state organizations, people, pressure groups, specialized associations and the like play more roles in the global issues. They believe that environmental issues, the crisis of international economical inequalities, avoiding the disputes, human rights and humanitarian aids, AIDS, population pressure, avoiding the local and ethnical disputes, migration, globalization paradoxes and other crises and challenges of international society are complex that nations, countries and traditional diplomacy can not alone cope with them. In new diplomacy, a new movement is formed in which it is attempted that with a new movement we can move toward solving the global problems and crises (Symbler, 2009:24). By a review of the definition of new and general diplomacy we can define the capacities of Hajj pilgrimage in applying such diplomacy. These capacities are aroused of the fact that most of the issues in the range of this new type of diplomacy are the issues of Islam world and gathering of people in this pilgrimage as a big NGO and ability of putting pressure by diplomacy and democratic capacities of Hajj, Islam world can use the new diplomacy.

Peaceful action

Another feature of Islamic world government is emphasis on peaceful actions. In the current condition and the current international system that Islam didn't reach a global government, we can mention Hajj as the greatest gathering of various Islamic nations with different national and sub

national basis to show the capability of transnational society based on Islamic principles in peaceful action in interaction with each other and interacting with outside. Indeed, Hajj test showed the capacity of Islam world for peaceful interactions with international system.

Another discussion in this paper is the method of challenging the structure of the current international power by Hajj pilgrimage. Indeed, we can say that by emphasis on the definition of politics from the view of politics and Islamic theory of international relations as a normative and critical theory, one of the functions of this approach is challenging the structure of the existing power and this issue is political. The political aspects of Hajj pilgrimage are considered from this view in the rest of the paper.

Challenging the existing order by holding Hajj ritual

As it was mentioned at the beginning of this chapter, one of the affairs that can turn a phenomenon to a political affair, the interaction of the phenomenon is with the issues related to power. As it is shown in theoretical section of this study and in some parts of this chapter, world knowledge and the study of knowledge of Islamic approach to international relations are different from other theoretical approaches of this discipline. Although there are some similarities between some of the theories as reflective and cultural theories. One of the similarities is challenging the existing international system. The existing international system is originated from the capitalism society theories and needs. According to neo- Gramscian theorists in international relations, we are faced with a kind of capital international sovereignty and the market. By accepting this theory, Hajj ritual challenges this system from some aspects:

The challenge with capitalism order via power maneuver

One of the most important features of the existing international order is coping with the structure of capitalism system power. Islamic theory challenged international theory based on normative and critical nature and based on trans-theoretical principles. One of the most important grounds of providing the possibility of showing such approach is the power demonstration of the Muslims during Hajj pilgrimage.

As it was said in the history, Hajj pilgrimage due to the focus of a part of Islam world population at a definite time and place can be a power maneuver and an instrument to put the existing international system on pressure at appropriate time.

Rejecting the dominant interpretation in the existing order from globalization

As the current international system is pursuing the development of such special type of globalization, various rituals as stoning the Devil can reject such similar global types. On the other hand, Hajj ritual gives the opportunity to the Muslim to state their special interpretation of globalization to the world. It seems that this opportunity means challenging the dominant international interpretation of globalization and challenging the existing order.

The combat on Islam phobia

The existing international system with hegemonic attribute and after USSR collapse, it searched for another definition for itself to continue his life. After the September 11, 2001 this is defined in the combat on Islam world and the order based on Islamic values. Thus, the existing order by some concepts as fundamentalism attempted to create some crises as propagation of Islam phobia in the world. It seems that Hajj by some aspects can be effective in overcoming this thinking.

- 1- Peaceful action of the millions of Muslims of various race, culture and ethnicity in the greatest gathering of the followers of a thinking system in the world showed the peaceful attribute of Islam religion.
- 2- The participation of both men and women in the manner of holding Hajj pilgrimage can show the equality attitude of Islam sharia.
- 3- Hajj by creating some opportunities for the various orders of Islamic nations can provide an opportunity for Islamic attitudes gathering to fight against anti-Islamism.

Thus, religious- political pilgrimage of Hajj can be a good ground for peaceful actions between the Muslim nations under the supervision of a unique actor in international system. On the other hand, besides showing peaceful biases of Islamic theories of international relations show the international relations that despite the existing international structures in making Islam and Islamic nation Muslims as threatful, identify the peaceful nature of international actions and emphasize on it.

Conclusion

The most important examples of political aspects of Hajj are as:

- 1- Participating in Tawaf as the demonstration of power of Tawhid to attain and increase the power
- 2- Applying Hajj as the demonstration of disagreeing with the existing order
- 3- Islamic consciousness in Hajj pilgrimage
- 4- Creating legal concept of Islamic citizen
- 5- Creating new social class with the title Hajj pilgrims
- 6- Consul interactions between Islamic countries with focus on Hajj time
- 7- Political economy of Hajj
- 8- The effect of the definition of common identity on solving the Islamic nations problems and close relation of the religions
- 9- Islamic unity
- 10- Hajj and Islamic global government
- 11- The capacities of Hajj in combat on Islam phobia

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Surveying basic facts of anthropology from Sohrevardi's point of view and educational deductions resulted from it

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Abstract: The aim of this study is to investigate basic facts of anthropology from Sohrevardi's point of view and educational deductions resulted from it. Sohrevardi's anthropological basic facts are theism, contemplation, seeking for maturity, seeking for society. The methodology of the present study is descriptive and it is an applied research. Statistical population includes works of and other experts (about Sohrevardi's thoughts). Data were gathered by interviewing with professionals in this field, note taking on cards from library information. In this direction, strategies have been suggested to develop above mentioned basics and their application can shift educational settings from external knowledge transfer to knowledge production (creativity).

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Keywords: Anthropology, Education, theism, contemplation, seeking for maturity, seeking for society

1. Introduction

Since human being is an intricate creature and has somniferous entity dimensions, each field of knowledge which engages in recognizing one dimension and aspect of human being, indeed that field has inspected the knowledge about man, and can be entitled as anthropology. So anthropology is surveying and analyzing human being (Mahruzade, 2007, p.28). The word "anthropology" is derived from Greek words "Anthropos" and "logos" that mean "human being" and "inspection" respectively. The literal meaning of the word "Anthropology" is; "to study man and his features". From Gerald Weiss's point of view, Anthropology is the science of studying a series of phenomenon that are related to human beings in every place and all the time (Valv and Robert, ghobadi hamedani, 1999, p.1). Aristotle use the word Anthropology for the first time, and his view about Anthropology was a science which its purpose was knowledge about human beings (Farbod, 2001. P.3). such an interpretation about the Anthropology did not have any concept till the renaissance, so that the concepts of "man and individual" had been paid new and different attention. In the early 19th century, Paul Brocca applied Anthropology as a concept of knowing man physically and naturally, and he chose the natural man as the subject of this science (Naragi, 2000, p.88). Anthropology is a science through which we can study man and his manners of living (Kneler, Ahanchiyan, 2009, p.1). In descriptive lexicon of educational science, Anthropology is studying man, specially his cultural, physical and social customs

and relations. As a whole, Anthropology should be considered as a science which study man or humanity (farmahini farahani, 1996, p.30). On the other hand, every kind of knowledge system which inspects human beings, one or some dimensions of the human being or some special group of human being, is called Anthropology (Rajabi, 2001, p.16). Human being, as a subset of world of being, is not condensed in the material dimension of body, but he has a non-material dimension called soul (Alavi, 2007, p.113). So human being is very different from other creatures. Man has special characteristics which let him have physical and spiritual ability and capability that are special to him. These characteristics and capabilities give man an especial position among other creatures (Shamli, 2005, p.10). In this research since the subject of Anthropology is important, we have surveyed the basic facts of Anthropology including theism, contemplation, seeking for maturity, seeking for society and its resulting educational deductions from Sohrevardi's point of view.

General Objective

Surveying basic facts of anthropology from Sohrevardi's point of view and educational deductions resulted from it.

Specific Goals

1- Surveying the subject of "seeking for maturity" from Sohrevardi's point of view and its resulting educational deductions.

2- Surveying theism from Sohrevardi point of view and its resulting educational deductions.

3- Surveying the subject, of "seeking for society" from Sohrevardi's point of view and its resulting educational deductions.

4- Surveying the subject of "contemplation" from Sohrevardi point of view and its resulting educational deductions.

Research Significance and Necessity

The most important question that the philosophy, as a branch of the huge tree of humanity recognition during the history of life, tries to answer is the issues of "man" and "man entity". On the other hand, to change human being without having any description and image about mankind is not possible. So description of man is a head stone in every educational system, because administration of educational system, such as; concepts, exemplifications, aims, principals, courses and education process control man's statues in some way (Bagheri, 2007, p.15). One of the special characteristics and differences of man from other creature is his being inspired by God's soul. Man is prostrated by angels, he is God's deputy on the earth, and has covenanted with God and also he has accepted a fideism from God, while all other inanimate creatures; such as earth, heaven and mountains, apprehend accepting this duty (Alavi, 2007, p.15). All elements of Education system including objectives, principles, factors and obstacles of pedagogy testify human status so it is necessary to know human being and his being aspects (Beheshti, 2000, p 45-46). Also human being is the basic axis of the education system, because he has many unique features which make him different from other creatures, so the basic subject of this research is emphasizing on anthropology and educational deductions resulted from it.

Methodology

This research is aimed to study basic facts of anthropology from Sohrevardi's point of view and these anthropological basic facts named theism, contemplation, seeking for maturity, seeking for society are variables. Another variable is educational deductions resulted from anthropological basics In descriptive research, the researcher pay attention to describing and writing report about the situations and incidents, based on information which have descriptive aspect merely (Naderi & Saif Naraghi, 2011, p.40). So the methodology of this research is descriptive and it is an applied research. The population of this research consists of Sohrevardi's writings and some other authorities' writings about

the ideas of, we have chosen and inspected the subject of anthropology from these writings.

In this research, the sample conforms to the population, because of selecting subjects from available references; we have not an especial selection in this research. so the sample group has been chosen from an available statistical population, the method for gathering data is using library including note taking from domestic and foreign sources. In addition, we have used fiche and interviewed authorities and masters of this field. The criteria of analyzing data are just reasons and documents. We also used descriptive statistics (assorting and categorizing ideas and stating differences and similarities).

The basic facts of anthropology from Sohrevardi point of view: intellectualization and contemplation, seeking for maturity, seeking for sociality and theism (seeking for God)

1) Principle 1: Intellectualization and

Contemplation: intellection and contemplation about universe, blessings of God and order of universe have important rule in training of man; because, not only rationality training depend on thinking permanently, but also innate purity is pending to intellectualization and contemplation (Nasr, 1993, book 3, p.396). The basic facts of intuition philosophy of soul are; reasoning, intellectualization, contemplation, ratiocination, purification of soul, expelling innate from materiality and paying attention to intellectuality (Imam, 1974, p.16). From Sohrevardi point of view, intellect is a decisive proof, and what is rejected is considering superstition as reasoning and abusing ratiocination. So the intuition philosophy of the soul is a field of knowledge which never is equal to mysticism (Ebrahimi Dinayi, 1987, p.49). The way for the philosophy of illumination of the soul has been shown by the lord of uprights, Imam Ali (peace be upon him) says: « we never see something unless we see God before, after and beside it» (Imam, 1974, p.18).

Although, from Sohrevardi's viewpoint, philosophers are owners of intuition, not the disciples of reasoning and proof, he prizes reasoning, intellectualization and contemplation, and tries to offer his intuitional ideas relying on proof and ratiocination, which has been gained under the protection of mortification (Beheshti, 2000, p. 80-82). Emphasizes about intellectualization, contemplation, and ratiocination and admires a philosopher who matures debate philosophy in the first instance and then reaches enthusiasm philosophy. Such a personality can transfer to the rational language of meditation

that has been gained through intuition (Naghizade, 2006, p.165). Although he respects philosophers such as; Plato, neo-platonics and the philosophers of ancient Iran, his criterion for accepting or rejecting their ideas is reasoning not the prominence of their science and knowledge. He recommends thinkers as follows: "never imitate me or others, but think based on reason, never accept an action without reason, because the reason is a criterion for realization and accepting". Sheikh Eshragh should not be considered as a mystic, because, although like mystics he considers innate purification as basic knowledge, he accounts the mystical traits as being misled, and gives serious importance to the intellectualization and contemplation, without philosophical reasoning and thinking (Beheshti, 2000, p.80-82).

In his most important work called "Hekmat-ol-Eshragh", which emphasizes on philosophical school and enthusiasm philosophy, and was an inspiration from God based on his own words, Sohrevardi tried to write it based on intellectualization, reasoning and ratiocination (Nasr, 1993, p.300). His ideas in two forms: one method is through reasoning, the other through story and parable. He used the method of reasoning in writing his book, Hekmat-ol-Eshragh, and used the second method for writing books such as; "the red reason", "the sign of Jabreil's feather" and "the story of nostalgia of stranger" (Naghizade, 2006, p.165).

Explicitly says; if somebody is not expert in the field of intellectualization, contemplation and ratiocination sciences, he will not reach intuitional philosophy and it won't be possible for him to understand facts. Although he had disagreement with Mashayi scientists, and had criticized them, the reason for his disagreement with them never was his disagreement about their reasoning, intellectualization and ratiocination (Ebrahimi Dinayi, 1987, p.48-49).

The threefold stage which cites in the introduction of his book "Hekmat Eshragh"¹ and the story that he says about the connection between reasoning and intuition, has three stages as follows: the first stage is rationalism, in this stage, recommends the aspirants of enthusiasm philosophy and the lovers of mysticism to learn the philosophy of mashayi, that is, learning the philosophy of reasoning-ratiocinative, and he also emphasizes on this kind of education till he makes clear this matter that the philosophy is a background for mysticism, and those who are not completely satisfied with reasoning and ratiocination, will not reach the shore of knowledge

and love. He believes that intuition is the best stage of reasoning and he also says: "the best seekers of knowledge are those who seek both for intuition and mysticism and also those who search for debate philosophy or rational philosophy" (Dabe, 2007, p.24). The second stage is intuition, from Sohrevardi point of view; in this stage those, who have gained maturity in the stage of reasoning-ratiocination, access the stage of mysticism and the high rank of reasoning (Dabe, 2007, p.24). The third stage is returning to the reason. In this stage, speaks about returning to the reason and ratiocination and says: "after discussing the intuition of the facts, I paid attention to deliberation and gave reasons to the affirmation of the facts about intuition" (Dabe, 2007, p.24). Also notices to the reason in the theism and his thesis "fi eeteghadel hokama" show his attention to the subjects of reasoning and rational ratiocination in the knowledge about God (Taheri, 2007, p.15).

Principle2: Seeking for maturity .Sheikh Eshragh points to the most important feature of man called "seeking for maturity". He believes that all men are seekers of maturity and beauty. Sohrevardi considers this feature special to mankind and believes that all creatures are found of maturity and try to reach high rank of goodness. God is mere good and mere maturity and even knowing him is one of the innate sciences that man confesses it not with a reason, but through awakening God's presence. The other features of men are seeking for virtue and fact and tendency to the self-preservation, we can consider these features as ramifications of seeking maturity. Maturity has several ranks and man gets various ranks according to their grade of maturity. In spite of this, man did not get his final maturity in this world; they can get the final maturity while getting rid of darkness of this world and reaching to the afterlife.

From Sohrevardi point of view, maturity is; "getting rid of darkness and abandoning belongings and everything unless God", calls this action as "annihilation". In this stage man understands that he is mortal and abandons both worlds, and his heart gets full of God's love and he did not see anything unless God. Such a man reaches the source of light and fact and enjoys from unbounded sciences of God and highest gratifications. This position, which is the position of annihilation, has several ranks. In the first stage the mortal mankind can hold both him and the world. In the second stage, which is called "the great annihilation", man forgets himself completely and only attends to God, but this stage is incomplete yet, because man is aware of this action of forgetting. In the third stage, that is "the annihilation within annihilation" stage, the seeker not only forgets himself but also forgets this forgetting action, and

Hekmat-ol-Eshragh, shahab-ol-din sohrevardi: Mosnagat sheikh eshragh (2), edited by : Hanri crien, the research center of humanity sciences and cultural studies, 2001, p. 12, 13.

intuits God, without awareness of his joining to the absolute rank (Beheshti, 2000, p.90-91).

In short, from Sohrevardi's point of view, the ways for gaining maturity are as follow:

1) **Awareness of one's own expatriation:** the first step for getting maturity is being aware of one's own expatriation and loneliness. If man knows that he has got prisoned in this world for a limit time and has been deprived from associating with heavenly natures and intuiting facts and light, and his original home is the world of God, he will understand that he is stranger in this world and so will seek for a solution.

2) **Abandoning interests:** one condition for gaining maturity is abandoning sensualities and materiality. For getting maturity, man should unveil dark material and body and get rid of every kind of attachments to non-God. If man seeks for materiality and world attachments, he won't get maturity.

3) **Observing divine law:** if man wants to gain maturity, he should observe God's commands and obey Koran. Religion consists of Koran and law and the seeker of maturity should settle these as criteria for detecting right and false. recommends to the seekers of maturity as follow: thou, my brothers, I recommend you for guarding religious precepts and leaving unlawful things, paying attention to God, leaving nonsense behavior and clavering and abandoning Satan (masnafat, book 2, p. 257-258).

Principle 3: Contemplation. The seeker of maturity should always deliberate about the secrets of order of universe, earth and heaven. If they always think about spiritual deeds, heavenly sparkles and divine intuition will descend to them.

4) **Love of God:** gaining maturity isn't possible without love; it is love that joins the lover to beloved, the extreme limit of loving is agape. Two basic requisite of getting love of God are amour and sapience (canon of Mosnafat, fi haghgte eshgh, book, 3, p.284-286).

Recommends following values, for getting maturity which are between God and mankind: Pietism, cutting off from everything unless God, praise of God, worshipping God, saying prayers and supplicating (Beheshti, 2000, p.101).

In addition to above mentioned values, there are some other values which are related to human, and man should pay attention to these values for getting maturity, these values are: abandoning oneself, reckoning deeds, undergoing mortification, eating, speaking and sleeping less, resisting, depletion, epiphany.

- 1) **sociality:** in the case of "sociality", which is one basic fact of anthropology, believes that: "God created man and made him different from other creatures and made humans dependent on each other in their technical works, because, if a man

wanted to do every needed works lonely, it would not be possible. Since man have many needs and one person cannot do them lonely, so man should arrange the works with the help of his fellow creatures, for example one grows wheat and the other makes instruments of bakeshop and etc., so human being should not be one person, but groups and individuals so that they can go living. Such kind of societies and living in groups lead man to found cities and make instruments of living in those lands. And when the system of world were like this and man is forced to have communion and bargain with his fellow creature for self-preservation, as a result man is also forced to have law and tradition based on just and laws, so that they can live under the production of that. (Haeri pur, 2006, p.45).

Principle 4: Theism (seeking for God): From Sohrevardi's point of view, God is devotee and God's willing is innate. Sohrevardi's meaning about the God's innate willing is equal to the translation of Ebne Sina who refers to the willing as the contentment because of its relation to innateness. So, like Sheikh-ol-Raeesi, he also considers contentment and love of God as the real meaning of God's willing. So this theory paves the way for expanding theoretical mysticism among the theosophists following him, and also, this theory shows the theosophical thoughts of and Buali Sina (sajadi, 2005, p.58). One of the most important philosophical issues is theism or believing in the reality of God's presence, there are many proofs in this regard, but Sheikh eshragh, citing the question of light, have different view to the question of theism. In the philosophy of, light has special position. From his point of view light is apparent innately and is the symbol for other creatures. Comments God as the light of lights, and founds his system of philosophy based on verbal science. From his point of view, reasons and souls have ranks and the highest rank is God, and the lightness of all the lights is the grace of his light. « because God grants live and bestows light». (Nurbakhsh, 2004, p.46). The word "nur-ol-anvar" (light of lights) is derived from the verse 35 of surah Nur: "Allah o nurol samavate valarz" that is; "God is the light of heavens and earth". And God's light is apparent because of his nature, and the other creatures get light from him and get apparent, so God is the light of all lights and the lightness of every lighted is under the shadow of God's light, so the heavens and earth get light from God.

There is another verse about light: "va ashraghta al arze be nure rabbeha" (and we enlightened earth by the light of its creator). In some of translations the word "light" is considered as one of the God's names. Has gave some other titles to "nur-ol-anvar", titles

such as; "holy light", "comprehensive light", "great light" (Nurbakhsh, 2004, p.46).

Educational deductions resulting from anthropology from Sohrevardi point of view

The literal meaning of education is; a trend through which the teacher gives subjects to the students. And generally, education is providing situations and reasons so that the learner gain a science (Alavi, 2007, p.38-39). Education is speaking and suggesting meaningful words so that the learner understands the meanings of those words, hereby he/she put into practice the talent of his education and became learned. (Amini, 2003, p.14). Education is a road which ends in evolution, and if an education didn't lead to evolution, it won't reach to its real meaning (Naghizade, 2006, p.16). When we are trying to teach students a specific subject, an education takes place (shoari nejad, 1995, p.177). The root of the Arabic word "tarbiat" (education) is "rbv" and its literal meaning is "making dehiscent", "putting into practice", "to grow", "to enhance" and "to bring up" (Alavi, 2007, p.39-40). The word "training" means; "to involve man with Devine"(Bagheri, 2007, p.64). Training means; "canceling the process of going to extremes and paving the way for moderation (Shokuhi, 1988, p.2). Training is not creating new talents in the creatures but is growing the existent talents (Alavi, 2007, p.42). From Plato point of view training is discovering natural talents and bringing up them (Kardan & et al. 2001, p.170), Plato believes that training is the most beautiful feature of man which is unfolded (Sharafi, 2000, p.22). From Aristotle point of view training is a kind of habit making (kardan, et al.2001, p.175). Training means providing suitable situation for abetting every kind of talent in a creature, so that this abetting can help him in getting maturity continually (Burumand, 2009, p.28). Training is "choosing a kind of suitable behavior and speech, creating necessary conditions and reasons and helping the trainee so that he can fertilizes his bosomed talents and moves toward his aim and maturity (Amini, 2003, p.14).

"Training or education is paying attention to fortification, confirmation and signaling man's features which are coordinated with human entity, and is equal to everybody, everything and every places, without paying attention to the conditions and transitory cultural and social (Naderi & Saif Naraghi 2011, p.4).

We try to approximate the aims of philosophy, mysticism and religion, and to coordinate reason, religion and mysticism. From Islamic point of view Training has two kinds of aims: "final aims" and "intermediation aims". The final aims are

ultimate aims which man should gain them, and the inter mediational aims are steps toward the final aims (Alavi, cited from Bagheri, 2007, p.129). Sohrevardi had paid little attention to behavioral aims; instead he had paid to the ultimate and intermediational aims. Naturally, all the aims are not equal, rather, God's affinity is the apex of all aims and the other aims are contexts and steps for the ultimate goal. From sheikh Eshragh point of view, aims are as follow: "God's affinity, thought nutrition, intuition, innate serenity, equilibrium of moral (Beheshti, 2000, p.103—105).

Educational methods from Sohrevardi point of view: Through adopting suitable training methods, we can realize training aims. The most important suitable methods of training from Sohrevardi point of view are: learning philosophy, right deeds, penance, meditation, rosary, praying, reading Koran (Beheshti, 2000, p.103-108).

Propounding the methods:

1) Emphasizes on intellectualization and contemplation. Although he calls the intuition and enthusiasm philosophy very important, he emphasizes on contemplation. Intellectualization, contemplation and intellectual development have special status in training and are some of the aims of education. One of the best methods, which are used in educating individual, is fostering and fortifying intellection power, because intellect has important rule in controlling animalism and inviting to good deeds and bounding to behavioral respects. The reason is the best advisor and most of the behavioral and social problems of man are the results of idiotism and weakness of intellect power. If the reason is powerful, it will capture the helm of materiality, and will conduct it according to real advices, and then such a person will be guided to the right pass (Amini, 2003, p.38).

2) The growth of creativity has effect on the developing of contemplating and intellectualization, and the teacher, as an important element of training, has important rule and effect on the growth of student's creativity and intellectuality, and using educational technology and suitable educational methods, such as pre-organizing methods, inductive methods and researching and etc., he can have great effect on the reasoning and intellectuality power of students and can have a rule as a guide or controller, till students learn the correct method of thinking and brain creativity, and while encountering the problems of life they will have a correct view. Naturally, it is obligatory for all the cultural and educational systems to collaborate till students step such stages (Turani, 1992, p. 38).

3) **Avoiding memory dependency:** in order to improve in the field of reasoning and

intellectualization, students should avoid memorizing unrelated subjects, because understanding subjects and apprehending themes hardly cause forgetting and so learning take place. (MirzaBeigi, 2011, p. 7).

4) **Developing correct viewing faculty:** one other method for developing reasoning and intellectualization is gaining correct viewing faculty. From the early time of education period, Students should be familiar with reasoning till they make a habit for accepting every matter with reason and develop the faculty of contemplation and intellectualization (Shariyat Madari, 2012, p.88).

5) **All men are seeking for maturity:** there are many educational factors for gaining maturity, from Nahj-ol-Balaghe point of view these factors are: theism, positivism, developing contemplation and intellectualization faculty and self-awareness (Hashemi Ardakani, 2009, p.177).

6) **"Family" as a most important factor in social education:** in addition to being a source for inheritable features and necessary talents for educating children, family is also the first environment that the child experiences it and makes relationship with the world. Family atmosphere is a factor that the child has the most contact with it, and it gives the shape to his character. Child's image of himself, his sense and perception about his environment, his relationship with others and quality of his methods for supplying his needs and etc. all and all take root from his experiences and relationships that he had with his family in the early period of his life (Tavassoli, 2000, p.75). Parents' behavior, autarchy, extreme freedom, being democratic, observing beside concession and adoption, kindness and asperities and etc. are elements that play rule in the process of Child's socialization and make him as an element for the future of the society (Haji Dehabadi, 1996, p.8). That is why Ali (peace be upon him) advised Malek Ashtar to choose his functionaries from individuals who are trained in a full-blooded family: "employ experienced and honest men who are from honorable families and believed to Islam sooner than others, because they have more munificent behavior and more desirable manner and are not avaricious but they are providential".

7) **Seeking for God is an innate feature** and how we can characterize it in students? There are some barriers hear; if we control these barriers we will expand the feature of God seeking in students. These barriers are: "impurity of soul"; impurity of the soul discards man from God and destroys original purity of the soul, so temperament of such man cannot be dehiscent. The other is "impurity of society"; merging the society with sensuality, agitating concupiscence, indolence and brutal features are

reasons for sinosity or destroying Godly mettle of man. The next factor and barrier for innate guidance of man is unsuitable environment. Expressing religion concepts incorrectly and in the form of creating unreasonable and non-scientific image of God and his attributes or creating conflict between religion and other natural tendencies of human being are some other reasons for suppressing religious innate of mankind (Musavi, 2002, p.4). Instead, there are some factors that awaken the innate feature of God seeking. The factors like; purity and abstractness of the society and environment, scientific and correct explanation about the concepts of religion.

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Investigation of Children and Teenagers crime and supports from Legislator

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Abstract: We have investigated Children and Teenagers crime and supports from Legislator in Iran. In this research, society of boy criminal has analyzed. Results indicate that prevention the crime is more important than its occurrence and it can prevent the crime considerably.

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1. Introduction

Children and teenager's sin is an important problem and in the other words, a complicated social problem. In related to cause of increasing in children's sin there are different ideas. Some of researchers believed that increasing the crime related to developed countries. Others believed that by improving the industry, factories buildings, noises increasing, cities developing. And population concentration in industrial centers human lost his peace. The others believed that sinfully increasing related to weak religious beliefs. Some contemporary scientists believed that more developing in antisocial behaviors is from cinema and Television developing and some others believed that war is main cause of children and teenager's committed crime increasing. Sin in children and teenagers is a main problem for today societies in world. if this problem in past years related to developed industrial countries, today by developing industry in the world or its results transferring and cities growth in the world, this problem become global problem. In present age, wondering of another world war which will be strong and destructive weapons war hurt children and teenagers and led to wondering and beardlessness them about their future. Present century is anxiety and speed century and children and teenagers are accelerated to reach their desire goals even by violation from rules and laws. Children sin have been discussed in many books from different countries and criminologists, judges, doctors, teachers, psychologists, sociologists and other who Faced by it, in all countries have respected to it and have studied it. Therefore, judge of children must have a special superiority to others and this superiority means during long term of his judgment, he faced by thauthands sinner children and has studies many life's of them. We have investigated Children and Teenagers crime and supports from Legislator in Iran. Overall effective factors on children and teenager's sin the factors which are effective on sins

by children can be divided to four main groups such as following:

- 1) Social factors (or social environment effects on children)
- 2) Biologic and individual factors (or mental and physical causes)
- 3) Exceptional and indirect factors and causes
- 4) Divorce and family interruption.

1.1. Social factors

a) Internal and familial environment:

We know that children as such as adults are also affected by social environment and around them. By first way familial environment of each child is effective on him more than others, because, family is the first core or foundation of society.

1) Effects of familial behavior and relations

We said that family is the main base of society. It means that children learn the first lessons from it. Thus, parents have a heavy duty for child's training and a little ignorance of them led to children's confusion and their deviation from right way and their falling to sin cliff. Aware and sympathetic parents, rather than treating and punishing their children must be explain faults of their action kindly and by a language which is understandable for the child and must encourage them to respect to other's ownership.

2) Effect of imitation

Parents (mother and father) are the first and the closest persons whom children imitate them. And they are actual patterns for their children. Thus it's necessary that they respect together in present of their children and don't forget politeness during talking together. Those parents, who don't care of their behaviors, will have children who are sinners more possible and they may conduct sinning activity such as rubbery, vituperation and properties destruction.

3) Punish and encouragement

Some persons believe that body punishing must be done and some others don't believe that and each of them have some reasons for their claim.

The third resolution which is offered is that they must avoid of punishing the child as possible, and try to warn him by logic and reasoning which is understandable for the child. And if they don't reach to a favor result, they can punish him lightly in manners that don't lead to mental and physical hurt in the child.

Of course, punishing mustn't be so severe that remain in tense physical and mental effects on the child, and this recommended in Islamic rules.

2.1. External environment and relatives

We all know that when a child doesn't have kind and sympathetic relative in him/her family, he/she actually feels unfortunate and tries to avoid of his/her family as possible and to find a peaceful and relax place in external environment. Being general, permanent conflict between parents lead to suffer in the child, more than other problems. And when this case is integrated by other problems, lead to hate feeling in the child related to his/ her home and absorbs him/her to streets and Alleys. Second discussion: personal factors: Biken Berg defined personal factors as a set of reactional trends which are in person in a given time actually. These trends may be earned or hereditary form. Some researchers and children sin experts believed that some physical factors and causes such as disability face ugliness effect on sin from children.

But, because these physical defects lead to physical ganglions which are main stimulant and motive for sin or anti-social behaviors, therefore, we don't know that physical factors are certain effective factors. In a suitable environment and among kind families which are able to train their children by accurate and enough caring each physical ganglions is lost from child's nature. it must be said that sometimes, some hereditary diseases in fathers and mothers lead to sin in children some well-known factors which their presents in parents affect on children's sin are:

A) Parental problems: parental problems are all diseases, addition and disorder those maybe physical or psychal problems. 1) Parent's addiction: 5 parents addiction to alcohol or opiates disaffect on the children. This effect not only as result of hereditary lead to mental and psychal backwardness, but also sometimes it may devote the child after observing unsuitable behaviors which are from alcohol or opiates using by father or mother. Today, from the medical view point, it's proved that alcohol hurts the liver, stomach and brain and sometimes may lead to cancer and other cerebral disorders.

2) discusses and physical causes of the parents It must be known that diseases whose presenting mother or father may be a cause of their children sin,

are ordinary divided to two groups: physical diseases and psyche diseases.

The most important physical disease whose presence in mother and father effect on their children sin, are shocker, syphilis, tuberwlosis etc. and they often lead to mental and physical disable children, birth.

3) Parent's mental weakness

Mental weakness means spiritual failures and mental disorders in one of the parents or both of them. It's clear that stupid and mad parents cont train their children and supervise their behave ours such children go gradually toward mistake ways and grow such ad profligate sapling.

However we can't claim that parent's mental weakness is effective for children sin increasing certainly, but many researchers and penal law scientists believe that this case is not ineffective on children and teenager's sin.

3) Personal problems

Some of effective personal problems on children sin are lack of mental balance and intelligence efficiency. However some criminologist and children sin experts believe that physical problems are also effective on children sin, but we don't take account physical problems as enough factors for this. Because, ever the time, more and more it's observed that some geniuses and famous persons in politics and science suffered of physical failures in childhood (or even adult hood). Children disability's influence depends on parent or relative's behaviors related to them. Thus, if their behaviors are free of humiliation and offense and if they respect to children's training, physical failure will not effect on children sin. About psyche misbalancing, some experts believe that this factor mustn't be taken account as an absolute factors for children sin, but is formed depend on social and family environment in which the child grow. Mentioned factors can more or less effect on sin activities.

In each case, a point is important and it's that based on statistics in European countries, ratio of mental and psyche disloalancing among sinner children is more than others.

The third discussion: exceptional and indirect factors and causes exceptional and indirect factors and causes are some problems which randomly and indirectly effect on children's behaviors such as sin actives. In the other words, these factors and causes aren't always present, and theirs effects on sin isn't also directly.

The most important factors are: war, internal turmoil's, natural events such as flood, earth quick, storm etc. and finally divorce and family focus breakdown.

1) War and internal turmoil's

If you refer to statistics of children's sin in Europe during Second World War, you will see that in some European countries, children's sin during the war radically increased. For example, in England based on children's sin statistics it's presented those children's sin in 1941 which faced to Second World War period in England, is in the peak and offer that gradually decreased and reduced its domain. In France, condition was also similar to that, it means statistics of young sinners in 1938 was only 1200, persons and in 1945 increased to 38000 persons (more than 3 times) here, it must be explained that increased children's sin during the war was not

Always quite in every place as it's observed previously, rate of increasing the children's sin during the war is different for different sins. But, overall it must be said that during the war or internal revolutions or turmoil's, in a hand, stability and survival of families become indecisive, and in the other hand, economic development of some countries will be stopped and public poverty are increase these two factors (instability of families- public poverty) and to children's sin.

Sometimes, in addition, in some families, father goes to battle and mother stays lonely in the home, and because she aren't able to control and supervise on her children's behaviors because of daily problems, children for lack if enough care and more freedom, trend to rebellion and fall gradually on sinning ways.

In these situations, school going condition is also unregulated.

Because some schools are compulsorily closed and some others are faced to lack of space and students density. These problems provide desire condition for children's sin.

2) Natural events

Natural events are some events which occurred by nature forces and lead to big decay and damages. It's certain that as a result of big natural events such as flood,

Storm, earth quick and mountain's emitting fire, many houses are destroyed and numerous children will be homeless and in disarray. In such situations, one of the most current sins among children is robbery which for satisfying hungriest. They Performed it. Fourth discussion: divorce and its effects on children's sin divorce accuracy between mother and father can be one of the exceptional causes of children's sin. This case, sometimes lead to deviance for disarrayed child and pull him/ her to crime way. One of important social calamities in the country, is divorce, that is weed's destroying between wife and husband, and will be increased every year than before, and go toward up. Based on statistics which are in newspapers and even is some research

books, in recent years, of each 3 wedding, one lead to divorce. We can account following factors as most important causes of divorce.³

1) Forced marriages

As observed from newspapers or news pages of different journals, many of forced marriages after a period lead to divorce. By respect to religious belief weakness, especially in cities and divorce increasing in citizens. It's appeared that forced marriages in cities and among poor families are for meeting family financial needs, welfare acquisition etc. and still Present by seriously and warring cases.

2) Husband addiction

Unfortunately, in present, husband addiction problem is spread and many of ladies, who demand to divorce, explain their fundamental problem, their husband addiction. It must be noted that his social problem lead to their children addiction and corruption, too.

3) Irrational age difference between wife and husband a collative marriages, a few age difference between wife and husband is necessary and this point may not be strange. But in forced marriages big age difference is important factor for lack of entente between wife and husband and as result for divorcing.

4) Superficial looking at marriage

Carelessness about marriage and family focus forming without responsibility feeling and without its results considering, is also one of important factors of divorce.

2. Discussions

Crime has a penal meaning defined as an action which is known guilt by the rules. Therefore children crime is a social problem on based on several offences which are conducted by children.

As mentioned previously, some researchers believe that increasing children and teenagers crime is for developed societies and the others believe that industrial developing, factories building ,sound pollution ,cities extension and population concentration in industrial centers are main causes of the crime and some others believe that the main cause of crime is religion beliefs weakening .Some researchers also believe that increasing action are related to medias completion such as cinema and TV and these due to crime increasing. Children and teenagers crime is today, the main problem for world societies. However this problem in last years for industrial improved society, today by industrial development in worldwide and its effects transferring and improvement in city living, this problem will be global. For analyzing the social causes of the crime, it can be said that perfect distinction social factor is impossible, because each social factor is a result of the other factor or affected by the other factor. Thus,

distinction and study each of them isn't an isolated line studying. On the other hand, these crimes are changed, affected by special social factors which have been known some of them so far. The most important factor that separates children and teenagers crime from adults one, is aging factor determination the age of crime beginning is related to study special rules of criminal children and penal laws and scientists researchers. Therefore, above meaning are different in each country, and comparing statistic of different countries is not a true a manner. Children crime in some countries includes conducted crime by children. But in some other countries they include all offences and even all anti-social behaviours which are censorious.

In some statistics, Criminal children are all children who are arrested by police. But in the others, they are only children who are sent to the court or who are condemned. Its interesting that determination the age limiting for children is different in different countries.

If we study the of criminals ages, we will see that conducted crimes statistics between 12to 20 years old are increased.

It's concluded that children crimes are a social problem which depends on childhood and adolescence aging.

In Iran, criminal child is a person who conducted an action which is forbidden by the rules or who didn't conduct an action which is necessary by the rules. Such person is criminal or guilty person in Islam and if he/she will be condemned based on judges opinion.

In overall, it can be said that important factors which are effective on children and teenagers crimes, are:

- 1) Social factors
- 2) Personal and biologic factors.

The most important role in social factors is for family environment .We knows that children similar to adults are affected by around and social environment .In particular, family environment of each child affect him/her more than others.

Because family is core or base of social construction. Family is the main basement of society. Its mean that the child learns the first lesson from family, Therefore parent have a heavy duty about their children s training and a little neglecting from them leads to their children s deviation and trend to the crimes. A ware and kind parents must explain their child disadvantages of the crime by such talking that is understand able for him/her and must encourage him/her to others owner ship that serious punishment or treatment .

Imitation from the parents, punishment and encouragement, and confliction between parents have

important roles in children s training. Characteristics of personal factors are:

- 1) Parents.
 - a) Parents addiction.
 - b) Physical disorders in parents.
- 2) Physical disorders in parents.
- 3) Mental disorders in parents.

Divorce between the parents can be considered a special cause of children crime.

This case may lead to deviation for UN supervisory child, and pull him/her to criminal way. Based on mentioned statistics in these years, in Iran one third of marriages lead to divorce. It indicates that from 1374 number of divorced families have been increased to %15.

Based on statistics, in 2006, one fourth of marriages lead too divorce. Iran is the fourth country whose number of divorce is large.

Its means that Iran is after America, Egypt and Denmark in most number of divorce. Based on research s by local and foreign research s, following factors are the most important factors for divorcing:

- 1) By forced marriages without know dement together.
- 2) Wife or husband's addiction.
- 3) Unacceptable aging difference between wife and husband.
- 4) Super facial looking to marriage problems.
- 5) Poverty and economic factors.

6) Several wives having.

7) Family s interfacing and using excuses by wife and husband. Crime from sociologic viewpoint: Sociologic research s indicates that bad and unsuitable performance by family is the most important factor which predicts crime in teenagers.

Effect factors on crime in this group are:

- 1) Social factors.
 - a) Cultural environment.
 - b) Natural environment.
 - c) Economic environment.
- 2) Cinema and TV.
 - a) Cinema and TV effect.
 - b) Newspaper and journal effects.

From sociologic viewpoint, family has an important role in children and teenagers crime increasing. Family is a social unit which formed by a man and woman wedding and children complete it. Family is the first global and general organization which is necessary for meeting human needs and society s life. However family is the smallest social unit, main core of society and basement of each large society, it also is the most important social unit for each human society.

Family .school and society are three main factors in social life completion. Father and mothers kindness in childhood and babyhood period have

vital values in personality and mental completion and growth in children. Some characteristics of family factor in children and teenagers crime increasing:

- 1) Pollution in the family.
 - a) Unbalanced family.
 - b) Addition in family members.
- 2) Conflition in family.
 - a) Imitation.
 - b) Lack of kindness
 - c) Familial conflition
 - d) Familial compulsion
- 4) Absence the father
- 5) Lack the parents

Those factors have been explained by details.

Investigation psychological factors for children and teenagers crimes: criminal problems aren't just related to physical and biologic factors. However in some cases biologic factors have effects on criminal actions, but these factors can't create antisocial behaviors lonely, and they should composite with psychological factors and both lead to criminal actions. Because human is a set of soul and body and these are depended on together, and separation them is impossible. As Arastu said, that soul is a center of body forces but without body, soul can't be lived. Thus, for knowledge the soul, body should be also studies. Zsigmondy Fruid believed that humans personality composed of, ID, EGO, and super EGO.

- 1) ID is a base of nature and personality in human.
- 2) EGO is opposite of ID. ID encourages human to enjoyment but EGO aware the human a bout rules and facts in the world and makes ready trends of ID with environmental situations by gradually growth in the child, contact with small society, family, and around s and environment in him/her is created.
- 3) Super EGO tries to make ready EGO against external world pressing and ID. It enforces from several sources. The first source is narcissism. Second is the parents super EGO. Mental disorders effects on the crime. Mental disorders in children and teenagers may be hereditary or created by a contagious disease. Psychologists and

Psychoanalysts analyzed IQ and mental condition of the children for analyzing crimes causes and knowledge children s personality. They be live that brain is center of intelligence and understand in each person and for each person and other organs per from these orders. Thus, if the smallest hurt is created in brain, the child will lose his/her understanding about result of his /her actions. Totally, mental disorders are divided in three groups:

- 1) By IQ less than 25
- 2) In became by IQ between 26to 50
- 3) Stupid by IQ between 51 to 70

As mentioned above, number of criminal persons who have mental disorder are more than normal persons and between 9to 36.5%of children and teenagers who have mental disorder like criminal actions.

Totally, social factors of crime include three following groups:

- 1) Crime against others properties and ownership such as theft, document forgery etc.
 - 2) Crime against person such as bash, transgressing and intentionally or UN intentionally murder etc.
 - 3) Crime against general discipline and security such as harlotry, drugs consumption and smuggling, revolting in general discipline and security, computer offence, violation against driving rules, vagrancy etc.
- Theft is increased proportional to development the city and industry and its kind are:

- 1) Simple theft
- 2) Theft from the homes
- 3) Theft the automobiles
- 4) Theft from the shops

Based on researches by professor Bataviya , laws teacher in Poland, theft in children are generally begun after 10years old. Supports by Iran legislator from children and teenagers crime.

- 1) Special conditions for judge's selection and legal capacity Determination for children s judges in Iran.
- 2) Performance in children courts.
 - a) Primary researches by the court.
 - b) Not open meetings for judgment.
 - c) Regard to legal rights of criminal child.
- 3) Decisions of children court.

The main aim of children crime judgment is not only justice establishing, but also reforming and training. The children .For this reason , legislator doesn't use of "order of the court" which presents legal violation and power and rather uses of "decisions" these decisions are almost different and are begun by advices and finished by prison.

- a) Decisions of the court about 6to12 years old children.
- b) Decisions of the court about 12to15years old teenagers.
- c) Decisions of the court about 15to18years old teenagers.

Reformation institute s performance one of the basic actions in this area is prisoners dividing and criminal children separation. This work was executed in 718in Italy and then in Poland, America and England. Other countries also executed this work after then. Reformation institute in Iran are composed of three separated sections:

- 1) Temporary imprisonment section
- 2) Reforming section
- 3) Prison

Each of above sections are separated of together and in each section the children are classed based on age, 23act of criminal children and teenagers court formation , history of conducted crimes by them and even kinds of crimes and their trainability.

Over ally, perfect eradication the children and teenagers crimes very difficult work. But there are ways by which children crimes are reduced and their expanding are limited. Therefore, needing to identify the causes of the crimes and their eradication are very important and they must be attention. Therefore, as mentioned previously, family and coeval groups have an important role on children and teenagers crime. Childrens experiments in the school and family environment complete their personality. Thus , if facilities and attractions of the school and family aren't enough , undoubtly , we will face to serious perversions among these children thus , society must be consider a priority to need and welfare of family and coeval group of the children which these priorities must be for the family and then for training. Programs and performances which provided by government society can provide conditions in which families can be trained about parent's role and duty for their children training and care. Government training form education should also atlined to who are exposed to risks. It seems that if an organization is established that by special. Places as a mediator directly between family and government, it can receive to suitable solution by that organization and receive the best and the most suitable training and legal supports for the Families. Control and supervising performance of education and training office in school can integrate coeval

groups and family as important factors. This work leads to suitable growth in teenagers by respect to their personality during the first period of their life. Personality is formed during children. Therefore, we should use different solution which is used by teenagers whose roles in future are important.

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Citizenship Education: A Fundamental Mission in Educational System

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Abstract: Due to the seriousness of globalization during the two last decades, the issue of citizenship has become the most important contemporary social issue and has attracted those involved in educational systems of most countries in the world. Fostering curiosity, independent thinking, emergence of abilities and talents, and strengthening the senses are among the issues emphasized in the new century which can be set into motion through designing and implementing citizenship paradigms. In this line, given the general object of fostering humans' personality, educational system has the most fundamental role in researching about the important responsibility of citizenship education. Schools and academic programs play a vital role in the educational materials, teaching methods, and an appropriate place they offer for extending the citizenship culture. So, the main mission of educational system is to socialize learners and equip them with the necessary knowledge, values, and skills for living in a society, or in other words, citizenship education. Of course, it is important to note that paying attention to merely one factor in institutionalizing the citizenship properties does not suffice as many factors in society are involved in educating a citizen in the present and future society.

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Keywords: citizenship education, citizenship properties and qualifications, educational system

1. Introduction

Due to the seriousness of globalization during the two last decades, the issue of citizenship has become the most important contemporary social issue particularly due to the fact that civil society is based on social institutions of citizenship system. Therefore, citizenship institutions such as the legislature and political sovereignty of people in form of democratic systems constitute the main basis of the civil society as a social and political system. Living in a civil society, thus, requires teaching and learning of civil morality and familiarizing with citizenship rights and responsibilities to, not only satisfy the different needs of individuals in a consistent manner, but also to develop stable social relationships. Although civil or citizenship education have been common in different forms in most countries, today, most people have not undergone the necessary training for performing social activities and this poses some problems in the society. As such, the necessity of citizenship education is felt particularly in the developing countries and is satisfied by an educational institution which has a main role in educating the society's citizens. Given the changes made in today's societies which are affected by industrialization, urbanization and communication, and globalization, citizenship education has a distinctive role in communities (Tobias, 1997).

Today, the survival and development of communities depends on active, participatory, informed and agent citizens, or in brief, agent humans. By informing individuals and specifically students about their rights and, consequently, the

vindication of those rights, they obviously become familiarized with their responsibilities towards the community, thus, the social order takes a more rapid trend and an active and dynamic society develops. Besides, solving the problems of the society and making some changes is achieved only through active participation of members of the society. If students are not informed about the civil, political and social aspects of their citizenship rights, the theoretical investment necessary for active participation in affairs cannot be obtained and citizens will not be able to properly convey their wishes to the political authority.

International assessments suggest that the developed countries have an active and critical citizenship education plan in their curriculum but this trend has not been fast enough in the developing countries. Therefore, citizenship education will be successful in obtaining its goals and objectives if it can foster informed, responsible and creative citizens and it cannot be achieved unless optimized citizenship training is practiced and citizenship culture is enhanced.

1.1. Citizenship education concept

Citizenship education is defined as the process of transferring knowledge, values, and attitudes required for participation and political stability of society from one generation to the next. The transfer involves several cases, such as Knowledge of the history and structure of political institutions, having the sense of loyalty due to the positive attitudes towards political authority, belief in

fundamental values, interest in political participation, and acquiring skills required for understanding general policies and monitoring them (Nikfar, 1378). Similarly, Elmohoda (1379) considers citizenship education as a network of connected processes of the institutions which directly or indirectly deal with fostering the members of a civil society. That is why the nature of citizenship education is highly affected by the civil society concept. In this definition, the main concern and goal of citizenship education is to reinforce civil society and preserve the spirit of democracy in people.

In general, citizenship is a kind of reciprocal social agreement and a set of reciprocal rights of "the people over the state" and "the state over the people". It is also a general shared feeling towards national and social identity in a clear limit. Therefore, if the society needs useful and effective citizens, it should ascertain that they are educated through opportunities for acquiring necessary skills, abilities, and information. At present, most educational systems, specifically the higher education which has the heavy responsibility of educating professional and expert citizens of the society, have focused their plans on deep considerations and scholarly reviews and try to train qualified people who fit the present situation so they can find their place in the highly competitive market in which the primary role is the knowledge and professional qualifications. Although learners participate in citizenship rights and responsibilities regardless of social and political place, information and skill, it is evident that, as a citizen, their efficiency and ability in effectively performing their responsibilities in the postmodern and over-complex society depends on the quality and quantity of the capacities fostered in them.

Citizenship education is an investment for the future of a given country in all dimensions. To familiarize the citizens of a society with citizenship rights and to expect them to be responsible, we must start promoting their participating in various fields since childhood or, generally, conveying the values, insights and skills along with patterns and ways of participation in a civil and social society. Hence, we are in need of citizenship and citizen-oriented education.

2.1. Educational system and citizenship education

The mission of educating at all times has been fostering generations of humans who meet the needs of the society, itself. Citizenship education, among the other things, has historically been one of the most important goals of the educational system. In other words, educational institutions in different societies has constantly made an effort to evolve democracy, local and national participation, social

and civil identity of the citizens through formal and informal planning. Hence, a school or a university is considered as a place to prevent the citizenship rights and responsibilities from different challenges and tough situations in life. Doubtlessly, educating good citizens is a main concern of most educational systems in many countries of the world, so it is placed at the forefront of the educational efforts and activities. It is also confirmed by the report of a study of citizenship education, i.e., the "International Association for the Evaluation of Educational Achievement", (IAE), which states that all contemporary societies have the obsession of how to prepare their adolescence and youth for a citizenship and civil life, and how to teach them ways of participating in social issues (Tobias, 1997).

In rapidly changing world of today, humans should be capable of being updated along with the changes. They should be able to obtain the information, knowledge and skills necessary for a successful life through using various communication and information resources. As a member who has commitment to himself, family and society, they should be able to take part in all positive aspects of life and solve problems using the simplest means to collaborate with local, national and international societies. The mission of education, along with developing and nurturing human values, is to help learners to create and develop knowledge, acquire insight about how it works, employ it and use technology together with the modern science of their time so, despite the challenges of a new era in the unknown world of information and communication, they can successfully act in their individual and social life. On this ground, the educational systems present in the world have two main responsibilities. The first includes tactics and efforts for familiarizing the young generation to the results obtained from the experiences of the previous generations so that by adding up the experiences of successive generations gradually cultural investments developed to be offered to the young citizens to benefit from it in a quality individual and social life. The second requires the educational systems to equip their products, that is, the future learners and citizens of local and national society, with specialized knowledge and skills so, apart from the problem solving ability, they will be able to challenge the issues raised in the local, national and international society in the future. On the other hand, citizenship is lifelong processes so all people are in need of an education which suits citizenship in all stages of life. Education should help children and teenagers to grow as responsible citizens, be active participants in society's social and cultural affairs, successful interested learners, and honest and self-dependent individuals. In line with

establishing the citizenship properties, school should be a place to prepare the necessary and appropriate opportunities for experiencing and training in different spheres of life so the required grounds for meeting the individual, family and social need of students is satisfied (Share Pour, 2007).

3.1. Desirable properties and qualifications of citizenship

It is clear that the educational system of any country is affected by the system of values dominant over the society and, indeed, the citizenship education should also be performed in line with religious and national culture and identity of the society. So, citizenship life should involve the visible context related to the Iranian living environment in which students live. Following this path, it is possible to localize the training for the national and local citizenship life and, thus, to prepare for the universal citizenship training. On the basis of the above discussion, a desirable citizen should have specific qualification in three areas as following:

- 1) Civil cognition; is defined as a body of knowledge, information, and understanding of civil which involves the following items: awareness of the way information is obtained, awareness of the structure and performance of the government, view of the major parties of the country, society's events and accidents, social rules and regulations, and personal and international rights.
- 2) Civil ability; is defined as a body of skills, capabilities and abilities that each individual requires for living in any society which involves the following items: ability to cooperate with others, to perform the affairs independently, to make a logical decision and to behave on the basis of desirable religious and moral principles.
- 3) Civil view; is defined as a body of attitudes, beliefs and views necessary for a good citizen which involves the following items: accepting and respecting the diversity of the community, having independent beliefs, having spirit of responsibility, patriotism, tolerance, critical thinking, and appreciation of cultural heritage and religious and national identity.

This is with reference to the above properties that the great and vital mission of education in the globalization era makes sense. Accordingly, besides attending to general policies of the educational system, it is necessary to address the stage of deep understanding, obtaining the sense

of citizenship education and provision of school life so the required grounds for paying increasing attention to this great mission (educating civil citizen) of the educational system is prepared (Fathi, 2001).

4.1. The mission of educational system

The duty of education is to train citizens who can make an effort for developing a democratic society and its renewal. Educational system aims at educating a generation who, in the present complicated world, can both add to their knowledge and create a group atmosphere which results in a multi-dimensional and collective responsibility achieved by enhancing their capabilities of togetherness and imprinting.

If we accept education as a basis for producing the civil knowledge of students who are considered as the main agents of the reproduction of this cognition, we have actually confirmed that education is the same strategic investments in developing citizenship culture and political growth of the country. In this line, an efficient education compatible with today's needs is required to satisfy the following expectations:

1. Having useful, effective and practical training
2. Educating the adolescence and young generation based on criteria accepted by the society
3. Facilitating the process of individuals' socialization and learning the better standards of a healthy life
4. Guiding the adolescence and young generation towards optimal growth and development
5. Educating participatory, systematic, responsible and effortful humans through institutionalization of law, avoiding violence and dominance, and prevention from tension
6. Cultivating the culture of partisanship and practicing participation in handling school and society affairs
7. Strengthen faith, spirit of courage, patience against misery and suffering, seeking justice, work ethics, social discipline, consultation, cooperation and altruism and devotion.

In 1994, the International Association for the Evaluation of Educational Achievement conducted a study on different and mutual properties of citizenship education in 24 countries of the world. At the end of the study, the researchers suggested a valid method for consistent conceptualization of approaches to citizenship education on the basis of

the objectives considered for these practices which involves three general goals as following:

- 1) Education on citizenship
- 2) Education via citizenship
- 3) Education for citizenship

Education on citizenship aims at preparing students and individuals to gain sufficient knowledge and understanding the national history and structures of life. Education via citizenship requires students' and individuals' learning via performing completely dynamic activities of participatory experiences in school or local community. Education for citizenship involves the two aforementioned processes and equips the students and individuals with a series of tools (including knowledge, understanding the skills, insights, values and trends) and enables them to have an active and logical participation in roles and responsibilities with which they encounter in their adulthood. This process connects citizenship education to the entire experience of the students (Bagheri&Bagheri, 2010).

In order to educate committed and responsible citizens, besides changing the goals, methods, and roles of teachers and students, we are required to review and change the planning of curriculum and those in charge of planning the curriculum and academic materials so, instead of an independent and detailed approach, we must use a general approach in academic planning. In this line, resorting to an interdisciplinary approach offers a comprehensive understanding of the complicated facts of the present world. In other words, we need a holistic education; the knowledge divided to separate parts in schools and higher education centers must be put together so learners can obtain a comprehensive understanding of the facts the world systems encounter. Furthermore, by substituting flexible and easily-transferred systems and reducing difficulties and stagnation of thought, we can act more successfully when encountering the real needs of learners and the universal and civil society. Actually, by demonstrating flexibility and creating some variations in time, location, approach and curriculum, we can keep up with the requirements of a universal education. As such, by decentralizing the curriculum at school and local level, making the academic plan interdisciplinary, training teachers according to the changes made in the curriculum, making teachers adopt to various academic approaches, adopting curriculum with challenges and opportunities of information technology and professionalizing it, collaboration among institutions and formal and informal academic centers and non-academic centers, the important goal of educating, effective, helpful,

and informed citizens at national and international level can be achieved.

The question raised here is that, along with disappearance of national boundaries, which items should be included in curriculum so active and informed universal citizens are educated? Since the duty of academic centers is to educate citizens, it would be useful to understand how citizenship is defined in academic centers. Some of the elements involved are as follows:

- Comprehensive knowledge on the world's political systems
- Comprehensive knowledge on the world's economic systems
- Critical thinking skill for analyzing issues related to political and economic affairs
- Inter-cultural communication skills
- Opportunities for practical participation as active citizens
- Opportunities for revealing sympathy towards others

2. Discussions

Due to the fact that citizenship education is considered as a national duty and its goals require exact planning, developing approaches and new and novel strategies to be achieved in the future, as shown by universal experiences, it cannot be implemented merely within the responsibilities of schools and formal educational system of the country. So, it is necessary to set up training courses for educating citizens with standards higher than those common in schools and academic centers and the entire society, namely family and school and other religious, political, cultural and social institutions start dealing and sincerely cooperating with this training. Then, we would be able to create a logical coordination between what is taught at school as a citizenship education and what is common in house, parish, area, and national society. In this way, the culture common at school will not be contradictory with norms and values present in society; rather, both of them complement the process of citizenship education and strengthen the inclination to accept social responsibilities and group work required for a healthy citizenship life. It is noteworthy that mass media and information devices such as radio and television have an important role to play in achieving this goal

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The foreign policy of U.S.A in the Middle East and Great Middle East policy

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Abstract: Strategy of a rule rarely appears in a decision making, but it is appeared in a series of the successive decisions that they have been chosen in attempt to reconcile the goals, values and benefits with conditions and features of the internal and external environment. Regarding to the geopolitics and unique sources of the Middle East and its importance from different views after the Second World War and in the dipolar international system era and even after Union of Soviet Republics decline, the Middle East has been one of the foreigner policy priorities of U.S.A, as any choice isn't replacing of the Middle East in U.S.A diplomacy (Ikenberry, G. John, ed. 2010) . The political behavior of heads of U.S.A expresses the reality that benefits of U.S.A in the Middle East is red line to that country and U.S.A is ready in order to protect it accept any risk.

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1. Introduction

The foreigner policy is formed within the national benefits, so we observe the continuity and stability in the foreigner policy of U.S.A since 1898 that has been living; also we observe that the national benefits of U.S.A are formed by interaction and confluence of four elements. So we must say that the national benefits of U.S.A are fixed. Therefore it makes no difference that which group or party be in White House, because these four elements are always vital. These elements are: the historical life and background, the geographic condition and situation, the liberal value culture and the international conditions.

Regarding to these elements, we must notice that not only they are permanent, but also the foreigner policy is searching. Because the conditions of world are always changing and definition of heads about the national culture and values are completely inference. It means that ideology of heads affects on the foreigner policy of U.S.A living. The presence of U.S.A in the Middle East has been after the Second World War. In that time the Middle East and Persian Gulf have been considered as the vital areas in strategies of U.S.A. The geopolitics and geo-economic position of the Middle East located that area in the vital benefits domain of U.S.A. So the heads of U.S.A have being followed the Middle East problems with the high sensitiveness. Policy of U.S.A in Middle East before the end of Cold War and Union of Soviet Republics decline has being followed these below three principals:

1- Maintaining the continuation of oil flowing towards west. 2- Preventing Communism influence and development. 3- Maintaining the security and constancy of Zionism regime.

When changes has happened in different. Times, strategies of U.S.A in the Middle East have being changed also. So we observe different doctrines from presidents of U.S.A in that area that is:

1.1. Truman doctrine and control of Soviet Union:

Control of Soviet Union and barrage against communism and preventing attack of Soviet Union to countries of the Middle East and Persian Gulf were three policies of U.S.A in Cold War era. That plan called Truman doctrine basically was established on magnification of Soviet Union danger and had several goals:

Justifying the increasing interferences of U.S.A near people wanting peace, calm, the economical condition improvement, decreasing tax and the social welfare, more development of influence in different areas of world formed by document against Soviet Union danger and introduction of U.S.A as head of the free world, democracy and human right in world. According to that doctrine U.S.A was obliged to supply the economical, political and more important of all military needs of an anti-communist state when and anywhere it has being threatened from several ways. Meanwhile maintaining the North belt of the Middle East (Iran, Turkey and so on) was forming one of the main bases of the Middle East policy of U.S.A. In this way two important actions were done: presenting 400 million\$ to Egypt, Turkey and Iran, then sending the military counselors to these countries and settling the military forces of U.S.A in the Middle East and Persian Gulf. In U.S.A view, in case of lack of help to Iran and Turkey as the direct neighbors of Soviet Union and its goal and the vital ring in anti-communist countries chain and the main oil sources

and access way to the Indian Ocean, we will observe the fall of these countries to communism skirt. The second base of that doctrine in the Middle East area was Palestine crisis. Basis of that policy was that Jewish state is established in Palestine. Truman noticed without any doubt and ambiguity: In my view the urgent statement that has promised to Jewish reestablishment in Palestine always has progressed with policies of Sharif Wilson specially the right of fate assigning principle (Jentleson, B. (2000) . So when the special UN commission of Palestine suggested the division under guardianship land into a Jewish and an Arab country and changing Jerusalem to an international area, president of U.S.A ordered Ministry of Foreign Affairs to support the division plan.

2.1. Eisenhower doctrine:

In this strategy in addition to communism, nationalism and Pan-Arabism were two serious threats for benefits of U.S.A in the Middle East and Persian Gulf. So the Middle East policy of U.S.A in that era differed with Truman era. Hate of the majority part of Arab world from the colonial behavior that had increased the influence bed of Soviet Union, nationalism of Jamal Abdel Nasser in Egypt and strengthening Pan-Arabism against Israel had created some serious crisis in the Middle East area that had compromised benefits of U.S.A. So setting the serious program for the Middle East was important for diplomacy of U.S.A.

Americans were attributed all of area changes to communism progress in own declaratory policy. Therefore according to Eisenhower doctrine interference in the critical countries and supporting the united states was base of the Middle East policy of U.S.A. Fall of Mossaddegh state in Iran in 1952, weakening Nasser state in Egypt, Supporting Hashemite family state in Jordan and presenting 10/000/000\$ gratuitous to that country and sending the sixth navy of U.S.A to east of Mediterranean to suppress the insurgents, interference in Syria affairs, the political interference in Iraq affairs, landing U.S.A soldiers in Lebanon were among Proceedings that were done according to Eisenhower doctrine. Beside above proceedings, the Middle East policy of Eisenhower about the Northern belt that was a strategic area besides Soviet Union chose prevention policy. In this regard, background of Baghdad treaty change to CENTO treaty was provided with Iran, Turkey and Pakistan membership.

3.1. Kennedy doctrine:

After Eisenhower, John F. Kennedy entered white house. He presented "unity to progress" doctrine about the third world that had roots in his

belief and his foreign policy team in necessity to destroy poverty, illiteracy and destruction in the third world countries in order to prevent their fall into communism.

Content of that plan had several goals such as: increasing the industrial productions, creating the social justice, fixing prices, increasing the agricultural productions, building the cheap houses, combat with illiteracy and doing land reforms, but it had more motto aspect being actually inefficient (Fitzsimons, Louise. 1972).

4.1. Johnson doctrine:

Supporting of Johnson from Israel role in the Middle East was accompanied with the internal problems to him specially failure to achieve the liberals support from his policy for Southeast Asia. Advisors of president were hopeful that government be able to attract the support of the main part of Israel fans in the liberal anti-war society of Vietnam with the strategic role of Israel and South Vietnam and emphasis on necessity of the defensive position of powerful U.S.A and the pragmatic intervention policies in outside as a way to protect benefits of Israel in the Middle East.

5.1. The two column strategy of Nixon (U.S.A the security governing of Persian Gulf):

After exit of U.K from the Middle East area, U.S.A accepted to make itself obliged to prevent the influence spread of Soviet Union and supplying the security of the Middle East and filling vacuum due to exit of U.K. In these years U.S.A was fighting with Vietnam and wasn't ready to replace U.K IN THE Middle East, as was replaced it in Egypt and Turkey in Truman era. So U.S.A was sought to suffice to the limited presence of own navy i.e. one destroyer and one battleship in Bahrain monitoring area. Because on the one hand, there was this danger that the more presence creates a motive to enter navy of Soviet Union and on the other hand, there was this tendency that this country avoids the military cost considerations. So this view was strengthened that the coastal states of Persian Gulf and the Middle East area must fill any power vacuum protecting the security and stability of area. So according to this (indirect presence strategy and divestiture of security responsible of area to the local powers) were chosen. This general trend in foreign policy of U.S.A caused Nixon doctrine plan or Nixon- Kissinger doctrine or Guam. Richard Nixon underpinned regarding to the Middle East own strategy called "two columns" also Nixon faith and "Guam island faith "in his trip to Philippines in 22 July 1969 and in his stay time in Guam Island. In this policy, U.S.A was obliged to use the local powers as possible for own goals in the

critical focuses of world preventing the direct military presence (McCormick, James M. et al. (2012). According to two columns Nixon strategy, the regional powers must fill the security vacuum of area to prevent the influence of Soviet Union and the revolutionary and nationalist movements and also the regional disparities. Choosing this strategy in the Middle East with the increasing role of Iran as the military column and Arabia as the financial column was continuing. They believe that U.S.A is able to control and maintain the security and stability of area from long-distance by strengthening and training of these two countries. Strengthening the military power of Iran and Arabia was base of Nixon doctrine. So that Iran is able to act as a regional power and more clear as "gendarme or the regional police". On the other hand, Nixon preferred diplomacy to other ways to rescue Israel and ending crisis of Arabs and Israel damaged due to Arabs and U.S.A relations.

6.1. Carter doctrine and forming rapid reaction:

Victory of Islamic revolution of Iran and new approach of revolution leaders in foreign policy according to no east no west motto, issuance of revolution plan and today Iran and tomorrow Palestine motto and finally happening some Islamic rising in area created the serious threats behind U.S.A benefits back in the Middle East area. In addition to Soviet Union attacked Afghanistan contemporary. It challenged benefits of U.S.A within the boundary of the Middle East area called "crisis crescent" by Berzhinsky. U.S.A that was depended on own economical benefits in this area was concerned about being in danger own situation in this vital section of world (Meiertöns, Heiko (2010).

The response of U.S.A heads to confront these challenges was avoiding from strategy "leaving the responsibility" and renewed tendency to "accepting the responsibility strategy". Carter state considered reviewing two- columns security order in the Middle East with counseling of Berzhinsky the national security counselor and Harold Brown head of Pentagon counselors designing strategy "without the regional column" and representing power against threats for U.S.A benefits directly. According to this strategy U.S.A undertook maintaining security and stability responsibility in the Middle East area directly. Carter president of U.S.A considered security of the Middle East related with the national security to defend from West benefits and U.S.A in the Middle East relying on "control of Soviet Union".

7.1. Ronald Reygan doctrine and choosing balance policy of the regional powers in The Middle East:

Ronald Reygan entered the international political field with renewed motto of excellence of

U.S.A against Soviet Union and strengthening and influence of that country to the third world in 1981. In this era process of the Middle East changes and Persian Gulf was worrying from U.S.A view. Reygan claimed that Carter rule years have been retreat era and weakness. So using force to remove the existing challenges was necessary. Carter considered choosing barrage policy against the revolutionary regimes and preventing policy to control presence of anti-west Regimes and using force to shoot down such regimes. The war with little intensity was the main tool of Reygan doctrine. Reygan state declared Islamic revolution of Iran a serious threat for own benefits in the Middle East area fortifying created security orders in Carter era to confront with it. He emphasized that he will not allow Saudi Arabia be other Iran and exit from West camp like that country falling in someone hands wanting to cut the vital oil flowing to West. In this regard, he created more spread proceeding of the military presence of U.S.A in area and for the probable military interference of Santcom central command forces in north of Arab sea helping to form "cooperation council of Persian Gulf" with Saudi Arabia pivotally and partnership of five countries i.e. Qatar, Kuwait, Bahrain, United Arab Emirates and Oman. Tool of Reygan state for the Middle East and Persian Gulf security was the behavioral pattern "power balance" between Iran and Iraq and using one of them against the other called "befriending and threat". Iraq war against Iran was exactly conformed to foreign policy goals of Reygan Formed within this strategy. The most of politicians of U.S.A was estimating that change "regional power balance" standard considering Iran focus of hard anti-American and Israel tendencies and same with Soviet Union dangers for U.S.A benefits in Cold War. They were suggesting locating Iran in focus of "prevention" attempts of U.S.A emphatically (Wittkopf, Eugene R. et al. (2007).

8.1. Soviet Union decline and end of Cold War:

One of the potential threat for U.S.A in order to achieve own goals in the Middle East was the presence of Soviet Union that was considering that country as the most essential threat of own national security during years after the second world war. When red troops of Soviet Union entered Afghanistan, this object was exacerbated by West district with U.S.A leadership. But Soviet Union decline and creating independent countries of the Middle Asia and Caucasus removed that potential risk for U.S.A and its West supporters taking U.S.A seeking excuses levers from it. But it created a new strategic environment in North of the Middle East that caused the regional life renewal. Besides above changes a set of the International changes affected on

strategic environment of the Middle East that the most important changes and objects are: changing U.S.A to only world superpower, being considered new world order discussion by Georg Bush and U.S.A attempt to perform that, being important Europe, Japan and China in world.

Economical field and recently Europe in the Middle East and Persian Gulf and changing the importance and priorities in the strategic problems. So U.S.A after Soviet Union decline and ending Cold War considered the Middle East area as the first own rival wanting field and proving own power and hegemony doing the spread programming to domain and constant presence in that area.

9.1. The great policy of U.S.A after Cold War:

1.9.1. Isolationists:

Isolationists have the limited definition about the national benefits of U.S.A considering limited it to the physical security, freedom and properties of U.S.A people. They want to dissolve the security responsibilities of U.S.A, decreasing the defensive costs and returning to protect the western hemisphere.

They believe that any power isn't to threaten the national benefits of U.S.A and Soviet Union decline has caused to create power balance in Eurasia. If any Soviet Union and China country develop own military power, the rich and powerful governments in two sides of Eurasia such as Japan and Europe Union control them, so the presence of U.S.A in the Middle East isn't necessary.

2.9.1. Power balance:

The second view is balancing role in Eurasia for U.S.A. Supporters of that view called "**power balance**" consider the existing international system as a multi polar system and believe that U.S.A must search a situation that it be able to utilize multi polar system. In that view U.S.A hasn't the sufficient power and will to maintain the internal and international peace in world level. It isn't able to act as unquestionable leader in one- polar world. They believe that peace between the great powers is one of the vital benefits of U.S.A.

Their reason is that as the first and Second World War concerned U.S.A, any war in Eurasia between Soviet Union, European states, China and Japan cause involving U.S.A. So U.S.A must try to maintain peace between the great powers. Supporters of power balance Consider Europe, East of Asia and the Middle East area as the vital benefits of U.S.A. But they believe that the allies of U.S.A must perform more attempts to defend from themselves.

3.9.1. Creating world order:

Supporters of that strategy called "Globalists" have a vast approach about the national benefits of U.S.A. They believe that U.S.A has many benefits in world peace considering peace comprehensive and indivisible. That strategy doesn't consider the great powers as the main problem because of having democracy or being in democracy way.

In view of globalists the main threats for U.S.A aren't states, but the collective world problems such as developing the collective elimination weapons, risk of developing the civil wars, threatening the economical depression for the economical security, the environmental problems that above cases are existing in the Middle East area are the serious threat for U.S.A. So using a world policy to control states of area is necessary.

4.9.1. One- polar system:

Supporters of that strategy believe that only supremacy of U.S.A on world support peace. In their view, maintaining U.S.A as the great power, preventing presence of the new hegemonic political-military power in Eurasia and maintaining situation of U.S.A in the third world specially in the Middle East are from the vital benefits of U.S.A. In view of supporters of that strategy U.S.A is only superpower of world having ideological and strategic domain performing the hegemonic influence and power. They believe that if U.S.A exits from the Middle East, the regional powers such as Japan and Germany may fill vacuum from U.S.A exit. So the goal of that strategy is maintaining excellence of U.S.A on any world challenger.

10.1. Importance of the Middle East after ending Cold War:

Regarding to decreasing systematic threats against U.S.A goals and benefits after Cold War, Americans considered own regional strategy according to the internal and regional priorities of the Middle East and did interactions with the spread level inevitably to supply own goals and benefits. So in view of the political officials and elites of U.S.A, the Middle East and Persian Gulf is one of war and struggle areas after Cold War. It is against goals and benefits of U.S.A that wants to create stability of area and destroying any reaction and confronting with the security patterns of that country (Blechman, B. M. (1990). U.S.A creates stability and using the former rules of the regional behavior to fix own regional benefits in the Middle East. Fulfilling this affair isn't possible without using the military tools regarding to the existing challenges and the centrifugal elements

in the Middle East area. However the behavioral indexes of the regional actors are effective in the regional and strategic focus of American forces in the Middle East and Persian Gulf. The main reason of that focus is within needs and tendencies of the ultra-regional actors and also the economical and strategic goals of those units. The comprehensive need of the industrial countries especially U.S.A to oil has caused increasing importance of oil as the major inherent

index of the Middle East. The Middle East area generally and Persian Gulf specially are very important in the geographical classification of new world structure as the main source to supply fuel of U.S.A in long- term and also an efficient lever to confront with the economical competitors of that country that all of them are related to oil(Herring, George C.(2008).

Table 1: Comparison foreign policy of U.S.A before and after Cold War in the Middle East

	Foreign policy of U.S.A before Cold War	Foreign policy of U.S.A after Cold War
Comparison foreign policy of U.S.A before and after Cold War in the Middle East	<p>The first and main principles of U.S.A policy:</p> <ol style="list-style-type: none"> 1- Maintaining continuation of oil flowing towards West. 2- Preventing communism development and influence. 3- Maintaining security and stability of Zionism regime. <p>The second principles:</p> <ol style="list-style-type: none"> 1- Interference in the critical countries and supporting the united states base of the Middle East policy of U.S.A. 2- Choosing barrage policy against revolutionary regimes and preventing policy to control the appearance of anti- west regimes. 	<ol style="list-style-type: none"> 1- Balancing role in Eurasia considered as “power balance”. 2- Choosing a world policy to control states of area. 3- Preventing appearance of a new hegemonic political- military power in Eurasia and maintaining U.S.A situation in the third world and the Middle East. 4- Maintaining excellence of U.S.A on any world challenger.

11.1. The new world order (George Bush doctrine):

George Bush believes that: As he said in his lecture, one of the goals of new order is creating new era: a new era without killing risk, the legal following with more power and security, attempt to peace, era to be successful world nations, east and west, north and south and living in harmony. George Bush emphasizing on that case said: **1-** It means that different countries attract together in new world order by having a common goal to achieve human world wishes that are: peace, security, freedom and rule of law. However these goals aren't the main goals of U.S.A, but when U.S.A is interested in these goals that they are suitable for its national benefits. Otherwise, none of these objectives has meaning for U.S.A. So we can observe other goals in author's writings that show that object. **2-** Maintaining existence and strengthening Israel as a fear factor and a tool for the political and military maneuvers among Arab countries, a factor that isn't able to take considerable part of income of the rich countries of west against weapons that more developed of them first gave to Israel, account U.S.A and West limiting possibility of development and investment in the comprehensive progress field of area. **3-** Own life survival and continuance as a free and independent country with maintaining the fundamental values and

security of organizations and people of U.S.A to reach that goal. Harvard University says: New world order, the collective security, the reciprocal dependence of countries, stopping the regional aggressive actions is in order to prevent fall of U.S.A. In this field, U.S.A will try to prevent any attempt to threat n the security of country confronting with threats such as terrorism that notice security, nations and benefits of U.S.A, improving approach stability, preventing to transfer technology and the sensitive military sources, specially nuclear, chemical and biologic weapons to enemy countries besides attempt to maintain the nuclear monopolistic power. **4-** Reach to the rich, safe, searching, developing and competitive economic. **5-** Establishing the healthy relations based on the excellent political position with allies and friend countries. **6-** Creating the safe and constant world that there are the political and economical freedoms, principles and human rights standards and democracy in it being regarded. It seems that all of the mentioned objects are result of good suspect to U.S.A policies and according to politician's sayings of U.S.A. Otherwise, actually U.S.A has only one goal i.e. maintaining hegemony and domain on world according to the short- term benefits of that country and world order is really an excuse to maintain that domain.

12.1. The great Middle East:

The plan of great Middle East first was proposed by Colin Powell in 12 September 2002. He stated establishment of Enterprise organization contemporary and got bound that U.S.A helps some countries such as Saudi Arabia, Lebanon, Algeria and Yemen developing the bilateral commercial relations with countries such as Egypt and Bahrain and support the regional programs to do the political, social Reforms and reforming the educational system and struggles of area citizens to get the political freedoms and establishing democracy. Subsequently, assistant of U.S.A president in January 2003 Dick Cheney in a summit of world economy organization (WEO) in Davos Switzerland proposed "forward strategy for freedom" that made U.S.A obliged to support people acting for reforms in the great Middle East being devoted. He emphasized that Bush state is persistent to promote democracy in the Middle East and beyond it. In the other side, Nicholas Burns representative of U.S.A in NATO invited Europe in own lecture in October 2003 in Prague to focus own attempts on creating peace and security in great Middle East. Bush declared own plan for great Middle East in November 2003. Subsequently U.S.A distributed draft of great Middle East between group 8 countries to investigate in the future meeting in June 2004 before informing Arab countries from its content. Plan of great Middle East in one side faced the strong opposition of Arab countries and in other side faced suspicion and doubt of Union Europe countries. Arab countries considered that plan as interference in own internal affairs with fear from its results for own states. European countries supporting that plan considered it unrealistic and ambitious. Yemen government held a regional meeting about democracy, human rights and role of the international courts in January 2004. Statement of that conference called "Senna" restated supporting all of representatives of democracy principles wanted to end Arab countries occupation suggesting formation of "forum of Arab democratic dialogue" to promote gadgets between states and civil society groups of Arab countries. In the same time, Bush suggested in a lecture to established a free commerce area between U.S.A and the Middle East during 10 years. Subsequent to Senna conference content of great Middle East plan chinked to Arab newspaper Zaban el Hayat distributed by that newspaper in February 2004. Reforms in Arab world conference held in Skandariyyeh Egypt in March 2004. The non-governmental organizations participating in that conference wanted all of Arab countries in a statement to perform own reforms programs. But fail of Arab Union heads summit in Tunisia in beginning March 2004 hit hardy Bush state goal to perform

great Middle East plan in meeting in June group 8. Egypt and Saudi Arabia proposed another plan to replace the great Middle East plan that wasn't successful. In May 2004 Arab League formed an extraordinary meeting in Tunes in order to approve a political reforms program taking the initiative and preventing to appear the Middle East reforms plan as program of group 8. But that summit was a cheap statement that only did a surface generalization about democracy and human rights not presenting a clear program to promote the economical and political reforms of area. Following hard opposition of Arab countries and lack of welcome of European countries, great Middle East plan was adjusted and Approved with new name "spread Middle East plan" in summit group 8 in See Island in June 2004. That plan consists of two sections: The first part is dedicated to necessity discussion of democracy establishment in the Middle East have the milder tone than the first draft (GMENAI) as it approaches to a general discussion about benefits of democracy, freedom, rule of law and human rights. The second section like the first draft is a relative comprehensive program to do the economical reforms in great Middle East area. In "spread Middle East plan justifying tone of the first part, the second part that was devoted to the economical reforms program seems more outstanding. In addition to, despite the first draft that Palestine and Israel object was ignored in it, text of "spread Middle East plan indicates to necessity of continuing attempts t resolve Palestine and Israel problem. Also subsequence to summit in June, group 8 distributing an independence statement emphasized on necessity of establishing peace between Israel and Palestine and key importance of road map(Haeri, Safa (2004-03-03) . Despite the done Adjustments, that plan is famous in the first name i.e. great Middle East plan. Countries of area are hardly opposite with that plan and European countries are cautious about it. Among area countries participated only Afghanistan, Iraq, Qatar, Bahrain, Jordan, Tunes and Yemen in the formal banquet summit of group 8. Saudi Arabia and Egypt are hardly opposite with the mentioned plan. Hosni Mubarak has remarked that the external attempts to impose the reforms are Illusion resulting chaos. Saudi Arabia avoided even to participate in Tunes summit to provide Arab countries response to great Middle East plan(Achcar, Gilbert (2004). In other side, American critics of spread Middle East plan believe that this plan relies on mainly on the economical affairs not paying attention to the political reforms and strengthening non-governmental organizations and society civil institutes. The first summit of spread Middle East plan held in Rabat Morocco in December 2004 called (Forum for the future). In addition to countries of

group 8, Representatives of some countries of area such as Pakistan, Morocco, and Turkey Participated in also. Indeed, (Forum for the future) is a frame for the regular Summits of the beneficiary countries ministers to codify and investigating progress of area reforms program. In that frame, some summits between the economical and social leaders specially the civil institutes of society of area countries are performing parallel to the regular summits of the political leaders of the related countries.

2. Discussions

New world order and these sentences shoe that U.S.A try to create a stable world within new world order using own hegemony that its clear example was in the second war of Persian Gulf that resulted in evicting Iraq from Kuwait. Indeed, new world order of those scanning is movements and changes formed after Soviet Union and east district decline. How creating and change in that affair is Considered with Berlin wall close and subsequently ending Cold War. New world order was created with mottos of Americans considering mottos such as "human emancipation" and "democracy" as international orientation thought and standard of U.S.A contract were as land of liberty. In that policy west values and liberal are proposed as the universal values. However that policy was proposed as "development oriented changing to intervention oriented later. Indeed, these concepts were proposing idealism. As end of any war is with Idealism, end of idealism Cold War was with "new order" and "development" and intervention later and that idealism addressed U.S.A to advertising and promoting democracy and new order. U.S.A must create a kind of balance between own opposite benefits in explanation of its policies in the Middle East. Certainly the Middle East is full of series of possible crisis, so it must choose exactly policies that are able to achieve the best results. The main object is that must U.S.A encourage the political stability in area or wanting to do democratic reforms? In addition to democratization process in the Middle

East is able to open on the nationalist and fundamentalist opposite groups with U.S.A benefits. In the past, U.S.A was supporting the governing regimes, when it was getting over two ways of maintaining stability of none- democrat alley and promoting the democrat changes.

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Investment in transportation and examining its influence on the economical Growth of Iran

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Abstract: Today, transportation is one of the substructure parts of society that not only affects the economical growth process, but also is changed in development. The transportation substructure is one of the substructure parts of services has an important position in the economical development of countries. An efficient and appropriate transportation network causes goods transportation and services costs and also trade expansion in the national level and so industry development. Regarding to the importance of investment in transportation and economical growth, the Granger causality relationship between investment in transportation and economical growth in Iran between 1963 and 2009 is examined in a study by using Tuda and Yamamoto methods. The obtained results shows that there is a one- sided relationship of Granger causality from the impure fixed capital formation under transportation section towards GDP.

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1. Introduction

Internal and mutual communication of transportation with the Economical, cultural and social development is undeniable. Access to the production sources, markets, increasing buyers and sellers, integration of markets and so buyers and sellers competition, increasing the efficiency of capital and labor are some reasons of transportation and the economical growth relationship. The set of services that cause the goods and production sources transportation have the economic value and are a part of production costs. Transportation not only affects the economical development process of Countries, but also helps to economic by employment. Transportation is an economical part of any country like industry and agriculture that creates job following service production affecting development of another sections. So today employment and created additional value in transportation part is considered as a substructure for the measurement criteria of the economical growth of countries. Regarding to the operated studies by UN, the export expansion causes the success in strategic programs in the south- east countries of Asia such as Taiwan, Korea, Malaysia and Singapore was mainly by the significant investment in substructures and equipment's of Transportation and increasing the management skills of it. The transportation investment is one of the permanent social capitals that cause the production increasing indirectly. The investment in transportation and its related factors merges the market areas reducing the space limitations of production area as possible. That matter causes increasing the buyers and sellers in the boundary points and contact in market area.

Transportation needs much capital and so it doesn't back the capital output rapidly and directly. So investment in some parts of transportation such as tracklayer, road construction and airport are only responsibility of government and the private sector. In other words, the private sector alone isn't able to invest sufficiently in substructure sections of transportation. Examining and reviewing the past studies has shown that connection method of investment in substructure of transportation on the economical growth in various areas was different. In other words, examining a cause – effect relationship between the economical growth and substructure growth of transportation in a economic is considered. According to that, in that study the relation between the investing in transportation and the economical growth in Iran will be examined by using the Granger causality method. The questions considered are:

1- Is there Granger causality relationship between investing in transportation? And the economical growth of Iran?

2- If there is a relation, does is that a one – sided causality relationship or Two – sided one?

2- A review on done studies and the empirical evidences:

Reviewing done studies literature about that case, different results have been positive communication substructure investment in transportation and the economical growth. For example de Long and summers (1991, 1992) shows that there is a one –sided Granger causality relationship from investment to the economical growth. So increasing amount of investment growth will be motive of the economical growth. In some of the done studies opposite of the mentioned

relationship has been obtained. Carol and Weil (1994), Summers and Heston (1991) and Blomstrom and colleagues (1996) have declared in their researches that the amount of the economical growth of Granger causality is the amount of investment growth. So rate of the fixed investment formation growth increases with increasing the rate of the economical growth. Pudrika and Carmeci (2001) examined Granger causality relationship between the fixed investment formation and the economical growth using Panel data about 104 countries. They have used investment share of GDP as an approximation of the fixed investment formation and the amount of GDP capita growth as the variant economical growth and declared that against the done studies there is a two – sided Granger causality relationship between two variants. In other words, investment share of GDP Granger causality is the amount of GDP capita and vice versa. Madsen (2002) examined Granger causality relationship between investment and the economical growth in 18 member countries of OECD in from 1950 until 1999. The results of that research show that investment in machinery and equipments is Granger causality of the economical growth if the economical growth is Granger causality of investment in non – residential buildings and substructures. So policies increasing the investment in machinery and equipment's will be the effective tools in increasing the economical growth. All of the founts of Nourzad (2000), Shuoji (2001), Mittink and Neumann (2001) and Everaert(2002) are indicator of the positive causality effect of government substructure investment in different areas on the economical growth in the industrial and developed countries. While Macmilan and Smith (1994) founts are indicator of lack of the causality relationship between such investments and the economical growth in the developed countries.

3- Investment in transportation and the economical growth:

In the economical growth literature always the benefits and substructure Importance of transportation section have been considered. The investment costs in transportation as a motive from request causes the economical growth and also helps to construct the economical areas. The investment in transportation section such as the roads development and railway changed the economical growth of different areas of world in the nineteenth. The substructure investment to decrease the transportation costs from the border and boundary areas to the central areas is very important. The decreasing of costs has an important role in decreasing of the regional differences and competition improvement by business and the production factors replacement. Also it causes being efficient the production and

distribution of products that create the economical profits opportunities and improvement and leads to increasing the skill and the logical changes of system and decreasing the costs. Finally this set of the positive effects result in improving the economical benefit and reforming the relative advantages in different areas. The transportation substructure growth can be by: **1-** Increasing the investment and improving the capital stock quality by constructing the new highways, airports and so on. **2-** Improvement in the effective usage or improvement of efficiency in usage such as creating the additional capacities of substructure capital stock, optimization of transportation organizations by tax, toll and so on. The most important aspect of examining the relationship between transportation and economic is role of substructure investment in transportation and the economical growth. Some of the economists believe that in some of areas that haven't faced to the general transportation compression yet can experience long – term growth in transportation without increasing the investment. Also other studies show that investment in transportation countries having the suitable development perform some developmental limitations on economy of area. Although competition of one area against the neighboring areas increases with the developing investment in transportation in short –term but it happens only in one short – term period because of motion of capital production factors and human power. Berchmen (2001) believe that in a logical range of the regional access having the sufficient substructure in transportation we can access to the economical growth by creating the peace and maintaining the order that hasn't been all in regarding to transportation necessarily. The substructure investment in transportation and improvement in presenting services result in decreasing the costs and increasing the access to actives of various markets such as the institutions presenters, human powers and the goods demanders that cause to market development. Also in that case opportunities for exports and imports increase. Because firstly export development results in the higher production levels and improvement possibility in efficiency. Those two cases is possible by renewal of the economical structure of existing and new agencies and also improvement in production learning processes that causes decreasing production costs and increasing the benefit. Secondly it provides the low transportation costs and easy and spread access to production markets factors. It causes that the production agencies use the production factors from the wider areas and with the higher features. Anyhow because of market compression, some of the interaction effects with production growth may modify the first

intense effects and the positive improvement of transportation. While the production development from market development increases the request for human and land power, wages and rents and results in replacement of part of decreasing the first costs and competition benefits so if the increasing the wages be permanent it causes to migrate the production factors. We must notice that transportation development results

in the economical continuous effects in some of the market interactions. So increasing the benefit and the economical growth are two clear results of the improvement in transportation substructure generally.

4- The importance of investment in transportation section:

Generally the transportation section has a special and vital importance in the economical development of countries. Indeed, the economical growth is stopped without access to sources and markets and lack of access to the transportation facilities reduces the quality and level of the life welfare. The empirical studies have shown that the investment in transportation facilitates the exchange. Also the business development in the national and international level provides the nations growth and development background. The done studies in the high economical level of countries that their economic is agriculture show that investment in transportation causes the increasing the economical growth in those countries and investment in transportation substructure by increasing the social efficiency in the private investments. In little economy view, investment in transportation causes decreasing the price of the agricultural data and the production costs directly. It also causes the increasing the access to market, various production achievements and finally development tools of the non – agricultural section of the rural areas. According to the formal reports during 1980 – 1992 the international trade has developed on the average %5 annually in sale and replacement aspects. That amount is a serious assistance on transportation importance in world trade growth in comparison with income level having only %3 growths annually. So the countries such as Japan and Korea found their rapid growth based on the production goods export. It is clear that isn't possible without investment in the internal, regional and international transportation.

5- Estimating, test and analysis of the pattern:

In Granger causality test to examine that matter that " X_t " hypothesis is Granger causality of Y_t a VAR model is formed such that:

$$Y_t = \sum_{i=1}^k \alpha_i Y_{t-i} + \sum_{i=1}^k \beta_i X_{t-i} + u_t \quad (1-5)$$

If $\beta_{i=0}$ Granger causality of Y_t is not, then X_t Surely in that test pause time K is optional relatively. Geweke (1984) states that importance of that test is related to grade of VAR model and variants permanency. If the variants is inconstant, credit of that test decreases. Granger states when that test is valid that variants aren't sum. So we must examine the permanency and relation of variants sum. If the permanency of variants is from first class not being sum, we can form a VAR model on the first vectors of variants and then perform that test. On the other hand, the results of Granger causality test are very sensitive to the stop time selection. If the selective stop time is less than the real stop time, deletion of the appropriate stops will make diagonal and if the selective stop time is more than the real stop time, the additional stops in VAR model cause that estimations be inefficient. Regarding to that standard test of Granger causality is very sensitive to stop time selection and different stop times often will cause different results, the systematic autoregressive method presented by Hsiao is used to select the optimum stop time for any variants. This method is performed in two steps. In the first step a set of regressions of regressive is estimated on the dependent variant. In the first regression equation, the dependent variant will have one stop and in the next regressions will add one stop respectively. M the regression that is estimated will be in this form:

$$Y_t = \alpha + \sum_{i=1}^m \beta_i Y_{t-i} + \varepsilon_{1t} \quad (2-5)$$

Stop time selection is on the basis of pattern capacity. It is better we select m large possibly. Also for the regression of any equation, the final error standard of FPE prediction is calculated as:

$$FPE(m) = \frac{T+m+1}{T-m-1} * \frac{ESS(m)}{T} \quad (3-5)$$

In that standard T pattern size and ESS is the sum of hysteresis squares. The optimum stop time (m^*) obtains the minimum standard of FPE. After determining m^* , the regression equations with stops affecting on other Variants are calculated as:

$$Y_t = \alpha + \sum_{i=1}^{m^*} \beta_i Y_{t-i} + \sum_{j=1}^n \gamma_j X_{t-j} + \varepsilon_{2t} \quad (4-5)$$

After that estimation for any regression, equation FPE standard is calculated according following equation:

$$FPE(m^*, n) = \frac{n+1+T+m^*}{T-n-1-m^*} * \frac{ESS(m^*, n)}{T} \quad (5-5)$$

The optimum stop time X creates the minimum standard FPE. We must compare FPE (m^*) with $FPE(m^*, n^*)$ for Granger causality test. If we conclude X_t is not Granger causality of Y_t . $FPE(m^*) < FPE(m^*, n^*)$ If $FPE(m^*) > FPE(m^*, n^*)$ X_t is Granger causality of Y_t . Despite being permanent all of the variants we must take vectors from them to make them permanent and then use the constant vectors of variants to do test.

6- Tuda and Yamamoto causality test:

Before Granger causality test, examining the unit root and cumulative is necessary, but as the unit root test have low power and the cumulative tests such as Johanson test aren't reliable in the small examples, that matter will cause the diagonal in Granger causality test. According to that, Tuda and Yamamoto suggested a method to do Granger causality test in 1995 not having those problems. They suggested a simple method as estimation of one modified VAR model to examine Granger causality relationship. They deduct that this method is valid even in conditions of existing the cumulative relationship between variants. In the first step we must determine the number of stops (K), optimum of VAR model and then the maximum permanency degree (d_{max}) creating a VAR model with stops number on the variants level ($K + d_{max}$). When $K \geq d_{max}$, the stop selection is valid. In Zapata and Rambadi (1997) view lack of need to have information about cumulative features is advantage of that method and knowing the grade of VAR model and the maximum permanency grade of variants is sufficient for test.

7- Introduction of variants:

The used variants in pattern consist of: (LI) logarithm of the impure permanent capital formation of transportation section to the permanent prices in 1997 and (RGDP) amount of the internal impure production growth to the permanent prices in 1997.

Table1: results of Diki – Fuller method test

variant		Width from basis	Number of stops	Test statistics	The critical quantities	Meaningful level
Level	LI	*	1	-2/71	-3/73	0/5
	RGDP	*	0	-3/61	-3/02	0/5
The first Vectors	DLI	*	0	-5/32	-3/02	0/5

Table2: The results of Valed test

Related variant	Effective variant	Hypothesis H_0	Valed statistics (x^*)*	result
RGDP	LI	$\beta_{21} = 0$	(0/06) 7/12	LI=RGDP
LI	RGDP	$\beta_{12} = 0$	(0/53) 1/83	RGDP=LI

The numbers in parenthesis are indicator of considered statistics p-value. References: The result of the research estimates.

8- Presenting model, test and analysis of results:

In Tuda and Yamamoto knowing the permanency grade of variants is necessary so the permanency of variants has been tested by using the generalized Diki – Fuller method. The results of that test have been summarized in the table1.

DLI and RGDP are permanent. References: The result of the research estimates. Regarding to logarithm table of the impure permanent capital formation, transportation section become constant by taking vectors in inconstant level and the amount of the internal impure growth of variant is in permanent level. To examining Granger causality relationship between logarithm variants of the impure permanent capital formation of transportation section (LI) and the amount of the internal impure growth (RGDP), one VAR model with the number of stops (2) is used. Two stops have been obtained from sum of grade of VAR model and grade of the maximum permanency. The grade of VAR model regarding to SBC criteria is equal with 1. Equations are:

$$RGDP_t = C_1 + \sum_{i=1}^3 \alpha_{1i} RGDP_{t-i} + \sum_{i=1}^2 \beta_{1i} LI_{t-i} + \epsilon_{1t} \quad (1-7)$$

$$LI_t = C_2 + \sum_{i=1}^3 \alpha_{2i} RGDP_{t-i} + \sum_{i=1}^3 \beta_{2i} LI_{t-i} + \epsilon_{2t} \quad (2-7)$$

The results of Valed test about being meaningful the coefficients with stops of the used in equations (1-7) and (2-7) has been shown in the table 2. According to the table logarithm of the permanent impure capital formation of Granger causality transportation section is the amount of the internal impure production growth. The opposite of that relationship doesn't exist. That obtained result by Delang and summers researches and studies is based on the one – sided Granger causality relationship from investment to the appropriate and harmonious economical growth.

4. Discussions

Affecting the economical growth process is changed in development process. Indeed, not only

investment in different fields of transportation causes to strengthen the market in various aspects but also it causes different backgrounds of employment and various usage of anyone from others production goods. Transportation is like bases of a bridge by playing role of a communicator in the usage market that different sections of society move towards the permanent development by passing it. Consequently it causes increasing growth and the economical development. In the present research, we examined Granger relationship between transportation section and the economical growth in Iran in 1963-2009 regarding to investment importance. In that research, the used variants

Consist of the permanent impure capital formation of transportation section and the amount of the internal impure production growth to permanent prices in 1997. To examine Granger causality relationship between

Variants, Tuda and Yamamoto methods have been used that finally a one – sided Granger causality relationship in long – term from the permanent impure capital the formation of transportation section to the amount of the internal impure production growth. The obtained results from the long – term pattern indicate the theoretic expectations and variant pattern such as investment in transportation section has a special importance in the internal impure production. So showing important the investment in transportation is effective on the internal impure production of Iran.

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Appropriate technology in developing countries

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Abstract: Achieving the desired state of development is the main goal of planners and decision makers in any society at local, regional, and national levels. If the goal of a society is to develop, it will not be realized without a transformation, mutation, and fundamental change. Achieving various breakthroughs in technology promises great potential facilities and unexpected hopes to all developing countries. Countries that fail to take advantage of these technologies will be at the risk of being marginalized in the world compared with other countries and their people may stay away from the mainstream of political, economic, and cultural life.

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1. Introduction

Achieving the desired state of development is the main goal of planners and decision makers in any society at local, regional, and national levels. Development is associated with multiple indicators and technology progress is of the basic and effective tools to achieve development. Development and expansion of health, medical, welfare, education, communications, security, and so on facilities will be realized through technology progress. Being content to low levels of technology means to abandon all facilities and services that are currently used worldwide. If the goal of a society is to develop, it will not be realized without a transformation, mutation, and fundamental change. Achieving various breakthroughs in technology promises great potential facilities and unexpected hopes to all developing countries. Countries that fail to take advantage of these technologies will be at the risk of being marginalized in the world compared with other countries and their people may stay away from the mainstream of political, economic, and cultural life. So, it is necessary to eliminate all barriers to individuals and nations to achieve technology and seriously avoid imitations and distortions that undermine the dignity and independence of nations. In terms of technology, most developing countries exhibit a strange mixture of tradition and modernity. Today, a significant percentage of people living in these countries use old and primary technologies in different fields of their life, especially in agriculture (Betz, M. J., McGowan, P., & Wigand, R. T. (Eds.). (1984). A large part of the technologies that are being used in new economies come from industrialized countries. These technologies are not too advanced or specialized in most cases. Such communities are highly vulnerable in relation to the situation of the world economy, and such technological innovations

can cause these countries face with difficult circumstances. The explosion of knowledge in the late 20th century, that is called the Information Age, has had great impacts on technological changes. Entering the 21st century, the industrial revolution has given way to the technological revolution. Globalization and technological developments provide opportunities and challenges to developing countries and the question arises that how these countries can bring the process of integration into global community, change its threats into opportunities, and take advantage of the great treasure of global knowledge. Technology has long been considered as one of the essential elements of production and development and has always changed with the growth of human knowledge, as technology is a strategic factor for the economic development of countries in the current age. Moreover, innovation in technology and effective use of new technologies is one of the main ways to gain power and influence and also getting involved in international competition for developing countries. In the past, the role of technology in the development process had been ignored and developing countries were basically run in a way by developed countries to remain in a static situation, according to attachment theory. Most of research questions on technology in the 1960s and the 1970s were associated with the discussion of appropriate technology, technology transfer, and related problems. After this period, various opinions were raised about the appropriate technologies for developing countries with abundant labor and scarce capital and expertise which can be divided into the following two categories:

- 1- Creating intermediate technologies for rural areas and small-scale industries
- 2- Adoption of advanced technologies in large scale.

1.1. Definition of Technology:

Technology is the most powerful factor for development in a society and its progress is continuous process. Technology is a new phenomenon in the contemporary world which is composed of two main pillars of "hardware" and "software". Hardware is any physical and material tool and software includes working practices or techniques of employing the tools. Many people visualize the technology in awe of machines, tools, devices, or hardware, while no hardware can do works alone. Contribution of human to efficiency power of any conceivable hardware is an indispensable factor. Therefore, technology means all the processes, tools, systems, methods, techniques, and knowledge as hardware and software that help the society to preserve, survive, and promote the life and solve practical problems (Baron, C. (1984). Any technology is divided into various degrees and has a continuous process. Since technology is the main core of development system complex, its changes affect all organs and system components.

Technology components are as follows:

- 1- Technology information
- 2- Research and development
- 3- Design and engineering
- 4- Manufacture of tools and machinery
- 5- Construction of industrial facilities and production units
- 6- Operation and maintenance of industrial facilities and production units
- 7- Storage, transport, handling, distribution, and sale of products

2.1. Appropriate technology:

Before selecting and using any kind of technology, the main concepts of appropriate technology and the process of its better management should be firstly understood and the results should be assessed. Hence, an appropriate and correct selection and design is considered a very critical and yet complicated duty in the process of national development and progress (Ghosh, P. K. (Eds.) (1984). Appropriate technology is any kind of technology that can suggest the most affordable way of using resources, facilities, capital, labor, technical skills of a country and promote the national and social objectives of that country. An appropriate technology should also be more productive than traditional methods, eradicate or minimize unemployment, and create new jobs. This technology should take the maximum use of raw materials and local production tools, save the foreign currency, and take advantage of domestic natural resources. Appropriate technology can help to develop skills in a country and environmentally provides an optimal protection. As raw materials are optimally used in an appropriate technology, it also provides the reuse of

industrial waste. Since developing countries have a limited scientific power and capital in terms of time, natural resources, manpower, and management, they should choose the appropriate technology be considering their talents and potentials and put it in operation innovatively. So, in countries with such limitations, an appropriate technology should be more "user", adapt its products with the market condition and demand, get more use of raw materials, and produce simpler goods according to the income limits of people (Linnell, C. (1995). Selection of an appropriate technology creates more efficient methods and introduces new aspects to human activities. This makes it possible to improve the quality of products, increase efficiency, reduce the time of product promotion, and satisfy the unlimited needs of human. There are always differences between a technology and a high technology that are listed in the following tables.

Table1: The list of differences between a technology and a high technology

Technology	High technology
Efficiency	Effectiveness
Economy of scale	Economic image and attitude
Knowledge of how	Knowledge of why
Data and information	Knowledge and wisdom
Standard - Goal setting	Continuous improvement
Systems and known status	Innovation, invention, and change
Specialization	System approach and integration
Optimization of current systems	Optimal systems design
One process, one method, or better	A process to another method or another process
Hardworking	Smart working

3.1. Major obstacles in the use of an appropriate technology:

Developing countries are always facing with problems in the use of appropriate technology that are considered the main causes of their underdevelopment. Some of these problems are as follows:

- 1- Communication failure and lack of knowledge about appropriate technology
- 2- Lack of suitable incentive systems which can lead to increased demand for products of inappropriate and inconsistent technology
- 3- Imbalance in spending on research and development that its impact can be observed at the global level
- 4- Lack of sufficient fund and discriminatory or inappropriate trade and exchange
- 5- Governance conditions (Lack of understanding of great consequences of technology revolutions by policy makers)
- 6- Insufficient training
- 7- Incompatibility of selected technology with environmental and geographical considerations

4.1. Important points in technology selection:

There are some points in technology selection and application that should be considered seriously and systematically:

1- A software approach toward technology, although it is a time-consuming process and wouldn't yield in a short term. However, it is obviously one of the correct, principled, and scientific options for technology development in developing societies.

In order of importance, manufacturing experience and skills, information and knowledge of production, and organization and management of production are of notable software components in a software approach to technology.

It should be noted that accomplishment of organization and management is subjected to the enough growth of the size and lifetime of production activities.

2- Developing countries need internal research and development, because it is a prerequisite for technology.

In order to realize this, there are some key points that should be taken into account:

- a- Scientific capabilities of researchers
- b- Goals setting
- c- Assessment of obstacles and problems
- d- Determination of tools and methods
- e- Having a thought out plan

It is noteworthy to say that, in the evaluation of research and development, three institutions of government, the private sector, and universities are assessed due to having no profit share.

3- Using the experiences of developed countries, considering political, economic, and social similarities with these countries.

If developing countries want to acquire knowledge and technology without taking advantage of existing knowledge that is the result of the efforts of researchers and scholars and their experiences, it leads to unreasonable waste of manpower, resources, and time in these countries causing irreparable damages.

4- In the selection of an appropriate technology, this basic principle should be noted that technology alone cannot develop a country; if the necessary condition to adopt it is not provided and also it is not complied with the environment is about to be used in, its losses would be more than its benefits.

5- There is no a single and fixed option for all nations to choose an appropriate technology.

6- The ratio of capital and labor must be economically justified.

7- External dependence in the selection of technology should be minimized to the possible minimum.

8- Investment in technology should be in accordance with the economic status of countries.

9- Competition and competitiveness is of the outstanding features of an appropriate technology.

10- Simplification of product and process should be taken into account.

11- Appropriate technology selection must be done in a way to improve the quality of products and easily develop them.

12- In communities where there is a problem of capital and the number of unemployed is high, user technology is necessary to be used.

13- The status of trained manpower or familiar with the technology should be investigated when choosing a technology or there should be program to train required manpower.

14- Appropriate technology must create the most value added for internal supply and resources.

15- Appropriate technology should have the highest correlation with domestic and traditional industries.

16- Required areas of science and research for a technology should exist in a society.

5.1. Technology development:

If it is supposed that growth and equity of developing countries are considered together in one direction, technology should be taken as one of the variables of development strategy. In this strategy, planning authorities will announce their guides to employers of the private sector through central decisions. Economic-political independence of developing countries lies at the development of their domestic science and technology. They have well found that they cannot only rely on developed countries to acquire knowledge and technology and should take advantage of their own capabilities and facilities to develop their technology, achieving economic-social progress, and decrease their dependence on other nations (JONES, G. 1971). Self-reliance in research and development doesn't mean to do again all research done by developed countries, but it means to use the research done in other countries and adapt them with the needs of domestic technology. Technology development is actually innocent of tyranny of mechanical humans any other kind of tyranny and arrogance and mostly pursues productive objectives. Technology development and change trend has two goals; higher performance and satisfying the public needs. Higher performance in technology means higher speed, greater capacity-building, development of cost effectiveness, higher efficiency, increased ability, reduced human efforts, more peace, and more mechanized applications. Technology development is considered as the infrastructure of economic growth. Any change in the economy of developed countries affects the economy of developing countries. Hence, technology development closes countries to each other.

Technology has a direct interaction with other environmental factors. Political, military, social, economic, organization & management, customers, competitors, and the market changes have always had an impact on the process of technology development, while technology development has a huge role in promoting the living standards and economic growth of nations. Knowledge management and outsourcing management in the process of technology absorption and synergy are the main topics of strategic management which create the highest value in the shortest time and provide services tailored to market needs during the technology development process. Technology development route in developing countries is often affected by the basic needs of society and available technologies. This double approach suggests a combinative model composed of market pull and technology push.

6.1. Technology transfer:

The importance of technology transfer and its role in the industrial development of countries and bridging the technological gap between developed and developing countries are not deniable. Developing countries, particularly in East Asia have improved the base and foundation of their technology through its transfer from developed countries and then tried to enhance their academic and research centers by providing a good economic infrastructure (Darrow, K. & Saxenian, M. (1993) .

Technology transfer process can be divided into three major sections:

- 1- Technology selection and acquisition
- 2- Adaptation, application, and absorption of technology
- 3- Technology development and dissemination

Any technology is considered an appropriate technology at its original place and time and also or it can be so at any time in future or in a different place if the environmental factors and its objectives are consistent with its origin. However, the use of imported technology has some limitations such as non-compliance with environmental and geographical conditions and need for heavy investment, professionals with high skills, and a developed infrastructure. Moreover, imported technologies cause the dependence, in terms of raw materials and experts on production and storage, last. The key to overcome these consequences for developing countries (which want to transfer technology) is to expand research and increase attention to the development of science and technology and also modifying these technologies in accordance with society's needs.

Green Revolution which led to self-sufficiency in food and agriculture in developing and populous countries such as India, Pakistan, Indonesia,

the Philippines, etc is a successful example of technology transfer and one of the fruits of adaptation of advanced technologies with environmental conditions of developing countries. Indeed, this success is largely due to the growth in research spending in these countries. Technology imports helps consumer goods to be produced in the first step, and then used to produce intermediate and capital goods, and finally leads to production of new goods (Willoughby, K. W. (1990).

Developing countries, in the course of globalization, should take advantage of appropriate capabilities and capacities to absorb and develop up-to-date technologies and enjoy them to produce new products and provide new services. This is led to creating value when the advantage of technology and, market entry, and sustainability in the global competitive environment are gained. Hence, the main issue of these countries is technology selection based on identified needs of present and future market and how to attract and acquire it. Modern and eminent technologies are usually knowledge-based require a heavy investment and a long time for development, while markets demand fast response, low price, strong support, capability of development, and high flexibility.

Transfer of technology to developing countries is faced with obstacles as listed below:

- 1- Disproportionate political and social structure
- 2- Weakness of the middle class and poor management
- 3- Weaknesses in public literacy
- 4- Population growth and non-use of manpower
- 5- Cultural factors
- 6- Weakness of the education system
- 7- Dependence on developed countries
- 8- Plundering of developing countries by colonial states
- 9- The level of technology in these countries
- 10- Infrastructural factors

7.1. Vulnerabilities and threats in the selection and use of appropriate technology in developing countries:

There are two major vulnerability and threat about selection and development of technology that if they are ignored, they can act as a poison to developing countries and seriously jeopardize the economic life of communities.

- 1- Giving priority to hardware in the selection of technology and downplaying the software. In other words, using the most advanced machinery is a clumsy notion of appropriate technology. Technology development through the selection, purchase, and use of advanced machinery is the most basic and unprincipled method to develop technology. Hastiness in buying machinery and a lack of detailed

studies on its consequences such as appropriate service, training, maintenance, supply of spare parts, and lack of optimum utilization of machinery and applying them in a level lower than embedded capabilities are obvious and dangerous examples of waste of energy and resources.

2- The use of any mechanical technology for any combination of manufacturing structure is not suitable and acceptable. In case of not being involved in other sectors of economy, application of this new knowledge which is inconsistent with social-economic structure, in addition to creating a variety of hazardous incompatibilities, brings obvious and hidden unemployment and over migration cities and towns and consequently causes inaccessibility to income and increases economic imbalance between different groups and regions in developing countries. Finally, the comments and ideas of two eminent theorists on technology in the world are mentioned here:

Dr. Misra mentions the following three views about technology and its place in developing countries:

1- The first view belongs to those who believe want developing countries to give up research and technical development and import the latest type of technology from developed countries.

2- The second view belongs to those who want a technology consistent with human skills and believe that developing countries should use a technology which that is compatible with their unskilled, illiterate, and impoverished population. Small seems beautiful and large seems ugly to these people and they are interested in simple life, small industries, etc.

3- The third view belongs to those who believe that developing countries should gain advanced technical knowledge and not the most advanced machinery. Using this knowledge, they can produce machinery which suit their own skills and needs.

In summary of these three views, Dr. Misra believes that none of them has understood the realities and urgent needs of developing countries. Developing nations should apply the newest technical knowledge required to exploit their final resources in order to survive. However, in order to enable the majority of poor and uneducated people to participate and have activity in the process of life, imported technologies are necessary to be rehabilitated and upgraded.

In terms of the type of technology in developing countries, the problem is not the selection of new or traditional technology, but we should see that which technology, for which purpose, and at which condition can solve the problems. For example, if the goal is full employment, user technology should be applied, while when we want make a weather satellite, we have no choice to apply

capital-consuming technology and it should not be set aside due to its limited employment (Huesemann, Michael H., and Joyce A. Huesemann (2011). Schumacher's views on technology and its impacts on the development are based on Gandhi's views.

Gandhi believed that mass production cannot help the poor of the world, but production by the masses can help them. In this regard, Schumacher believes that production system by the masses immobilizes all priceless resources that are owned by human beings, that is to say bright minds and skilled hands and equips them with classy tools. Technology of mass production inherently is violent, harmful to the environment, and cause of vulgarity and absurdity of human, while technology of production by the masses, in addition to using the best knowledge and modern industrial experience, approaches decentralization, is compatible with ecology rules, uses the scarce resources of nature very slowly, and make machines to serve humans, instead of reducing the dignity of human as a servant of machines. Schumacher calls this technology as "Intermediate Technology", because it is beyond the primitive technology of bygone epochs and yet much easier, cheaper, and freer than super technology of rich countries. However, it can be called self-help democratic technology or popular technology (Kaplinsky, R. (1990). Schumacher also emphasizes on small technology. Introducing this type of technology, he believes that developing countries should not look for great technologies. Schumacher says, "I have no doubt that a new approach can be given to technology development; a direction that causes technology to approach the real needs of human. Man is small and, therefore, small is beautiful. Seeking great and huge things will have no result except paving the way for demolition of ego.

4. Discussions

It can be inferred from all mentioned before that economic, social, cultural, and political development of any community is affected by many factors. Technology and its growth is one of the indicators of development in a community. Hence, developing countries must enrich themselves in this field. However, every technology cannot be effective. There have been many countries that sought a specific type of technology but not only didn't achieved remarkable progress using the desired technology but also provoked many economic, social, and cultural problems of their society. Such technology has had many negative consequences.

An appropriate technology must concur with scientific thought of society, industrial and scientific knowledge and research, manpower, capital stock, national resources, values and cultures, industrial management, popular participation, vocational and

higher education, and policy making and planning system of society particularly in science and technology. Development of science and technology should be valued more than the adaptation and transfer of technology. Science and technology must be deeply rooted in a society, so scientific and technical education should be begun from elementary schools or even earlier in order to cause children become familiar with the spirit of science and scientific thinking, because imported science and technologies cannot deeply address the urgent needs of people in developing countries.

In order to improve the level of technology in a society, research & development centers, manufacturing and service centers, universities and centers of higher education, and laboratories should be also established.

Manufacturing, economic, and social structure and context should be transformed and the place and position of technology in production should be changed. Hence, planning for economic-social development and technological progress is necessary.

Technology may have a good or bad nature, but what makes it be useful and valuable is technology management and its application.

Technology management is the management of systems that provide suitable substrates for creation, absorption, and development of technology.

Science and technology should be the servant of people, not their master. If technology is considered separate from science, it will have negative consequences. Although technology has brought many problems and issues for human society, these problems and negative consequences can be minimized and the society can be directed towards economic, social, and cultural development by adopting a systematic and rational policy in selection, adaptation, or transfer of technology. Leading science and technology to serve human considering the determinative role of rapid developments of science and technology in providing the causes of human happiness and fulfillment of his dreams from one hand and new issues and unprecedented problems such as loss of natural resources, environmental pollution, nuclear war, etc. raise very important and ambiguous questions.

The question is that how the interaction between human and technology can be led in the next

future to ensure happiness, peace, and good destiny of all humans. Although many tasks of humans are done by machines or other inventions, the necessity of harmony between man, nature, and, machine is mainly due the fact that man is the only creature that can create surprises and wonders. No invention and technology is as wonderful as man. Machines never can replace humans and that's why man, machine, and nature must work in harmony.

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