Prevalence of thyroid nodule among kafrelsheikh population

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Abstract: Thyroid nodule is a common clinical problem with high prevalence. Although the vast majority of thyroid nodules are benign a small percent of these nodules may undergo malignant transformation so early detection and evaluation of these nodules is so important. The aim of the study is to determine the prevalence of different types of thyroid nodules in Egypt. **Patients and methods:** This study was done in Kafr-Elsheikh governorate, 400 healthy subjects were examined clinically especially head and neck examination, then they exposed to neck ultrasound and thyroid function (T3, T4 and TSH), subjects with thyroid nodule will be subjected to: Laboratory investigation including:, fasting blood glucose, liver enzymes, renal function tests. CBC. Cholesterol and triglycerides, thyroid antibodies (Thyroid peroxidase antibody (TPOAb) Thyroglobulin antibody (TgAb). Fine needle aspiration cytology and Isotopic thyroid scan. **Results:** This study estimated that about 4% of the populations have a palpable thyroid nodule, and about 15% have a nodule detectable by ultrasonography. With the frequent use of computed tomographic scans and carotid ultrasound studies, many thyroid nodules are found in asymptomatic patients. Females were affected than males the male to female ratio was 1:3.Cellular abnormality (atypia) was about 1.5%.Nodular patient according to thyroid function were subdivided into Euthyroid and their percent was about 80%.Subclinical hyperthyroidism and their percent was about 11%. Subclinical hypothyroidism and their percent was about 9%. Radioisotope scanning revealed that about 8% are cold nodule. Hot nodules account for 11% of all nodules and 71% were warm nodules. **In conclusions**: Nodules are characterized as entirely solid, mixed cystic-solid, spongiform, or purely cystic. Biopsy is recommended for all solid hypoechoic nodules that exceed 1 cm in diameter. Isoechoic or hyperechoic nodules exceeding 1 to 1.5 cm should undergo biopsy. Biopsy is recommended for mixed cystic-solid nodules that exceed 1.5 to 2 cm, if they have irregular margins, micro calcifications, or infiltration of the surrounding tissue. The recommendation for mixed cystic-solid nodules without suspicious ultrasonographic features is for biopsy if they are larger than 2 cm. Those nodules exhibiting a spongiform echotexture should undergo biopsy only if they are larger than 2 cm in diameter. Finally, purely cystic nodules do not require biopsy.

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1. Introduction

Thyroid nodules are a common clinical problem. Epidemiologic studies have shown the prevalence of palpable thyroid nodules to be approximately 5% in women and 1% in menliving in iodine-sufficient parts of the world ***(Tunbridge et al., 1977)***. In contrast, high-resolution ultrasound (US) can detect thyroid nodules in 19–68% of randomly selected individuals with higher frequencies in women and the elderly ***(Guth et al., 2009)***. The clinical importance of thyroid nodules rests with the need toexclude thyroid cancer, which occurs in 7–15% depending on age, sex, radiation exposure history, family history and other factors ***(Hegedus et al., 2004)***. Differentiated thyroid cancer (DTC), whichincludes papillary and follicular cancer, comprises the vast majority (>90%) of all thyroid cancers ***(Sherman et al., 2003)***. In the United States, approximately 63,000 new cases of thyroid cancer were predicted to be diagnosed in 2014 ***(Siegel et al., 2014)***. Compared with 37,200 in 2009 when the last ATA guidelines were published. The yearly incidence has nearly tripled from 4.9 per 100,000 in 1975to 14.3 per 100,000 in 2009 ***(Davies et al., 2014)***. Almost the entire change has been attributed to an increase in the incidence of papillary thyroid cancer (PTC). Moreover, 25% of the new thyroid cancers diagnosed in 1988-89 were < 1cm compared with 39% of the new thyroid cancer diagnoses in 2008-9 ***(Davies et al., 2014)***. This tumor shift may be due to the increasing use of neck ultrasonography or other imaging and early diagnosis and treatment ***(Leenhardt et al., 2004)***, trends that are changing the initial

treatment and follow-up for many patients with thyroid cancer. A recent population based study from Olmsted County reported the doubling of thyroid cancer incidence from 2000-2012 compared to the prior decade as entirely attributable to clinically occult cancers detected incidentally on imaging or pathology ***(Brito et al., 2015)***. By 2019, one study predicts that papillary thyroid cancer will become the third most common cancer in women at a cost of 19-21 billion dollars in the U.S. ***(Aschebrook et al., 2013).*** Furthermore, patients with a recent diagnosis of cancer were >2.5-fold more likely to file for bankruptcy than those without a cancer diagnosis. Patients with thyroid cancer had one of the highest risks for filing bankruptcy (approximately 3.5-fold), suggesting that the increasing incidence and treatment of thyroid cancer can carry many risks. Optimization of long-term health outcomes and education about potential prognosis for individuals with thyroid neoplasms is critically important. In 1996, the American Thyroid Association (ATA) published treatment guidelines for patients with thyroid nodules and DTC ***(Singe et al., 1996)***. Over the last 15-20 years, there have been many advances in the diagnosis and therapy of both thyroid nodules and DTC, but clinical controversy exists in many areas. A long history of insufficient peer-reviewed research funding for high quality clinical trials in the field of thyroid neoplasia, may be an important contributing factor to existing clinical uncertainties ***(Aschebrook et al., 2013)***.

Aim of the work: is to determine the prevalence of different types of thyroid nodules in Egypt (kafrelsheikh population).

2. Patient and methods

This study was carried out on 400 Egyptian individual without history of thyroid disease. Sample people aged from 20-50 years, 200 males and 200females. All are collected from multi centers in kafr-elsheikh governorate between March and November 2015.

Inclusion criteria:

Normal persons, not diabetic not hypertensive no history of thyroid disease or any chronic illness.

All persons will be subjected to: *Full history*: including personal history (name, age, sex, residence…etc.).

Neck ultrasonography:

High-resolution ultrasound (US) is the most sensitive imaging test available for the examination of the thyroid gland, to detect thyroid lesions, accurately calculate their dimensions, identify the internal structure and vascularization and evaluate diffuse changes in the thyroid parenchyma. Thyroid US is able to confirm the presence of a thyroid nodule when the physical examination is equivocal and differentiate between thyroid nodules and cervical masses from other origin, like cystic hygroma, thyroglossal duct cyst and lymphadenopathy. Thyroid US is able to detect thyroid nodules in especial clinical scenarios like patients with a history of head and neck radiation, multiple endocrine neoplasias (MEN) type II and to diagnose lymphadenopathy in jugular, submandibular and supraclavicular chains ***(Gharib et al., 2006).***

Several sonographic feature are helpful for differential diagnosis including nodule echogencity, morphology, cystic changes, presence of echogenic foci with comet-tail artifact representing colloid, presence of calcification and its type and flow pattern (peripheral or central).

Ultrasound Characteristics That Suggest a Benign Nodule:

1- Sharp edges are seen all around the nodule.

2- Nodule filled with fluid and not live tissue (a cyst).

3- Lots of nodules throughout the thyroid (almost always a benign multi-nodular goiter).

4- No blood flowing through it (not live tissue, likely a cyst).

Radioisotope scanning:

Radioisotope scanning can be used to determine if a thyroid nodule is functioning, but it does not provide an accurate measurement of size. Radioisotopes that have been used are technetium (^{99m}Tc), ^{123}I, and ^{131}I, and though similar information is obtained with similar amounts of radiation exposure, radioiodine is preferred ***(Shibuya et al., 2003).*** About 80 to 85% of thyroid nodules are cold, and about 10% of these nodules represent a malignancy. Hot nodules account for 5% of all nodules, and the likelihood of malignancy is less than 1% for these nodules. Taken together, the sensitivity for the diagnosis of thyroid cancer is 89 to 93%, specificity is 5%, and the positive predictive value of malignancy is only 10% ***(Cases et al., 2000)***. Except for obviating the need to perform an FNAB on a hyperfunctioning nodule in a thyrotoxic patient, the use of radioisotope scanning has been nearly abandoned in the initial workup of a thyroid nodule.

IV- Biologic and hematologic profile of the patient:

Thyroid function tests were done by radioimmunoassay. Biologic and hematologic profiles for patients were done at different centers at kafr-elsheikh city.Fasting blood glucose, liver enzymes, renal function tests. CBC cholesterol and triglycerides. thyroid antibodies (TPO-Ab) and (Tg-Ab) were estimated by routine methods.

V- Fine needle aspiration:

Fine-needle aspiration (FNA) biopsy of the thyroid gland is an accurate diagnostic test used

routinely in the initial evaluation of nodular thyroid disease **(Gharib *et al.*, 2007).**

A survey of clinical members of the American Thyroid Association revealed that most endocrinologists (96%) perform FNA biopsy for diagnosis of thyroid nodules **(Solomon *et al.*, 1996).** Thyroid FNA biopsy, particularly under US-FNA, is very safe. No serious complications such as tumor seeding, nerve damage, tissue trauma, or vascular injury have been reported **(Belfiore *et al.*, 2001).**

An adequate specimen of good technical quality is considered diagnostic or satisfactory and may be benign, suspicious, or malignant. A benign (negative) cytological diagnosis is reported for 50% to 90% of the specimens (average, 70%), **(Castro *et al.*, 2005).**

False-negative results:

False-negative results mean missed malignancy. False-negative rates generally vary from 1.5% to 11.5% (average, <5%), **(Hamburge *et al.*, 1994)**. The false-negative rate is defined as the percentage of patients with benign cytology in whom malignant lesions are later confirmed on thyroidectomy.

False-positive: False-positive rates vary from 0% to 8% (average, 3%) **(Giuffrida *et al.*, 1995).** A false positive diagnosis indicates that a patient with a malignant FNA result was found on histological examination to have benign lesions.

3. Results

Our study includes 400 randomized subjects without previous history of thyroid disorders, not diabetic or hypertensive. By palpation 12 cases had palpable thyroid nodule (3%). Ultrasonic study of all studied subjects reveled 60 subjects had thyroid nodules with percent 15% of total number.

The sonographic features of these nodules were as follow: 46 subject with single nodule ≤1.5 cm and 14 subjects were with multiple nodules (table 1). Of these 60 subject 59 subject showed sonographic feature suspecting benign nodule in the form of: large cystic component about 66%, hyperechoic solid was about 16% and comet tail artifact was 15% (table2).

There was only one case with sonographic feature suspecting malignant nodule this was male, 33 year and his neck ultrasound showed, single, solid nodule about 2.5 cm, irregular borders and high vascularity with lymph node involvement. Lab. investigation revealed that the patient was subclinical hypothyroidism (figure 1).

Of these 60 subjects; there is 15 males and 45 females with high incidence in females with a percent of 75% females and 25% males (table 3).

Thyroid function tests revealed that 388 subjects had normal thyroid function tests, 7 patients had subclinical hyperthyroidisms in the percent of 11.7% (elevated T3 and T4, but still within normal reference range with low serum levels of TSH below normal reference range), while other 5 subjects had subclinical hypothyroidism in the percent of 8.3% (low serum levels of T3 and T4, but still within normal reference range with high serum levels of TSH above normal reference range (table 4,5).

Thyroid antibodies (TG-Ab-TPO-Ab were significantly higher in all patients with subclinical hyperthyroidism. Thyroid antibodies levels were normal at the other subjects and in patients with thyroid nodule with normal thyroid function (table 6).

Radioisotope scanning revealed that about 8% are cold nodule (5 cases), and susceptible malignant nodules are about 20% (one case) of cold nodular patient corresponding to Ultrasonography and FNA. Hot nodules account for 11% (8 cases) of all nodules and there was no susceptibility of malignancy in them, and 47 cases (71%) were warm nodules (table 7).

Fine needle aspiration biopsies were taken from 60 patients with thyroid nodules. The results of thyroid biopsy were normal in all patients except one patients with subclinical hypothyroidism had suspension of malignancy

The biopsy composed of spindle shaped tumor cells. Nuclear pleomorphism is mild and mitotic count is very low. Abundant amyloidal materials were seen in the background (H and E, × 400), the characteristic sonographic feature of this female patient was irregular border, Micro calcifications and Intranodular vascularity (figure 1).

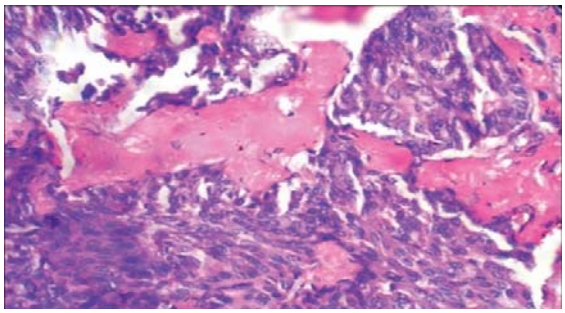

Figure (1): Histological section showing thyroid nodule composed of spindle shaped tumor cells. Nuclear pleomorphism is mild and mitotic count is very low. Abundant amyloid materials were seen in the background. (H and E, ×400).

Table (1) shows Sonographic feature of thyroid nodule number

Sonographic feature of thyroid nodule number	Number	Percent%
Multiple nodules ≥2	14	23%
Single nodule	46	77%

Table (2) shows Sonographic Criteria of the thyroid nodules

Criteria of the nodules	Number	Percent %
large cystic component	40	66.6%
hyperechoic solid	10	16.6%
comet tail artifact	9	15%

Table (3): Shows subject with thyroid nodule male to female percent

Gender	Number	Percent%
Female	45	75%
Male	15	25%

Table (4): Descriptive analysis of data collected from the patients

	Mean	± SD	Median	IQR	
				25th Percentile	75th Percentile
T3 (pg/ml)	1.30	0.25	1.27	1.12	1.45
T4 (pg/ml)	8.20	1.65	8.04	7	9.20
TSH (mIU/L)	2.20	1.50	1.90	1.11	3.09
HGB (gm/dl)	11.17	0.82	11	10.50	11.80
SGOT (U/L)	30.41	8.03	32	24	37
SGPT (U/L)	36.50	7.03	38	32	42
Creatinine (mg/dl)	0.99	0.19	1	.90	1.10
Urea (mg/dl)	26.45	5.97	25	22	30
RBS (mg/dl)	118.73	11.07	120	110	125
S. Cholesterol (mg/dl)	172.79	31.31	180	150	198
Triglycerides (mg/dl)	151.96	27.95	150	131	171
Anti TPO (U/ml)	20.32	11.56	17	12.5	23
Anti-Thyroglobulin (IU/ml)	71.98	30.04	65	50	85

Table 5: Frequency of thyroid function aberrations in patients with thyroid nodule:

Euthyroid	48 (80%)
Subclinical Hyperthyroid	7 (11.7%)
Subclinical Hypothyroid	5 (8.3%)

Table (6): Correlations between thyroid auto-antibodies and other parameters in patients with thyroid nodules:

	Anti TPO (U/ml)		Anti-Thyroglobulin (IU/ml)	
	r	P Value	r	P Value
Anti TPO (U/ml)			0.715**	**< 0.001**
Anti-Thyroglobulin (IU/ml)	.742**	**< 0.001**		
T3 (pg/ml)	-.010	.938	-0.110	0.404
T4 (pg/ml)	.537**	**< 0.001**	0.481**	**< 0.001**
TSH (mIU/L)	-.345**	**0.007**	-0.234	0.072
HGB (gm/dl)	-.096	.465	-0.172	0.188
SGOT (U/L)	-.121	.356	-0.171	0.192
SGPT (U/L)	-.094	.477	-0.072	0.586
Creatinine (mg/dl)	-.007	.956	-0.056	0.673
RBS (mg/dl)	-.132	.316	-0.184	0.160
S. Cholesterol (mg/dl)	.029	.826	-0.073	0.580
Triglycerides (mg/dl)	.055	.679	-0.137	0.298

Table (7) Shows numbers and percent of nodular patient" isotopic scan and their relation to FNA cytology and thyroid function.

	Number	Percent	Relation to thyroid function	Relation to FNA cytology
Cold nodule	5 subjects	8.3 %	Subclinical hypothyroidism	Spindle shape tumors cell in 1subject
Hot nodule	8 subjects	13.3%	Sub clinical hyperthyroidism	Normal FNA cytology
Warm nodule	47 subjects	78.3%	Euthyroid	Normal FNA cytology

4. Discussion

The term thyroid nodule refers to an abnormal growth of thyroid cells that forms a lump within the thyroid gland. Although the vast majority of thyroid nodules are benign (noncancerous), a small proportion of thyroid nodules do contain thyroid cancer. In order to diagnose and treat thyroid cancer at the earliest stage, most thyroid nodules need some type of evaluation ***(Cibas et al., 2009)***.

In our study percent of thyroid nodule detected by palpation was about 3% but when randomized subjects were exposed to neck Ultrasonography the percent was 15% of total 400 subjects. In agreement with, ***Stang et al. (2009)*** found that Palpable Thyroid nodules can be detected in 3% to 7% of adults**.** However, they are found incidentally in up to 40% of patients who undergo Ultrasonography of the neck (***Yoon et al., 2008)***. Some studies estimate that 20% to 76% of the population has at least one thyroid nodule ***(Stang et al., 2009).***

It is accepted practice to perform ultrasound examination of all thyroid nodules as the first study, or in conjunction with FNA. Good technique demonstrates nodules if more than 3 mm in size, indicates cystic areas, may demonstrate a capsule around the nodule, and the size of the lobes. It often displays multiple nodules when only one is noted clinically. The technique is more sensitive than scintiscanning, It is noninvasive, involves less time, allows serial exams and it is usually less expensive.

In present study there were no any of malignant criteria like calcification, increased vascularity, but most of them showed inflammatory condition except in one subject who was with sonographic feature suspecting malignant nodule, this was male, 33 year and his neck ultrasound showed, single, solid nodule about 2.5 cm, irregular borders and high vascularity with lymph node involvement.lab correlation revealed that the patient was subclinical hypothyroidism. About this represent about 1.5 %, 60% are found to be large cystic component, and about 16% hyper echoic solid and about 9% were found to show commit tail artifact.

In disagreement with present study **(*Leboulleux et al. (2007)*** found that From 3-20% of lesions are found to be totally or partially cystic. Purely cystic lesions are reported to have a lower incidence of malignancy than solid tumors (3% versus 10%), and diagnosis of a cyst raises the possibility of aspiration therapy.

The Framingham Study estimated the annual incidence of new palpable thyroid nodules to be 0.09%, 5 which would have meant about 300,000 new nodules in U.S. patients in 2005. Because many more nodules can be detected with Ultrasonography or computed tomography than can be palpated, the true incidence is much higher ***(Castro et al., 2005).*** Factors associated with increasing numbers and size of thyroid. Thyroid cancer represents 1% of all malignancies ***(Tee et al., 2007)***.

In our study fine needle aspiration revealed that about 1.6% of total nodular subject revealed malignant criteria in the form of spindle shaped tumor cells. Nuclear pleomorphism is mild and mitotic count is very low. Abundant amyloid materials were seen in the background. (H and E, ×400), the others showed no abnormal nuclear shape number revealed no abnormality.

The rate of malignancy is 1.5% to 17% in nodules detected on imaging performed for non–thyroid-related reasons ***(Yoon et al., 2008)***. However, the true rate of malignancy is unknown, because many nodules are small enough to escape detection, and because many malignancies in small nodules appear to have a benign course and do not cause clinically evident disease ***(Castro et al., 2005).***

The present study showed that females are more affected than males the females percent was 75% and males 25% there was no history of radiation exposure and no family history of thyroid disorder in nodular patient.

In agreement with present study ***Cooper et al., (2009)*** found that Palpable thyroid nodules are more common in women, and male/female ratio ranged from 1.2 to 4.3.

In disagreement with present study ***Stang et al. (2009)*** have shown that men to be at higher risk than women.

In our study subjects with thyroid nodule were subdivided to Euthyroid, subclinical hyperthyroidism and subclinical hypothyroidism the percent of subclinical hyperthyroidism was about 11%, subclinical hypothyroidism percent was about 8% and 81% were Euthyroid subjects.

In disagreement with present study In a cross sectional survey in a previously iodine deficient area of Germany thyroid function was measured in 3941

participants without known thyroid nodule between the ages of 20 and 79 years, A TSH <0.3 mU/l was found in 11.3% Subclinical hyperthyroidism (TSH <0.1 mU/l and normal serum free thyroxin and free tri-iodothyronine levels) was found in 1.8%, distributed similarly among women and men, but age dependent with higher percentages in the older decades. In conclusion, the prevalence of subclinical hyperthyroidism varies depending on the criteria used and is age dependent ***(Volzke et al., 2003).***

Radioisotope scanning can be used to determine if a thyroid nodule is functioning, but it does not provide an accurate measurement of size. Radioisotopes that have been used are technetium (^{99m}Tc), ^{123}I, and ^{131}I, and though similar information is obtained with similar amounts of radiation exposure, radioiodine is preferred ***(Shibuya et al., 2003).***

In our studyRadioisotope scanning revealed that about 8% are cold nodules, and susceptible malignant nodules are about 20% of cold nodular patient corresponding to Ultrasonography and FNA.

Hot nodules account for about 11% of all nodules and there was no susceptibility of malignancy in them, and about 71% were warm nodules**.**

In other study about 80 to 85% of thyroid nodules are cold, and about 10% of these nodules represent a malignancy. Hot nodules account for 5% of all nodules, and the likelihood of malignancy is less than 1% for these nodules. Taken together, the sensitivity for the diagnosis of thyroid cancer is 89 to 93%, specificity is 5%, and the positive predictive value of malignancy is only 10% ***(Cases et al., 2000)***. Except for obviating the need to perform an FNAB on a hyper functioning nodule in a thyrotoxic patient, the use of radioisotope scanning has been nearly abandoned in the initial workup of a thyroid nodule.

Recommendations:

It is important to ask whether the patient has a history suggestive of a high risk for thyroid cancer. Risk factors include radiation exposure during childhood, rapid growth of a nodule, hoarseness, vocal cord paralysis, dysphagia, or a family history of thyroid cancer or multiple endocrine neoplasia syndromes. If the patient has a high-risk history, the recommendation is to obtain a biopsy specimen from any thyroid nodule larger than 5 mm in diameter with suspicious features.

Nodules are characterized as entirely solid, mixed cystic-solid, spongiform, or purely cystic. Biopsy is recommended for all solid hypoechoic nodules that exceed 1 cm in diameter. Isoechoic or hyperechoic nodules exceeding 1 to 1.5 cm should undergo biopsy. Biopsy is recommended for mixed cystic-solid nodules that exceed 1.5 to 2 cm, if they have irregular margins, micro calcifications, or infiltration of the surrounding tissue. The recommendation for mixed cystic-solid nodules without suspicious ultrasonographic features is for biopsy if they are larger than 2 cm. Those nodules exhibiting a spongiform echotexture should undergo biopsy only if they are larger than 2 cm in diameter. Finally, purely cystic nodules do not require biopsy.

Unfortunately, very few thyroid nodules will escape biopsy. In light of the epidemic proportions of thyroid nodular disease, coupled with the overall favorable outcome of most cases of thyroid cancer (many of which likely remain undiagnosed throughout a patient's life), many patients will undergo biopsy and a surgical procedure for a disease that possibly would not have an adverse outcome if simply followed without intervention.

The diagnosis of thyroid nodules based on activity patterns of the radionuclide is not efficient. Most malignant thyroid nodules are photon deficient, but so are thyroid cysts, some adenomas, and inflammatory nodules. Conversely, most benign thyroid nodules are hot, but thyroid cancers also can be hot.

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