Evaluation Of Fetuin-A And Bone Mineral Denisty In Female Patients With Type 2 Diabetes Mellitus

Ahmed AM Shoaib [1], Heba A Esaily[2], Mahmoud M Emara[3], Eman A E Badr [4], Amany S Khalifa [5], Mayada M M Abdel-Raizk

[1]Internal Medicine Dep.-Faculty of Medicine- Menoufia University, Egypt.
[2] Physical Medicine and Rehabilitation Dep. - Faculty of Medicine-Menoufia University, Egypt.
[3] Internal Medicine Dep.-Faculty of Medicine- Menoufia University, Egypt.
[4] Medical Biochemistry Dep. -Faculty of Medicine- Menoufia University, Egypt.
[5]Clinical Pathology Dep. -Faculty of Medicine- Menoufia University, Egypt.
drmayada158@yahoo.com

Abstract:- Objectives: This study was done to evaluate fetuin-A and bone mineral density in female patients with type 2 diabetes mellitus. **Background:** In clinical practice, the fetuin-A, which is a serum protein produced by the liver and promotes bone mineralization, is an independent risk factor for type 2 diabetes, whilst type II diabetes is associated with an increased incidence of osteoporosis or fractures. **Patients and methods:** - seventy postmenopausal female patients with type II diabetes and thirty postmenopausal female as control. In this study measurement Fetuin-A together with metabolic parameters and DXA in wrist, hip and spine, bone alkaline phosphatase (ALP), CBC and measured blood glucose level (FBS, PP2Hand HBA1c)was determined in all participants. **Results: -** Fetuin-A levels highly significant (p-value < 0.001 between female diabetic and non-diabetic subjects, Also we found negative correlation between fetuin-A and DEXA scan in spine. osteoporosis represents 12.9% in spine area and 7.2% in hip and wrist areas in diabetic patients. While osteopenia were found in 58.5%, 57.1%, and 37.1% in diabetic patients in spine, wrist, and hip respectively prevalence of osteoporosis higher in diabetic patients than non-diabetic. **Conclusion: -** Fetuin-A level inversely correlation with BMD in postmenopausal women with type II diabetes.

[Ahmed AM Shoaib, Heba A Esaily,Mahmoud M Emara,Eman A E Badr, Amany S Khalifa, Mayada M M Abdel-Raizk. **Evaluation Of Fetuin-A And Bone Mineral Denisty In Female Patients With Type 2 Diabetes Mellitus.** *Nat Sci* 2014;12(9):15-21]. (ISSN: 1545-0740). http://www.sciencepub.net/nature. 3

Key word: fetuin-A, BMD, postmenopausal, DM type II.

1.Introduction:

Diabetes mellitus is a disease characterized by hyperglycemia resulting from defects in insulin secretion, insulin action, or both. The chronic hyperglycemia of diabetes is associated with long-term damage, dysfunction and failure of different organs, especially the eyes, kidneys, nerves, heart, and blood vessels. (1)

Osteoporosis (OP) is a painless weakening of the bones that constitutes an enormous socioeconomic crisis, with a harmful impact on morbidity and mortality,(2,3) It leads to increased skeletal fragility and micro architectural deterioration of bone tissue, causing a decrease in bone mineral density (BMD), bone quality, and strength. (4)

After menopause, because there is a lack of ovarian function and estrogen, the activity of osteoclasts and the pace of bone destruction increases, which will result in 25-30% destruction in bone mass during a 5-10 years period.(5)

Fetuin-A, which is a serum protein produced by the liver and promotes bone mineralization, is an independent risk factor for type 2 diabetes, whilst type 2 diabetes is associated with an increased incidence of osteoporosis or fractures. It is not known how fetuin-A levels relate to parameters of bone metabolism in type 2 diabetes. (6)

Fetuin-A, which is also known as alpha2-Heremans-Schmid glycoprotein (AHSG), is a bone regulatory protein synthesized in the liver. It is a prominent serum glycoprotein as well as a major no collagenous component of mineralized bone in mammals. *In vitro,* fetuin-A can inhibit or stimulate osteogenesis, depending on its concentrations.(7)

Recent studies have associated high levels of fetuin-A with an increased risk of incidence of type 2 diabetes, (8) insulin resistance and metabolic syndrome. (9)

The present study aimed to evaluate if there is a relation between the level of Fetuin A and the presence of type 2 diabetes mellitus and osteoporosis or both.

2.Patients and methods:-

The study was carried out in Menoufia University Hospital during the period from July 2012 to July 2013. Seventy postmenopausal female patients with type 2 DM were selected for this cross-section study from the outpatient clinic, of Internal Medicine

and Physical Medicine departments. Their ages {50-70years}.

They were classified into:-Control group consist of 30 healthy post-menopausal female and patients group consist of 70 post- menopausal female with type 2 diabetes.

The following patients were excluded from this study ;patients with impairment renal function, cardiac or pulmonary diseases, impaired hepatic function, Patients received anti-osteoporotic drugs or calcium supplements…etc.), Patients with abnormal thyroid and parathyroid function and Patients with history of old fracture.

After approval of the local ethical committee and informed consent from each one, patients who were selected scheduled to undergo a sheet was taken to all patients subjected.

Venous blood samples were taken after fasting for 10-12 hours, 2 ml of venous blood were transferred to EDETA tubes for Complete blood picture measured by Pentra – 80 automated blood counter. (ABX–France –Rue du Caducee-Paris Euromedecine-BP-7290.34184 Montpellier-Cedex 4.) and for quantitative colorimetric determination of glycated hemoglobin[10]

The rest of venous blood was transferred slowly into a plain tube, allowed to clot, and then centrifuged for ten minutes. The clear supernatant was separated in several aliquots, kept frozen at -20 °C, till analysis of Fasting and post prandial blood sugar, Liver enzymes (ALT-AST) and albumin, Renal function tests (blood urea and serum creatinine), Serum Alkaline phosphatase on autoanalyzer SYNCHRON CX5 (Beckman Inst, USA).

Quantitative measurement of human Fetuin-A (ng/ml) by ELISA techniques . The assay utilizes the two site "sandwich" technique with two selected polyclonal antibodies that bind to different epitopes of human Fetuin-A. [11]

The diagnosis of Osteoporosis was established by lumbar spinal, hip and wrist BMD measurements using DXA according to World Health Organization diagnostic criteria:-

The T score: - Normal (0 to –0.99), Osteopenia (–1 to –2.49), Osteoporosis ≤ –2.5 (egg, –3.0, –4.0; remember that these are negative numbers), Severe or established osteoporosis ≤ –2.5with a fragility fracture.

Statistical analysis of the collected data:-

Data were collected, tabulated, statistically analyzed by computer using SPSS version 16.

The quantitative data were expressed as mean and standard deviation (Mean ±SD). The qualitative data were expressed as number and percentage and analyzed by the chi-square test (x^2) and the student's t test for the normally distributed variables and for the none normally distributed variables. The student t-test for comparison between two means. All these tests were used as tests of significance at $p<0.05$ level.

3.Results:-

The present study was carried out 70 post-menopausal female patients with type II diabetes mellitus and 30 apparently healthy post-menopausal females as a control group.

Demographical characteristics of the two groups were similar including age and postmenopausal. Period while there is a significant increase in fasting and postprandial blood glucose level, HBA1c and ALP level in patients group when compared to control. Also, serum fetuin-A levels were found to be significantly higher in the diabetic group (304.94 ± 21.85 ng/ml) than in the control group (109.21 ± 7.94 ng/ml) ($P < 0.001$) (Table 1).

Table 1:- The comparison between patients and controls regarding different parameters.

Parameter	Patients No=70	Controls No=30	T test	*P* value
Age (years)	57.95±5.69	56.06±4.68	1.51	> 0.05
Disease duration (years)	10.8±5.49	---------	----------	----------
Postmenopausal period (years)	8.44±6.05	9.06±5.84	0.721	> 0.05
Fasting blood glucose (mg/dl)	173.42±46.17	96.9±9.12	8.94	< 0.001
Postprandial blood glucose (mg/dl)	293.13±79.67	123.6±8.24	7.31	< 0.001
HBA1c%	9.713±2.32	6.13±3.94	6.27	< 0.001
ALP (IU/L)	114.67±33.86	51.2±23.12	6.41	< 0.001
fetuin A (ng/ml)	304.94±21.85	109.21±7.94	7.31	< 0.001
DXA T-score	-2.09±1.62	-1.71±1.19	0.689	> 0.05
Spine				
Hip	-1.12±1.40	-0.29±1.17	2.06	> 0.05
Wrist	-1.72±1.39	-1.28±1.12	1.55	> 0.05

Additionally a significant negatively correlated between FBS and BMD of hip area (<0.05) (Table 2) and between 2hpp and HBA1c with BMD of spine area in diabetic group (<0.05) (Tables 3, 4), Also, there was a significant negative correlation between fetuin-A levels and BMD of lumbar spine (r = -0.314) (*P* = <0.05) in the diabetic group (Table 5).

In this study, osteoporosis represents 12.9% in spine area and 7.2% in hip and wrist areas in diabetic patients. While osteopenia were found in 58.5%, 57.1%, and 37.1% in diabetic patients in spine, wrist, and hip respectively (Table 6).

Table (2):-the correlation between fasting blood glucose level and different parameters in patients group.

Fasting blood glucose level(mg/dl)	Patients	
	Pearson's correlation Coefficient "r"	*P*- value Significance
Age (years)	-0.022	> 0.05
Disease duration (years)	0.218	> 0.05
Postmenopausal period (years)	0.127	> 0.05
Postprandial blood glucose (mg/dl)	0.655	<0.001
HBA1c%	0.569	<0.001
ALP (IU/L)	0.347	< 0.05
fetuin A (ng/ml)	0.098	> 0.05
DXA T-score	-0.159	> 0.05
Spine		
Hip	-0.356	<0.05
Wrist	-0.078	> 0.05

Table 3:-the Correlation between 2hours post prandial blood glucose level and different parameters in patients group.

2h postprandial blood glucose level(mg/dl)	Patients	
	Pearson's correlation Coefficient "r"	*P* value Significance
Age (years)	-0.051	> 0.05
Disease duration (years)	0.207	> 0.05
Postmenopausal period (years)	0.048	> 0.05
Fasting blood glucose (mg/dl)	0.655	<0.001
HBA1c%	0.803	<0.001
ALP (IU/L)	0.340	<0.05
fetuin A (ng/ml)	0.099	> 0.05
DXA T-score	-0.361	< 0.05
Spine		
Hip	-0.257	> 0.05
Wrist	0.120	> 0.05

Table 4:-the correlation between glycated hemoglobin and different parameters in patients group.

HBA1c%	Patients	
	Pearson's correlation Coefficient "r"	*P* value significant
Age (years)	-0.69	> 0.05
Disease duration (years)	0.237	>0.05
Postmenopausal period (years)	0.081	>0.05
Fasting blood glucose (mg/dl)	0.569	<0.001
Postprandial blood glucose (mg/dl)	0.803	<0.001
ALP (IU/L)	0.308	<0.05
fetuin A (ng/ml)	0.071	>0.05
DXA T-score	-0.365	<0.05
Spine		
hip	-0.254	>0.05
Wrist	-0.056	>0.05

Table5:-the correlation between fetuin-A level and different parameters in the two studied groups.

Fetuin-A(ng)	Patients		Controls	
	Pearson's correlation coefficient "r"	P- value significant	Pearson's correlation coefficient "r"	*P*- value Significant
Age (years)	0.004	> 0.05	-0.431	> 0.05
Disease duration (years)	0.326	**< 0.05**	0.123	> 0.05
Postmenopausal period (years)	0.037	> 0.05	-0.207	> 0.05
Fasting blood glucose (mg/dl)	0.098	> 0.05	0.123	> 0.05
Postprandial blood glucose (mg/dl)	0.099	> 0.05	0.140	> 0.05
HBA1c%	0.071	>0.05	-0.043	> 0.05
ALP (IU/L)	0.206	>0.05	-0.166	>0.05
DXA T-score	-0.314	**< 0.05**	-0.059	> 0.05
Spine				
Hip	-0.053	>0.05	0.149	> 0.05
Wrist	0.003	>0.05	0.291	> 0.05

Table 6:-Number and percentage of subjects with normal and abnormal BMD evaluated by DXA scan.

Parameter	Patients No=70		Control No=30		Chi square	*P* value
	No	%	No	%		
DXA spin T Normal Osteopenia Osteoporosis	 20 41 09	 28.6 58.5 12.9	 06 15 09	 20 50 30	5.71	.> 0.05
DXA hip T Normal Osteopenia Osteoporosis	 39 26 05	 55.7 37.1 07.2	 21 09 00	 70 30 00	3.44	> 0.05
DXA wrist T Normal Osteopenia Osteoporosis	 25 40 05	 35.7 57.1 07.2	 11 18 01	 36.7 60 03.3	2.129	.> 0.05

4.Discussion:

Rates of diabetes have increased markedly over the last 50 years. in 2010 there are approximately 285 million people with the disease compared to around 30 million in 1985. Long-term complications from high blood sugar can include heart disease, stroke, diabetic retinopathy and nephropathy. [(12)]In addition, DM has been found to be associated with metabolic bone diseases, osteoporosis and low-impact fractures, as well as other bone-related events including falls in geriatric patients.[(13)] Osteoporosis is a widespread metabolic bone disease characterized by decreased bone mass and poor bone quality. It leads to an increased frequency of fractures of the hip, spine, and wrist. [(14)] Type 2 diabetes mellitus and osteoporosis are two chronic conditions whose prevalence and associated costs continue to increase, particularly among the elderly. [(15)]

Fetuin-A is shown to act as an endogenous inhibitor of the insulin receptor tyrosine kinase in liver and skeletal muscle, resulting in IR in these target tissues. In several epidemiological studies, higher serum fetuin-A levels are associated with IR, metabolic syndrome (MS) and Type 2 DM. [(16)]Fetuin-A supports bone mineralization, the relationship between it and BMD has not been clearly understood.[(17)]

This study was aimed to evaluate the serum fetuin-A levels and bone mineral density in elderly female patients with type 2 diabetes mellitus and their relation with each other.This study revealed that after adjusting for age, sex, length of menopause and BMI, type II diabetes cannot be considered as a risk factor for osteoporosis, although in diabetic patients,

metabolic control of diabetes was related to bone density in diabetic patients.

In this study we found no difference in BMD between patient and control groups while glycemic parameters were found to be correlated with BMD as following; FBS was significantly negatively correlated with BMD in hip area while 2hpp and HBA1c were significantly negatively correlated with BMD in spinal area measured by T-score in DXA scan.

These result were similar to the study conducted on 40 diabetic and 40 healthy post-menopausal women matched in terms of age, length of post-menopausal period and body mass index . They evaluated BMD in three sites (spine, hip, and wrist) with DXA and found no significant difference in BMD between diabetic and non-diabetic women, although they found HBA1c to be in a significant relationship with lumber spin BMD in diabetic women. They explain their finding by the presence of hypercalciuria following hyperglucosuria in poorly controlled diabetic patients which eventually a cause for bone loss. [18]

Also two other studies found significant relationship between hip BMD and HBA1c in diabetic patients. [19, 20]Older women with DM was found to be more rapid bone loss than those without DM at the hip, spine, and calcaneus areas, but not the radius area. [21]While another two studies found no relationship between BMD and HBA1c in diabetic patients. [22, 23]

Another study done in Saudi Arabia found that the frequency of osteoporosis in diabetic postmenopausal women was higher than normal group. [24]

In contraindicated to this study one study found BMD in diabetic patients to be significantly higher than non-diabetic subjects. Also HBA1c in their study were found to be positively associated with higher BMD in diabetic patients. [25]

On contrary to the present study, a study done by Saeed *et al.* shown that postmenopausal women with type II Diabetes Mellitus apparently have higher BMD and slow bone turnover when compared with matched controls. However, the difference in BMD between the two groups became non-significant after adjusting for the effect of BMI. [26] Patients with type II DM display an increased fracture risk despite a higher BMD, which is mainly attributable to the increased risk of falling. [27]

One study found that type II diabetic patients have significantly lower T- score value and more frequency of osteoporosis than healthy post-menopausal women. Also they found a positive correlation between HBA1c and BMD in hip area but not spinal area. [28]

In the present study fetuin-A level found to be significantly higher in diabetic group than non-diabetic group. Also another studies found that women with impaired glucose tolerance had elevated fetuin-A levels compared with women with normal glucose tolerance. They concluded that higher fetuin-A concentrations were independently associated with an increased risk of developing type 2 diabetes in older women but were not related to diabetes risk in older men. [29, 30]

In contrast, a pervious study found no significant difference in fetuin-A level between diabetic and non-diabetic groups. [31]

Also in a prospective study performed among women aged 53- 79 years a positive association between plasma fetuin-A and risk of type II diabetes was found, which was independent of liver enzymes and of other established risk factors for diabetes. [32]In one study found that plasma fetuin-A level to be positively associated with diabetes risk after adjustment for age. [33] Another study conducted on 80 patients with type II diabetes [40 men and 40 women matched for age, body mass index (BMI) and time since diagnosis of diabetes]. They conducted an independent association of fetuin-A levels with markers of bone turnover in male and female patients with type II diabetes. [7]

In the present fetuin-A found to be negatively correlated with BMD in diabetic patients in spinal area. Up to our knowledge no other studies discussed such relationship between fetuin-A and BMD in type II diabetes mellitus, while some investigators discuss the relationship between fetuin-A and BMD in healthy postmenopausal women they conducted their study on 90 participants divided into three groups including 30 patients in each group. Group 1 consisted of patients who were newly diagnosed with postmenopausal osteoporosis, group 2 consisted of patients who were previously diagnosed with postmenopausal osteoporosis and received treatment, and the control group consisted of healthy volunteers with normal postmenopausal BMD values, they found that significant positive relationship between serum fetuin-A levels and BMD scores in spine and hip areas. Also they found that serum fetuin-A level was lower in patients with postmenopausal osteoporosis compared to control group. And concluded fetuin-A a marker for bone mineralization, can be used as a biomarker in the diagnosis and treatment of postmenopausal osteoporosis. [34]

Also study investigated the relationship between serum fetuin-A level and BMD. In 3075 older persons (70-79years) and conclude that higher fetuin-A levels are independently associated with higher BMD among well-functioning community-dwelling older women but not older men. [35] The relationships between serum fetuin-A concentration, serum lactoferrin concentration, and bone density in elderly women, and found a significant association between

serum fetuin-A level and bone mass and bone markers in elderly women. [36]

In this study, there was highly significant increase of ALP in diabetic compared to non-diabetic post-menopausal women in agreement with this **Meena *et al.*** found a highly significant difference of ALP between diabetic and non-diabetic post-menopausal women. [37]

Also in the present study no significant correlation between ALP and BMD were found, while another study found that the alkaline phosphatase levels showed a negative correlation with BMD at all sites in women with type 2 diabetes mellitus. [38]

Conclusions: -In conclusion, the present study found that type II diabetes cannot be considered as a risk factor for osteoporosis; while glycemic parameters (FBS, 2hpp and HBA1c) and serum Fetuin A levels were correlated with BMD, decision making for diagnosis and treatment of osteoporosis should be individualized and based on glycemic control and fetuin A level.

Corresponding author:-
Mayada Mohamed Mohamed Abdel-Raizk,
Address: Internal Medicine department, Faculty of Medicine-Menoufia university,
Shebin Elkom, Menoufia-Egypt.
E.mail: drmayada158@yahoo.com

References:-

1. American Diabetes Association. Standards of medical care in diabetes—2013. Diabetes Care 2013; 36 (1): 11- 66.
2. Hadjidakis D, Mylonakis A, Sfakianakis M, Raptis A, Raptis S. Diabetes and premature menopause: is their co-existence detrimental to the skeleton? Eur J Endocrinol. 2005; 152(3):437–442.
3. Raisz LG. Pathogenesis of osteoporosis: concepts, conflicts, and prospects. J Clin Invest. 2005; 115(12):3318-25.
4. S.A. New S. Bone health: the role of micronutrients. Br Med Bull. 1999; 55(3):619–633.
5. Samere A. Evaluation of usage preventing of osteoporotic behavior in menopausal women. Bulletin of 1st International congress of prevention, diagnosis and treatment; pp. 2005; 106–16.
6. Baiat N, Haji Amini Z, Alishiri GH, Ebadi A, Hoseini MS, Laloie A. Frequency of osteoporosis and osteopenia in postmenopausal military family's women. Army Univ Med Sci J.2008; 6:25–30.
7. Sazan Rasul, Ilhan A, Reiter MH, Todoric J, Farhan S,Esterbauer H, *et al.* Levels of fetuin-A relate to the levels of bone turnover biomarkers in male and female patients with type 2 diabetes. Clinical Endocrinology. 2012; 76: 499-505.
8. Ix JH, Wassel CL, Kanaya AM, Vittinghoff E, Johnson KC, Koster A, Cauley JA, Harris TB, Cummings SR, Shlipak MG**.** Fetuin-A and incident diabetes mellitus in older persons. JAMA, 2008; 300, 182–188.
9. Stefan N, Hennige AM, Staiger H, Machann J, Schick F, Kröber SM, Machicao F, Fritsche A, Häring HU.Alpha2-Heremans-Schmid glycoprotein/fetuin-A is associated with insulin resistance and fat accumulation in the liver in humans. Diabetes Care. 2006; 29: 853–7.
10. Gonen B and Rubenstien AH. Determination of glycohemoglobin. Diabetologia 1978; 15: 1-5.
11. Price PA, Thomas GR, Pardini AW, Figueira WF, Caputo JM,Williamson MK. Discovery of a high molecular weight complex of calcium, phosphate, Fetuin, and matrix gamma-carboxyglutamic acid protein in the serum of etidronate-treated rats. J Biol Chem. 2002 Feb 8; 277:3926-34.
12. Fasanmade, OA; Odeniyi, IA, Ogbera, AO.Diabetic ketoacidosis: diagnosis and management". African Journal of Medicine and Medical Sciences, 2008; 37 (2): 99–105.
13. Brown SA and Sharpless JL. Osteoporosis: an under-appreciated complication of diabetes. Clin Diabetes, 2004 ; 22: 10-20.
14. Lane JM, Serota AC, Rapheal Osteoporosis: Differences and Similarities in Male and Female Patients. Orthop Clin N Am, 2006; 37; 601–609.
15. Cowie CC, Rust KF, Byrd-Holt DD, Eberhardt MS, Flegal KM, Engelgau MM, Saydah SH, Williams DE, Geiss LS, Gregg EW. Full accounting of diabetes and pre-diabetes in the U.S. population in 1988-1994 and 2005-2006. Diabetes Care. 2009; 32, 287–294. B.,
16. Song A, Min Xu, Yufang Bi, Yu Xu, Yun Huang, Mian Li, Tiange Wang, Yaohua Wu, Yu Liu, Xiaoying Li, Yuhong Chen, Weiqing Wang, and Guang Ning, Aimin Xu, EditorSerum fetuin-A associates with type 2 diabetes and insulin resistance in Chinese adults. PLoS One. 2011; 6: e19228.
17. Heiss A, DuChesne A, Denecke B, Grötzinger J, Yamamoto K, Renné T. Structural basis of calcification inhibition by alpha 2-HS glycoprotein/ fetuin-A. Formation of colloidal calciprotein particles. J Biol Chem, 2003; 278:13333-41.
18. Sharifi F, Ahmadimoghadam N, Mousavinasab Nthe relation between type2 diabetes mellitus and bone density in post menoupasal women Int J Endocrinol Metab 2006; 3: 117-122.
19. Heap J, Murray MA, Miller SC, Jalili T, Moyer-Mileur LJ. Alterations in bone characteristics associated with glycemic control in adolescents with type 1 diabetes mellitus. J Pediatr 2004; 144: 56- 62.
20. Majima T, Komatsu Y, Yamada T, Koike Y, Shigemoto M, Takagi C, et al. Decreased bone mineral density at the distal radius, but not at the lumbar spine or the femoral neck, in Japanese type 2 diabetic patients. Osteoporos Int 2005; 16: 907-13.

21. Ann V. Schwartz, Susan K. Ewing, Anne M. Porzig, Charles E. McCulloch, Helaine E. Resnick, Teresa A. Hillier, Kristine E. Ensrud, Dennis M. Black, Michael C. Nevitt, Steven R. Cummings, and Deborah E. SellmeyerDiabetes and Change in Bone Mineral Density at the Hip, Calcaneus, Spine, and Radius in Older Women, Front Endocrinol (Lausanne). 2013; 4: 62.
22. Leidig-Bruckner G, Ziegler R. Diabetes mellitus a risk factor for osteoporosis? Exp clin Endocrinol diabetes 2001; 109 Suppl 2: S493-514.
23. Wakasugi M, Wakao R, Tawata M, Gan N, Koizumi K, Onaya T. Bone mineral density measured by dual energy x-ray absorptiometry in patients with non-insulin-dependent diabetes mellitus. Bone 1993; 14: 29-33.
24. Al-Maatouq MA, El-Desouki MI, Othman SA, Mattar EH, Babay ZA, Addar M. Prevalence of osteoporosis among postmenopausal females with diabetes mellitus. Saudi Med J 2004; 25: 1423-7.
25. Lili Ma, Ling Oei, Lindi Jiang, Karol Estrada, Huiyong Chen, Zhen Wang, Qiang Yu,Maria Carola Zillikens, Xin Gao, Fernando Rivadeneira. Received:Association between bone mineral density and type 2 diabetes mellitus: a meta-analysis of observational studiesEur J Epidemiol (2012) 27:319–332.
26. Saeed BO, Nixon SJ and Weaver JU. Peripheral Bone Mineral Density and Bone Turnover in Postmenopausal Women with Type 2 Diabetes. J Diabetes Metab;(2012) S1:007.
27. Shaymaa Abdalwahed Abdulameer, Syed Azhar Syed Sulaiman, Mohamed Azmi Ahmad Hassali, Karuppiah Subramaniam, and Mohanad Naji Sahib. Osteoporosis and type 2 diabetes mellitus: what do we know, and what we can do? Patient Prefer Adherence. 2012; 6: 435–448.
28. Nasrin Moghimi; Ezat Rahimi; Siamak Derakhshan; Fariba Farhadifar, Osteoporosis in Postmenopausal Diabetic Women; Prevalence and Related Factors Iran J Nucl Med 2008; 16(2): 28-33.
29. Gail A., Elizabeth B, Kevin M. Cummins, Lori B. Daniles, MAS Christena L. Wassel, Joachem H. IX, MAS Sex-Specific Association of Fetuin-A With Type 2 Diabetes in Older Community-Dwelling Adults DIABETES CARE, 2013: 36:p 1994:2000.
30. Ou HY, Yang YC, Wu HT, Wu JS, Lu FH, Chang CJ. Serum fetuin-A concentrations are elevated in subjects with impaired glucose tolerance and newly diagnosed type 2 diabetes. Clin Endocrinol (Oxf). 2011 Oct; 75(4):450-5.
31. Katsuhito Mori, Masanori Emoto, Hisayo Yokoyama, Takahiro Araki, Megumi Teramura, Hidenori Koyama, Tetsuo Shoji, Masaaki Inaba, and Yoshiki Nishizawa,. Association of Serum Fetuin-A with Insulin Resistance in Type 2 Diabetic and Nondiabetic Subjects, diabetic care, 2013; 545-8585.
32. Qi Sun, Marilyn C. Cornelis, JoAnn E. Manson and Frank B. Hu Plasma Levels of Fetuin-A and Hepatic Enzymes and Risk of Type 2 Diabetes in Women in the U.S. Diabetes. 2013; 62(1):49-55.
33. Norbert Stefan, Andreas Fritsche, Cornelia Weikert, Heiner Boeing, Hans-Georg Joost, Hans-Ulrich Häring, and Matthias B. Schulze, Fetuin-A Levels and the Risk of Type **2** Diabetes Diabetes. 2008 October; 57(10): 2762–67.
34. Aylin SARI Turan USLU. The Relationship Between Fetuin-A and Bone Mineral Density in Postmenopausal Osteoporosis, Department of Physical Medicine and Rehabilitation Turkish journal of rheumatology.2013,28;3;195-201.
35. Jochim Ix JH, Wassel CL, Bauer DC, Toroian D, Tylavsky FA,Cauley JA, *et al.*Fetuin-A and BMD in older persons: the Health Aging and Body Composition (Health ABC) study. J Bone Miner Res, 2009:24:514-21.
36. Chailurkit L, Kruavit A, Rajatanavin R, Ongphiphadhanakul B., The relationship of fetuin-A and lactoferrin with bone mass in elderly women. Osteoporosis International, 2011; 22, 2159–64.
37. Meena Varma, Sangeeta Paneri, Preetha Badi. Correlative study of bone related Biochemical parameters in normal postmenopausal women and hyperglycemic postmenopausalwomen *Biomedical Research* 2005; 16 (2): 129-132.
38. Irzal Hadzibegovic, Blazenka Miskic,a Vesna Cosic, b Deiti Prvulovic,a Dragica Bistrovica Bistrovica Increased bone mineral density in postmenopausal women with type 2 diabetes mellitus Ann Saudi Med 2008; 28(2): 102-104.

8/15/2014