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Association of Serum Fetuin-A Concentration and Bone Mineral Density in Women with Postmenopausal Osteoporosis

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Abstract:
Osteoporosis is a chronic, progressive, skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility. Biological pathways leading to osteoporosis remain incompletely understood. The discovery of novel pathways for osteoporosis could lead to new preventive strategies or therapeutic targets. Fetuin-A is a hepatic-derived, serum protein that regulates calcium mineralization. We aimed to evaluate the correlation between serum Fetuin-A concentrations and bone mineral density (BMD) in postmenopausal women.52 postmenopausal women were enrolled in the current study, divided to 2 groups; Group I: 31 postmenopausal osteoporotic women, not on osteoporotic treatment, group II(controls): 21age-matched post-menopausal women with normal BMD. Exclusion criteria included; females with surgical menopause or secondary osteoporosis, those with acute infection, malignancy, myocardial infarction (MI) within the previous month, a history of severe trauma, surgery, burns, diabetes mellitus (DM), liver or kidney disease, , a history of smoking or alcoholism, patients taking steroids, anticonvulsants, chemotherapy,hormone replacement therapy (HRT), and L-Thyroxine. Basic laboratory investigations were done, plus parathyroid hormone(PTH), serum vitamin D3 levels, and serum Fetuin-A levels. Women in osteoporotic group had significantly lower BMI, vitaminDlevels, and higher PTH levels. Also, women in osteoporotic group had significantly lower Fetuin-A

levels. BMD of femur neck and lumbar spine were significantly lower in osteoporotic group. Fetuin-A was significantly correlated to BMD of femur neck and lumbar spine. We concluded that serum fetuin-A might be related to osteoporosis and it may provide necessary information on its pathogenesis. Fetuin-A can be used as a biochemical parameter within the scope of the diagnosis and treatment of postmenopausal osteoporosis.

Keywords*: Osteoporosis, Fetuin-A, Postmenopausal, Bone mineral density.*

Introduction

Osteoporosis is a chronic, progressive, systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility [(1)] .Osteoporosis represents an increasingly serious health and economic problem in all-around the world[(2)]. Osteoporosis is a preventable disease that can result in devastating physical, psychosocial, and economic consequences. Affected individuals experience pain, disability, and diminished quality of life as a result of having this condition.

Despite the adverse effects of osteoporosis, it is a condition that is often overlooked and undertreated, in large part because it is so often clinically silent before manifesting in the form of fracture. The National Osteoporosis Foundation revealed that 86% of all women aged 45-75 years had never discussed osteoporosis with their physicians, and more than 80% were unaware that osteoporosis is directly responsible for disabling hip fractures[(3)].

The World Health Organization's (WHO) defines osteoporosis based on bone mineral density (BMD) as BMD ≥2.5 SD below the normal mean for young-adult women or T-score ≤ –2.5 [(4)]. Whereas the T-score is the patient's bone density compared with the BMD of control subjects who are at their peak BMD, the Z-score reflects a bone density compared with that of patients matched for age and sex [(4,5)] .The WHO definition applies to postmenopausal women and men aged 50 years or older.

Globally, osteoporosis is by far the most common metabolic bone disease, estimated to affect over 200 million people worldwide [(6)]. The National Osteoporosis Foundation (NOF) released updated prevalence data estimating that a total of 54 million American adults age 50 and older are affected by osteoporosis and low bone mass[(7,8)]. Egyptian studies show that 53.9% of postmenopausal women have osteopenia, whereas 28.4% have osteoporosis [(9)]. 50% of all women older than 50 years, experience one or more osteoporosis-related fractures in their lifetime [(10)].

Osteoporosis has been divided into several classifications according to the etiology and localization in the skeleton. Osteoporosis is initially divided into localized and generalized categories, and these two main categories are further classified into primary and secondary osteoporosis [(11)].

Postmenopausal osteoporosis (type I osteoporosis) Occurs in postmenopausal women with estrogen deficiency and characterized by a phase of accelerated bone loss, primarily from trabecular bone. Risk factors for osteoporosis include [(12,13)]; Advanced age (≥50 years), white or Asian ethnicity, genetic factors, such as a family history of osteoporosis, thin build or small stature, amenorrhea, late menarche, early menopause, physical inactivity or immobilization, use of certain drugs as anticonvulsants, systemic steroids, thyroid supplements, heparin, chemotherapeutic agents, insulin, alcohol and tobacco use.

Osteoporosis can be caused both by a failure to build bone and reach peak bone mass as a young adult, and by bone loss later in life. Accelerated bone loss can be affected by hormonal status, as occurs in peri-menopausal women, and can be secondary to various disease states and medications.

Hormones are possibly the most crucial modulators of bone formation. It is well established that estrogen, parathyroid hormone,

and to a lesser extent testosterone are essential for optimal bone development and maintenance. Of these, estrogen is believed to have the most direct effect on bone cells, interacting with specific proteins, or receptors, on the surface of osteoblasts and osteoclasts [14]. Actually, biological pathways leading to osteoporosis remain incompletely understood. The discovery of novel pathways for osteoporosis could lead to new preventive strategies or therapeutic targets.

Fetuin-A (also called a-2 Heremans Schmidglycoprotein [AHSG]) is a 64-kDa serum protein that regulates calcium mineralization. It is synthesized by the liver and secreted in the serum [15].Fetuin-A complexes with calcium and phosphorus and prevents the precipitation of these minerals from serum. Several observations suggest that fetuin-A may play a role in the regulation of bone mineralization [16,17].Fetuin –A is among the most abundant non-collagenous proteins found in bone. In vivo, fetuin-A knockout mice develop osteomalacia by 3 months of age [18]. For some time the mechanism of how fetuin-A might regulate bone mineralization remained unknown. Later, it was hypothesized that fetuin-A may simultaneously inhibit calcium precipitation in serum and promote calcification within bone [19]. The investigators recently showed that fetuin-A directly promoted calcification within bone in an in vitro system. This important observation provides novel insights to the role of fetuin-A in bone homeostasis.

There are limited human studies on fetuin-A to define its exact mechanism [20]. In the current study, we aimed to evaluate the correlation between serum fetuin-A concentrations and bone mineral density (BMD) parameters in postmenopausal women.

Materials and Methods:

52 postmenopausal women who attended the Geriatric outpatient clinic at the Main Alexandria University Hospital, or gynecological outpatient Clinic at El-Shatby University Hospital were enrolled in the present study. The aim, purpose, and benefits of the study were explained to all participants and an informed written consent was obtained. The proposal was accepted by the ethical committee of faculty of medicine-Alexandria University. The participants were divided into two groups. Group (I) included 31women who were diagnosed recently with postmenopausal osteoporosis and not on osteoporotic treatment, group (II); included 21age-matched post-menopausal women with normal BMD levels, and served as a control group. The term "postmenopausal" describes women who have not experienced any menstrual flow for a minimum of 12 months, assuming that they do still have a uterus, and are not pregnant or lactating[21]. Exclusion criteria included; females with surgical menopause or secondary osteoporosis, those with acute infection, malignancy, myocardial infarction (MI) within the previous month, a history of severe trauma, surgery, burns, diabetes mellitus (DM), liver or kidney disease, a history of smoking or alcoholism, patients taking steroids, anticonvulsants, chemotherapy, hormone replacement therapy (HRT), and L-Thyroxine.

A thorough medical history was taken from all participants, and full clinical examination was carried out. Basic routine laboratory investigations were done for all participants, plus parathyroid hormone (PTH) levels, and serum 25-hydroxyvitamin D3 concentrations. Serum Fetuin-A concentrations were measured using aHuman Fetuin- A ELISA Kite using serum samples collected after 10-12 hours fasting.

The Hologic QDR-2000 Bone Densitometer was employed to measure bone mineral density (BMD) of lumbar spine and femoral region. According to the World Health Organization (WHO) criteria; osteoporosis is defined as BMD measurement 2.5 standard deviations (SDs) below the typical peak bone mass of a young healthy woman (i.e., the T score was equal to or less than -2.5 SD) [4].

Statistical methods: Data were fed to the computer and analyzed using IBM SPSS software package

version 20.0. Qualitative data were described using number and percent. Quantitative data were described using range (minimum and maximum), mean, standard deviation and median. Comparison between different groups regarding categorical variables was tested using Chi-square test. The distributions of quantitative variables were tested for normality. For normally distributed data, comparison between two independent populations were done using independent t-test. Correlations between two quantitative variables were assessed using Pearson coefficient. For abnormally distributed data, comparison between two independent populations were done using Mann Whitney test. Correlations between two quantitative variables were assessed using Spearman coefficient. Significance of the obtained results was judged at the 5% level.

52 postmenopausal women were enrolled in the present study, divided into two groups; group I (osteoporotic group): 31women, recently diagnosed with postmenopausal osteoporosis and not on osteoporotic treatment, their mean age was 57.29 ± 3.89 years, and group II (control group): 21age-matched post-menopausal women with normal BMD levels, their mean age was 55.86 ± 2.39 years, with no statistical difference between both groups (p=0.107). The age at menopause was significantly higher in the control group (p=0.047). Women in control group had significantly higher BMI compared to women in osteoporotic group (p=0.013). Vitamin D levels were significantly lower in osteoporotic group than control group (p<0.001), and parathyroid hormone was significantly higher in osteoporotic group than control group (p<0.001).Fetuin-A was significantly lower in osteoporotic group than in the control group (p<0.001). Table 1

Results:

Table 1: Demographic and clinical characteristics of the two studied groups:

	Osteoporosis Gr (n = 31)	**Control Gr (n = 21)**	**p**
Age	57.29 ± 3.89	55.86 ± 2.39	0.107
BMI	29.27 ± 1.75	30.79 ± 2.46	0.013*
Age at menopause	50.10 ± 2.15	51.24 ± 1.70	0.047*
Vitamin. D (ng/mL)	19.98 ± 4.18	34.08 ± 2.98	<0.001*
Normal	3 (9.7%)	21 (100.0%)	<0.001*
Abnormal	28 (90.3%)	0 (0.0%)	
PTH (ng/mL)	107.0 (75.90 – 201.30)	33.60 (22.60 – 63.0)	<0.001*
Normal	6 (19.4%)	21 (100.0%)	<0.001*
Abnormal	25 (80.6%)	0 (0.0%)	
Fetuin –A (ng/mL)	23.03 ± 3.45	67.67 ± 19.10	<0.001*
Normal	3 (9.7%)	21 (100.0%)	<0.001*
Abnormal	28 (90.3%)	0 (0.0%)	

*: Statistically significant at $p \leq 0.05$

Femur neck and lumbar spine BMD were significantly lowerin osteoporotic group compared to those of the control group (p<0.001). Table 2

Table 2: Comparison between the two studied groups regarding BMD:

	OsteoporosisGr (n = 31)	Control Gr (n = 21)	p
Femur neck	-3.20 (-4.50 – -2.60)	0.90 (-1.0 – 2.0)	<0.001*
Normal	0 (0.0%)	21 (100.0%)	
Low bone mass	2 (6.5%)	0 (0.0%)	<0.001*
Osteoporosis	29 (93.5%)	0 (0.0%)	
Lumbar spine	-3.20 (-4.50 – -2.50)	0.70 (-1.30 – 1.90)	<0.001*
Normal	0 (0.0%)	19 (90.50%)	
Low bone mass	0 (0.0%)	2 (9.5%)	<0.001*
Osteoporosis	31 (100.0%)	0 (0.0%)	

*Statistically significant at $p \leq 0.05$

Fetuin-A was significantly positively correlated to BMD of both femur neck and lumbar spine, as shown in table 3.

Table 3: Correlation between fetuin-A levels and both lumbar and femoral BMD:

		Fetuin-A	
		Osteoporosis Gr	**Control Gr**
Femur neck	**r_s**	0.523*	-0.096
	p	0.003	0.678
Lumbar spine	**r_s**	0.499*	-0.128
	p	0.004	0.581

*Statistically significant at $p \leq 0.05$

Discussion:

Osteoporosis is the most common metabolic bone disease associated with aging population worldwide, results in devastating physical, psychosocial, and economic consequences. The exact pathophysiology of this condition is poorly understood. In vivo and in vitro studies have helped to further understand bone biology and identify the factors that are associated with osteoporosis. Fetuin-A is a glycoprotein associated with bone formation and remodeling has been recently, implicated in the regulation of bone mineralization [16,17], although the exact mechanism is not clear. One of the important functions of fetuin-A is that it inhibits calcium phosphate (Ca-P) precipitation [22].In addition, fetuin-A inhibits the formation of apatite in in-vitro osteoblast cultures[23]. Studies with fetuin-A gene-ablated mice showed an irregularity of bone mineralization that reinforced the role offetuin-A in this process[24,25].An in-vitro study by Toroian and Price [26], they demonstrated that mineral formed only within collagen fibrils when fetuin was present, but mineral formed only in solution outside the fibrils when fetuin was absent. They suggested that fetuin-A may be selectively inhibiting crystal formation outside the fibril and thus promoting fibril mineralization.

Triffitt et al.[27] studied binding of fetuin-A to mineralized bone matrix and described it to be the most robust binding phenomenon by far. The high affinity of fetuin-A for bone mineral mediates

selective fetuin-A accumulation from plasma into bone [27]. We showed that fetuin-A also has a particularly high affinity to nascent apatite mineral and is an inhibitor of de novo apatite formation from supersaturated mineral solutions[28].Fetuin-A has also been reported to correlate with bone turnover markers [29].

Few studies analyzed the correlation between fetuin-A and BMD levels [20,30]. In our study, we hypothesizedthat post-menopausalosteoporotic women will show lower fetuin-A levels.

Results of our study showed that Serum fetuin-A levels were significantly lower in the osteoporotic women than the control group. In accordance with our results; IX et al. [30] analyzed the serum fetuin-A levels of 580 subjects aged (70–79 years) whose BMD values were already known. They found that higher fetuin-A levels were correlated with higher BMD values in older women. EsinÖzkan et al.[31] in their study which involved 50 postmenopausal females, found that Serum fetuin-A levels of the osteoporosis group were significantly lower compared to the control group. Also, Aylin and Turan in their study [32], showed that serumfetuin-A concentrations were lower in the patients with postmenopausal osteoporosis than in the controls. We also, found a statistical significant correlation between fetuin-A levels and both lumbar and femoral BMD. In accordance with our findings; Aylin and Turan [32] found a statistically significant relationships between the fetuin-A concentration and lumbar AP T and Z scores, femur total T and Z scores, and femoral neck T and Z scores. In another study by Chailurkit L et al.[20], fetuin-A levelswere found to be positively correlated with lumbar, butnot femoral BMD values. Also, EsinÖzkan et al.[31],found that fetuin-A levels correlated more with lumbar BMD values than femoral values.

Detection of low concentration of fetuin-A in postmenopausal women with osteoporosis suggests that it may play a role in the formation and development of this disease.

Postmenopausal osteoporosis is characterized by low levels of estrogen and high levels of bone mineralization markers. Likewise Rasul et al.[33] showed that fetuin-A has a positive correlation with estrogen and a negative correlation with C-Terminal cross-linked telopeptide of type I collagen (CTX), a bone mineralization marker. Although fetuin-A blocks the TGF-β/BMP system to inhibit osteogenesis, and deposition of calcium-containing matrix in mineralizing cell cultures[34], it may affect the role of other regulatory mechanisms with regard to bone metabolism conferred through osteoblasts, osteoclasts, or other bone cells. This aspect need further studies to elucidate the mechanisms that underlie these pathways.

In conclusion, our findings suggest that serum fetuin-A might be related to osteoporosis and it may provide necessary information on its pathogenesis.Fetuin-A can be used as a biochemical parameter within the scope of the diagnosis and treatment of postmenopausal osteoporosis. Further studies with larger samples are required to define the exact role of fetuin-A in bone metabolism and its possible reflections on osteoporosis.

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