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RESEARCH ARTICLE

Fetuin-A in postmenopausal women with osteoporosis: Active player in the field

Yasser S. Sheta[1], **Abdallah Nawara**[1], **Elsayed A. Elgohary**[1], **Fatma M. Awad**[2]

1. From the department of Internal medicine, Faculty of Medicine, Zagazig University

2. Radiology department, Faculty of Medicine, Cairo University

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Corresponding Author

Yasser S. Sheta

Abstract

Background: Fetuin-A is a glycoprotein formed by liver cells and is secreted into the serum in high concentration. It regulates the process of osteogenesis by inhibiting transforming growth factor-β (TGF-β) and bone morphogenic protein. Fetuin-A plays a role in bone metabolism and it has various functions such as ectopic calcification inhibition. One of the functions of fetuin-A is the restriction of formation and expansion of extra osseous hydroxyapatite crystals. The exact correlation of fetuin-A with bone mineral density (BMD) has not been clearly elucidated. ***In this study, we aimed*** to assess the relationship between BMD and fetuin-A in postmenopausal women. ***Materials and Methods*:** Forty postmenopausal women (20 with osteoporosis, 20 healthy controls) were included in the study. All participants were comparable for age and body mass index. None of the osteoporotic patients had received any medical treatment for osteoporosis. Serum fetuin-A levels were measured by ELISA method. ***Results:*** BMD scores of the groups were statistically significant ($P < 0.001$). Serum fetuin-A levels of the osteoporosis group were significantly lower compared to the control group ($P < 0.001$). Additionally, there was a mild to moderate positive correlation between fetuin-A and lumbar BMD ($r = 0.407$, $P = 0.054$) in the osteoporotic group, though it did not reach statistical significance. ***Conclusion:*** Decreased fetuin-A levels in women with postmenopausal osteoporosis suggest that fetuin-A may have a role in the development of osteoporosis. Further studies are required to define the exact role of fetuin-A in bone metabolism.

INTRODUCTION

Sixty-six years have elapsed since the discovery of fetuin in 1944, but its importance in mammalian physiology has only recently been appreciated (9). Fetuins are blood proteins that are made mainly in the liver and secreted into the bloodstream. They belong to a large group of binding proteins mediating the transport and availability of a wide variety of cargo substances in the bloodstream. The best known representative of these carrier proteins is serum albumin, the most abundant protein in the blood plasma of adult animals. Fetuin is more abundant in fetal blood, hence the name "fetuin" (from Latin, *fetus*). Fetal calf serum contains more fetuin than albumin, while adult serum contains more albumin than fetuin (9-3). Fetuin-A (2-Heremans–Schmid glycoprotein) is expressed not only from the liver, but also from the kidney and choroid plexus (4). Fetuin-A is highly expressed in the noncollagenous bone matrix during fetal life and affects bone growth via antagonizing the effects of transforming growth factor beta (11). Lack of

fetuin-A has been shown to result in severe systemic calcification in mice and humans (8-10). Fetuin-A serves as a mineral chaperone, a carrier protein facilitating transport and clearing of potentially proinflammatory and procalcific cargo (waste).Fetuin-A facilitates the removal of hydroxyapatite crystals by increasing the calciprotein particles in the bloodstream and, therefore, inhibiting intravascular calcification (5-16). No matter what the preferred mechanism of atherosclerotic lesion calcification is, deranged mineral homeostasis, dyslipidemia, compromised scavenging and debris clearing, inflammation, apoptosis, matrix mineralization, and osteogenesis are all known pundits ("partners in crime"), and it seems like fetuin-A counters many of them and thus is a highly pleomorphic protein and is truly a systemic regulator of mineralization(8). Osteoporosis prevalence is consistently increasing due to increased life expectancy worldwide. It is known that one of the most common causes of hospitalization among elderly people, and especially postmenopausal women, is hip fractures due to osteoporosis (14-12). Nearly half of all women are expected to suffer an osteoporotic fracture in their lifetime (12). Twenty percent of the patients with hip fracture become functionally dependent and require long term nursing care. Additionally, post fracture mortality rate is as high as 20% within the first year (7). Thus, most relevant studies are aimed at developing new treatment modalities to alleviate the burden of this health problem. Although it is well known that the age and female sex are strong risk factors for osteoporosis, biological pathways possibly leading to osteoporosis are still unclear(4). Discovery of these pathways effective in osteoporosis may lead to development of new preventive or therapeutic strategies in the management of these patients (6). A regulatory role of fetuin–A in adult bone health and development of osteoporosis is suspected because its effect on osteogenesis, mineralization and calcification however, there are limited human studies on fetuin-A to define its exact mechanism (6-2). ***In this study, we aimed*** to assess the relationship between BMD and fetuin-A in a group of 40 postmenopausal women.

Materials and Methods

Twenty postmenopausal women with osteoporosis and 20 age- and body mass index (BMI)-matched healthy postmenopausal women were included in the study .All participants provided written informed consent. The study protocol was approved by the local ethics committee of Zagazig University Hospitals. Patients with vertebral fractures, surgical menopause, secondary osteoporosis, or other medical conditions that may affect the skeletal tissue or metabolism were excluded from the study. Patients previously treated with bisphosphonates, calcitonin, and anabolic steroids or who received hormone replacement therapy at any time after menopause were also excluded. The diagnosis of osteoporosis was established by lumbar spinal and femoral bone mineral density (BMD) measurements were made using dual-energy X-ray absorptiometry (DXA; QDR-4500, Hologic, Bedford, MA, USA) according to World Health Organization diagnostic criteria; Cut-off value for the diagnosis of osteoporosis of the hip and femoral neck was 0.648 gm/cm^2, while that for the lumbar spine was 0.740 gm/cm^2 (17). Fetuin-A was measured in duplicate using an ELISA kit (BioVendor Laboratory Medicine GmbH, Heidelberg, Germany) following the instructions of the manufacturer. Coefficients of intra-assay and inter-assay variations of serum fetuin-A levels were found to be 3.0% and 5.4%, respectively. Venous blood samples were collected after a 12-h fasting period into tubes containing clot activator to obtain serum. The tubes were allowed to clot before centrifugation. All tubes were then centrifuged at 2000 × *g* for 10 min. All sera were stored at –80 °C until final analysis.

Statistical analyses were performed using SPSS 11.5 for Windows (SPSS Inc., Chicago, IL, USA). Normality tests were performed by one-sample Kolmogorov–Smirnov test. Appropriate statistical tests were then selected. Mean values were compared using Student t-tests and correlations were analyzed by using Pearson and Spearman rank coefficients. Statistical significance was set at $P < 0.05$.

Results

Patient characteristics are presented in the Table 1. Demographical characteristics of the 2 groups were similar, including age and BMI. Serum fetuin-A levels were found
to be significantly lower in the osteoporotic group (0.78 ± 0.14 mg/L) than in the control group (0.94 ± 0.16 mg/L $P < 0.001$ Figure 1). Although there was a mild to moderate positive correlation between fetuin-A levels and lumbar ($r = 0.407$, $P = 0.054$) BMD in the osteoporotic group, it did not reach statistical significance. There was no statistically significant correlation of BMI or serum Ca levels with fetuin-A.

Table 1. Demographic and clinical characteristics of the postmenopausal osteoporotic women in the study group and the control group.

Parameters	Control group (n = 20)	Osteoporosis group (n = 20)	P-value
Age (years)	64.68 ± 7.44	65.48 ± 8.26	NS
BMI (kg/m2)	29.64 ± 2.00	29.31 ± 2.15	NS
Serum total Ca (mg/dL)	9.40 ± 0.60	9.39 ± 0.54	NS
Lumbar BMD (gm/cm2)	1.04 ± 0.15	0.70 ± 0.09	<0.001
F. neck BMD (gm/cm2)	0.84 ± 0.08	0.61 ± 0.06	<0.001
Fetuin-A (ng/mL)	0.94 ± 0.16	0.78 ± 0.14	<0.001

All data are reported as mean ± SD.
Ca: Calcium; F: femoral; BMI: body mass index; BMD: bone mineral density

Figure 1.Comparison of the mean value of serum fetuin-A (ng/mL) levels of osteoporotic patients and control subjects (P <0.001)

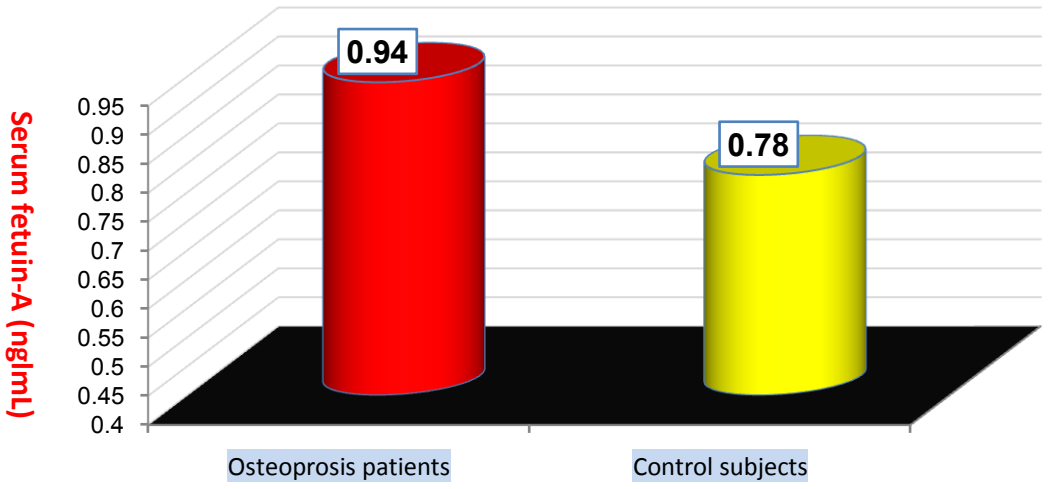
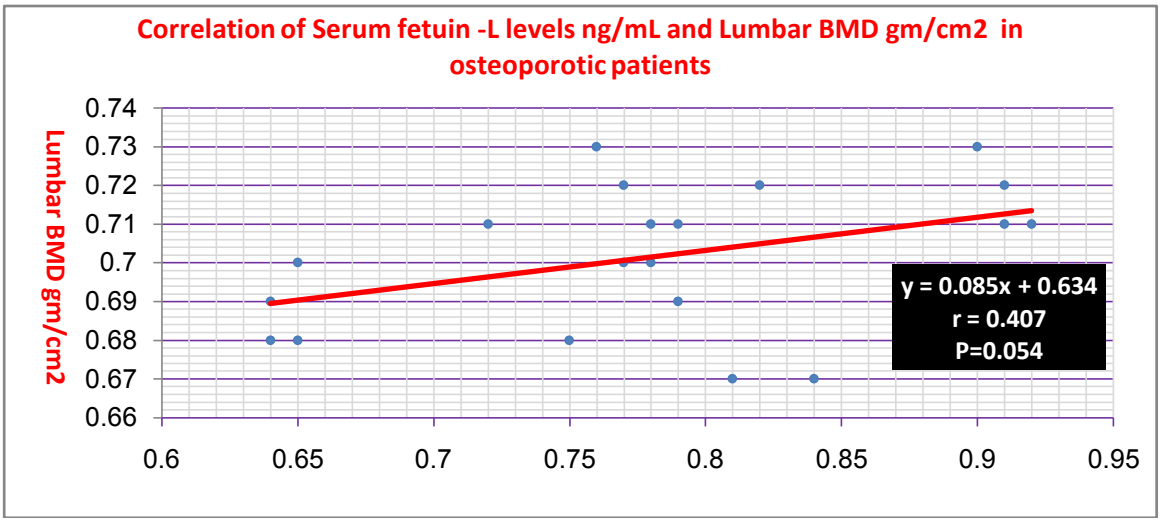


Figure 2.Correlation of serum fetuin-A levels (ng/mL) and lumbar BMD (DXA) in osteoporotic patients



Discussion

The final step of biomineralization is a chemical precipitation reaction that occurs spontaneously in supersaturated salt solutions. Genetic programs direct precursor cells into a mineralization-competent state in physiological bone formation (osteogenesis) and in pathological mineralization (ectopic mineralization or calcification). Therefore, all tissues not meant to mineralize must be actively protected against chance precipitation of mineral (16). Fetuin-A is a liver-derived blood protein that acts as a potent inhibitor of ectopic mineralization. Fetuin-A deficiency is associated with soft tissue calcification in mice and humans (8-10). On the other side a regulatory role of fetuin–A in adult bone health and development of or protection against osteoporosis is suspected because its effect on osteogenesis, mineralization and calcification (4). However, there are limited human studies on fetuin-A to define its exact role or mechanism (6, 2, 1). ***In this study, we aimed*** to assess the relationship between BMD and fetuin-A in postmenopausal women. In 2002, Szweras et al. (13) examined bone growth and remodeling in fetuin-A deficient mice. They found that fetuin-A–deficient mice seemed to be skeletally normal at birth, but growth retardation was observed between 3 and 18 months of age due to deficient maturation of the chondrocytes in the growth plate. In our study, fetuin-A levels were found to be lower in osteoporotic elderly women with low BMD values. In their study in 2008, Toroian and Price (15) 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. The first study in the literature that analyzed the association between fetuin-A and BMD was done by Ix et al. (6). They found that higher fetuin-A levels were correlated with higher BMD values in older women but not in men. In another clinical study, fetuin-A levels were found to be positively correlated with lumbar, but not femoral, BMD values (2). Another study in 2014 done by Esin et al. demonstrated that there was a mild to moderate positive correlation between fetuin-A levels and lumbar and femoral BMD in the osteoporotic post-menopausal Turkish ladies (4). According to our results, osteoporotic women had significantly lower fetuin-A levels than normal control subjects similar to the previously mentioned studies but, fetuin-A levels positively correlated only with lumbar BMD values but not reach statistical significance.

In conclusion

Our preliminary findings suggest that serum fetuin-A might be related to osteoporosis and it may provide necessary information on the pathogenesis. Further studies with larger samples are required to define the exact role of fetuin-A in bone metabolism and its possible reflections on osteoporotic fractures.

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