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Background/aim: One of the functions of fetuin-A is the restriction of formation and expansion of extraosseous hydroxyapatite crystals. The exact correlation of fetuin-A with bone mineral density (BMD) has not been clearly elucidated yet. In this study, we aimed to assess the relationship between BMD and fetuin-A in postmenopausal women.

Materials and methods: Fifty postmenopausal women (25 with osteoporosis, 25 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 ($P = 0.009$). Additionally, there was a mild to moderate positive correlation between fetuin-A and lumbar ($r = 0.381$, $P = 0.06$) and femoral ($r = 0.143$, $P = 0.50$) BMD 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.

Key words: Fetuin-A, bone mineral density, osteoporosis

1. Introduction

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 (1–3). Nearly half of all women are expected to suffer an osteoporotic fracture in their lifetime (4). Twenty percent of the patients with hip fracture become functionally dependent and require long-term nursing care (5). Additionally, postfracture mortality rate is as high as 20% within the first year (6). 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. Discovery of these pathways effective in osteoporosis may lead to

development of new preventive or therapeutic strategies in the management of these patients (7).

Fetuin-A ($\alpha 2$ -Heremans-Schmid glycoprotein) is a glycoprotein that is expressed not only from the liver, but also from the kidney and choroid plexus. Normal serum concentrations of fetuin-A in healthy adults range between 0.5 and 1.0 g/L. Fetuin-A is highly expressed in the non-collagenous bone matrix during fetal life and affects bone growth via antagonizing the effects of transforming growth factor beta (8–10). Lack of fetuin-A has been shown to result in severe systemic calcification in mice and humans (11,12). Fetuin-A facilitates the removal of hydroxyapatite crystals by increasing the calciprotein particles in the bloodstream and, therefore, inhibiting intravascular calcification (9).

The exact mechanism of fetuin-A on bone mineralization has not been completely elucidated. During their in vitro rat study, Toroian et al. noted that

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fetuin-A stimulated calcification within bone (13). There are limited human studies on fetuin-A to define its exact mechanism (7,14). In this study, we aimed to evaluate the correlation of fetuin-A levels and bone mineral density (BMD) in a group of 50 postmenopausal women.

2. Materials and methods

Twenty-five postmenopausal women with osteoporosis and 25 age- and body mass index (BMI)-matched healthy postmenopausal women were included in the study (Table). All participants provided written informed consent. The study protocol was approved by the local ethics committee of Gülhane Military Medical Academy.

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 BMD measurements were made using dual-energy X-ray absorptiometry (DXA; QDR-4500, Hologic, Bedford, MA, USA) according to World Health Organization diagnostic criteria (15).

Fetuin-A was measured in duplicate using an ELISA kit (BioVendor Laboratory Medicine GmbH, Heidelberg, Germany) following the instructions of the manufacturer. Coefficients of intraassay and interassay 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 $P < 0.05$.

3. Results

Patient characteristics are presented in the Table. 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 (0.82 ± 0.14 mg/L) than in the control group (0.93 ± 0.12 mg/L) ($P = 0.009$). Although there was a mild to moderate positive correlation between fetuin-A levels and lumbar ($r = 0.381$, $P = 0.06$) and femoral ($r = 0.143$, $P = 0.50$) 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. Additionally, correlation coefficients between fetuin-A and lumbar and femoral BMD in the osteoporotic group were $r = 0.381$, $P = 0.06$ and $r = 0.143$, $P = 0.50$, respectively.

4. Discussion

Recent clinical studies have shown that fetuin-A plays a role in the regulation of bone homeostasis and stimulates bone mineralization (10,16,17). However, the exact mechanism of action and its effects are still uncertain. There are limited studies about the relationship between fetuin-A and osteoporosis BMD levels (7,14). Our hypothesis in

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

Parameters	Control group (n = 25)	Osteoporosis group (n = 25)	P-value
Age (years)	62.48 ± 7.44	65.88 ± 7.26	0.11
BMI (kg/m ²)	28.62 ± 3.00	27.34 ± 2.76	0.13
Serum total Ca (mg/dL)	9.60 ± 0.50	9.59 ± 0.44	0.95
Lumbar BMD (DXA)	1.01 ± 0.13	0.72 ± 0.06	<0.001
F. neck BMD (DXA)	0.82 ± 0.09	0.65 ± 0.07	<0.001
F. total BMD (DXA)	0.92 ± 0.13	0.75 ± 0.14	<0.001
Fetuin-A (ng/mL)	0.93 ± 0.12	0.83 ± 0.14	0.009

All data are reported as mean ± SD.

Ca: Calcium; F: femoral; BMI: body mass index; BMD: bone mineral density.

this study was that elderly osteoporotic women with lower BMD results will show lower fetuin-A levels.

In 2002, Szweras et al. (18) 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. Cortical thickness, trabecular bone remodeling, number of osteoblasts, and bone formation were also found to be increased in the same study. 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 (17) 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. Fetuin-A has also been reported to correlate with bone turnover markers (16).

The first study in the literature that analyzed the association between fetuin-A and BMD was done by Ix

et al. (7). They analyzed the serum fetuin-A levels of 580 people in a group of 3075 well-functioning black and white persons (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 but not in men. In another clinical study, fetuin-A levels were found to be positively correlated with lumbar, but not femoral, BMD values (14). According to our results, osteoporotic women had significantly lower fetuin-A levels than normal control subjects and, similar to the previously mentioned study, fetuin-A levels correlated more with lumbar BMD values than femoral values. Although we determined a statistically significant difference of fetuin-A level between osteoporotic and healthy people, we could not show dose-response association by correlations.

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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