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Association Between the Serum Levels of Zinc, Copper and Lipid Profile With Osteoporosis in Iranian Postmenopausal Women

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Background: Trace elements and lipids have an important role in the development of osteoporosis that is a major health problem of postmenopausal women.

Objectives: The purpose of this study was to compare the serum levels of zinc (Zn), copper (Cu) and lipid profile between the postmenopausal women suffering from osteoporosis and the healthy controls. Furthermore, we aimed to determine whether there is an association between the parameters mentioned above and the bone mineral density (BMD).

Patients and Methods: The study was conducted on 116 postmenopausal women; 58 osteoporosis (age 60.6 ± 3.9 years) and 58 control group (age 55.4 ± 1.7 years). The serum levels of Zn and Cu were measured by atomic absorption spectrophotometry and BMD was analyzed by DEXA scan.

Results: The serum levels of Zn and Cu were similar in the both groups ($P > 0.05$). Serum levels of low density lipoprotein (LDL) and total cholesterol (TC) in osteoporosis group was statistically significant when compared to the controls ($P < 0.05$). Correlation analysis showed that there was significant association between body mass index (BMI) and BMD values ($P < 0.05$). There was no correlation between serum Zn, Cu levels with lipid profile ($P > 0.05$). However, we found a negative significant correlation between BMD with LDL ($r = -0.31$, $P = 0.001$) and total cholesterol levels ($r = -0.26$, $P = 0.006$).

Conclusions: This study suggested that dyslipidemia might be an independent risk factor of osteoporosis in Iranian postmenopausal women. Moreover, the trace elements did not directly and correlatively influence BMD.

*Keywords:*Osteoporosis; Postmenopause; Bone Density; Lipids; Zinc; Copper

1. Background

Osteoporosis is the most common metabolic bone disease and a major cause that leads to increase fragility of the bone tissue (1, 2). The disease is more common in women than men because they have a smaller bone mass, and during post menopause in women, they produce less sex steroid hormones, which decreases the body's ability to retain calcium in the bones (2). Evidence indicates that osteoporosis affects up to 50 percent of Iranian men and women over 50 years. Osteoporosis is characterized by reduced bone mineral density (BMD) and loss of bone microstructure (3, 4). The best way to measure BMD is using dual energy X-ray absorptiometry (DXA) (4). There are various factors such as: genetic factors, race, age, smoking, alcohol consumption, exercise and nutrition that play roles in the incidence of osteoporosis (5). The risk of nutritional disturbances, particularly trace element deficiency is high during menopause (6). It has been known that Zn and Cu are essential cofactors for enzymes involved in bone metabolism (6, 7). Clinical studies reported that Zn deficiency is associated with retarded growth, alopecia, congenital skeletal disorders and dermal lesions (8-10). Similarly, the evidences from human and animal studies showed that a lock of Cu lead to unsuitable bone formation and bone fracture (11, 12). In the past years, studies have also demonstrated that Zn and Cu deficiency can cause an increase in the risk of bone resorption by inhibiting bone growth and subsequently progression of osteoporosis (7, 13). Some investigators have also shown that atherogenic lipid profile might be associated with osteoporosis in postmenopausal women (14-16). The elderly patients with osteoporosis have a higher risk of cardiovascular disease which is important factor of morbidity and mortality (15, 16). Dyslipidemia in menopause is a known feature in women, leading to significant increase in the development of coronary heart disease (CAD) (17). Griffith et al. found that lipid components are accumulate on bones or vessels around bone and promote reduced BMD in rats (18). Several studies

Implication for health policy/practice/research/medical education:
Effects of trace elements and lipid profile on osteoporosis postmenopausal women are the implication of our study.

have been shown that subjects with an atherogenic lipid profile might have lower BMD than those with normal lipid levels (15, 16). However, the previous results are controversial. In addition, results from studies that oxidize LDL (ox-LDL) directly blocks differentiation of osteoblasts have suggested lipid profiles as a risk factor of osteoporosis (19, 20).

2. Objectives

The aim of the present study was to evaluate the status trace elements and lipid profile levels in Iranian postmenopausal women with or without osteoporosis. Furthermore, we considered the association the changes in serum lipid profile, trace elements and BMD in these subjects.

3. Patients and Methods

This cross-sectional study was conducted on 116 postmenopausal women who were referred to the Buali hospital Qazvin, between January 2011 and February 2013. The study was approved by the ethics committee of Qazvin University of Medical Sciences, Qazvin, Iran. Fifty-eight of these women had osteoporosis (osteoporosis group) with a mean age of (60.6 ± 3.9 years) and 58 healthy postmenopausal women (control group) with a mean age of (55.4 ± 1.7 years). The women in all two groups were carefully matched for BMI. None of the participants were on a special diet, none were cigarette smokers, and none were alcohol consumption. Women were excluded from the study if they had self-reported fracture history, familiar dyslipidemia, premature menopause, systemic disease such as: thyroid dysfunction, diabetes mellitus, parathyroid disease, liver disease and renal failure that might affect bone metabolism or trace elements status. None of the subjects had received hormone replacement therapy and anabolic steroids, bisphosphonates, calcitonin, lipid-lowering drugs, calcium vitamin D supplements during the six months preceding the onset of the study. All of the participants were completed a questionnaire included demographic characteristic includes: age, BMI, nutritional status, previous fracture and usage of medicine.

3.1. Bone Mineral Density Measurements

BMD (g/cm^2) was measured in the femur neck and lumbar spine 1-4 (L1-4) by DXA QDR 2000 (Hologic, Bedford, MA, USA). The coefficient of variability values of DXA measurements was 1.0% for lumbar spine vertebra, and 1.2% for femoral neck (21). Subjects with spine or femur neck BMD 2.5 standard deviations (SD) below a reference range (T score ≤ 2.5) were accepted as having postmenopausal osteoporosis (22). The control group (non postmenopausal osteoporosis) was consisting women with a T score ≥ 1.5 on these sites.

3.2. Determination of Serum Parameters

Peripheral fasting blood samples were taken and subjected to centrifuge at 800×g for 5 minutes. The resulting sera were stored at -70°c for later simultaneous measurement. Total cholesterol (TC), HDL (high density lipoprotein) and triglyceride (TG) were determined by standard enzymatic methods using device (selectra XL-VITA lab. Holland) (23). LDL was calculated using the Friedewald equation (24). Serum total calcium (normal range 8.5-10.5 mg/dL) was measured by using a colorimetric assay and serum vitamin D was determined using the Enzyme-Linked Immunosorbent Assay (ELISA) method (Alpco Diagnostics, Windham, United States). Serum Zn and Cu levels were measured by atomic absorption spectrophotometry (Avanta PM; GBC, Australia). For Zn and Cu measurements an air acetylene flame was used at the 213.9 nm wavelength for Zn and 324.8 nm for Cu with deuterium background correction. Commercial Zn and Cu calibrators were used as standards (1 g/L) by serial dilutions and were determined based on a standard curve.

3.3. Statistical Analysis

Values were presented as the mean ± SD, and statistical significant was defined as P values less than 0.05. Statistical significant differences in mean measurements between different parameters were performed using t-test. Correlation analysis between variables was performed by calculating Pearson's correlation coefficients. All analyses were carried out using a Statistical Software Package, SPSS for windows version 11.0 (Chicago, IL, USA).

4. Results

Demographic data and clinical characteristics are shown in Table 1. Women with postmenopausal osteoporosis had significantly higher age ($P < 0.001$) but similar BMI compared to non-osteoporotic controls. The serum Zn and Cu levels and other biochemical findings were similar across each group ($P > 0.05$) (Table 2). Comparison of lipid profile in patients and controls are shown that the TC levels of the osteoporosis group was higher than the control group (216.3 ± 50.3 mg/dl vs. 191.5 ± 33.6 mg/dL, P = 0.002) and also the LDL levels of the osteoporosis group was higher (123 ± 22.5 mg/dL vs. 104.8 ± 11.8 mg/dL, $P < 0.001$). The TG levels were not significant different between the both groups (osteoporosis: 107.5 ± 18.8 mg/dL vs. control: 115.1 ± 43.9 mg/dL, P = 0.225).Similarly the HDL levels were not significant different between the both groups (osteoporosis: 45±6.4 mg/dL vs. control: 46.5 ± 7.3 mg/dL, P = 0.243) (Table 3). Correlation analysis between clinical and laboratory characteristics, lipid profile and BMD are presented in Table 4. We found a positive correlation between BMI and lumbar spine BMD (r = 0.23, P = 0.013), femoral neck BMD (r = 0.24, P = 0.009) and serum Cu levels (r = 0.25, P = 0.007). There was no correlation between Zn, Cu and lipid profile ($P > 0.05$). There was a negative association between TC levels and femoral neck BMD (r = -0.26, P = 0.006), lumbar spine BMD (r = -0.21, P

Table 1. Demographic and Clinical Characteristics in Study Groups (n = 58) [a, b]

	Control	Osteoporosis	P Value
Age, y	55.4 ± 1. 8	60.6 ± 3.9	< 0.001
BMI, kg/m^2	28.6 ± 3.3	27.5 ± 2.7	0.059
Femoral neck BMD (T-Score)	-0.25 ± 0.87	-2.31 ± 0.78	< 0.001
Lumbar spine BMD (T-Score)	-0.48 ± 0.62	-2.81 ± 0.76	< 0.001

[a] Abbreviation: BMD, bone mineral density.
[b] Data are presented in Mean ± SD.

Table 2. Comparison of Serum Trace Element Concentration and Biochemical Parameters in Patients and Controls (n = 58) [a, b]

	Control	Osteoporosis	P Value
Ca, mg/dL	9.6 ± 0.5	9.5 ± 0.6	0.328
Vitamin D, nmol/L	36.8 ± 10.4	37.8 ± 10.1	0.620
Cu, μg/mL	97.8 ± 24.6	93.4 ± 24.4	0.326
Zn, μg/mL	72.7 ± 17.3	70.3 ± 20.5	0.504

[a] Abbreviations: Ca, Calcium; CU, Copper; Zn, Zinc.
[b] Data are presented in Mean ± SD.

Table 3. Comparison of Lipid Profile Serum Parameters in Patients and Controls (n = 58) [a, b]

	Control	Osteoporosis	P Value
TC, mg/dL	115.2 ± 43.9	107.5± 18.8	0.225
CHL, mg/dL	191.5± 33.7	216.4± 50.3	0.002
LDL, mg/dL	104.8± 11.8	123.1± 22.6	< 0.001
HDL, mg/dL	46.6± 7.3	45.1± 6.4	0.243

[a] Abbreviations: CHL, cholesterol; HDL, high density lipoprotein; LDL, low density lipoprotein; TC, total cholesterol.
[b] Data are presented in Mean ± SD.

Table 4. Correlation Analysis Between Serum Elements, Lipid Profile and BMD

	BMI	Femoral Neck BMD	Lumbar Spine BMD	Ca	VitD	CU	Zn	TG	CHL	LDL
Femoral neck BMD	0.231 [a]		-	-	-	-	-	-	-	-
Lumbar spine BMD	0.241 [b]	0.724 [c]	-	-	-	-	-	-	-	-
Ca	-0.040	0.082	0.036	-	-	-	-	-	-	-
VitD	0.045	-0.120	0.000	-0.048	-	-	-	-	-	-
Cu	0.248 [b]	0.081	0.093	0.146	-0.047	-	-	-	-	-
Zn	0.089	0.009	-0.091	0.118	-0.076	0.094		-	-	-
TG	0.129	0.185 a	0.180	0.067	-0.073	0.187[d]	0.023	-	-	-
CHL	-0.0070	-0.255 [b]	-0.216 [a]	0.022	0.139	-0.004	-0.137	0.158	-	-
LDL	-0.052	-0.313 [b]	-0.413 [c]	-0.144	0.134	0.070	-0.098	0.093	0.652 [c]	-
HDL	0.021	0.145	0.145	-0.132	0.032	0.095	0.070	0.032	0.141	0.153

[a] P < 0.05.
[b] P < 0.01.
[c] P < 0.001.
[d] r Pearsons correlation coefficient.

= 0.006). The LDL levels also negatively related to femoral neck BMD (r = -0.31, P = 0.001) and lumbar spine BMD (r = -0.41, P = 0.0001). However no correlation was found between TG, HDL, trace elements and BMD values (P > 0.05).

5. Discussion

The main finding of our study is that the lipid profile is related to BMD. However, no significant difference was found between serum Zn and Cu levels with BMD values of Iranian postmenopausal women. Lipid accumulation in bone may affect the osteoblastic cells and thus can inhibit their adequate bone forming activity (25). Increase in the oxidation of lipids and lipoproteins in bone tissue can lead to increase adipogenesis of marrow stromal cells and also may induce osteoclastic differentiation, subsequently resulting in bone loss (26). Our data show that the TC and LDL levels are inversely correlated with femur neck and lumbar spinal BMD in postmenopausal women. These finding were consistent with previous studies (27-29). However, previous studies on the relationship between TC with BMD showed several inconsistencies. Some studies found no significant correlation between TC and BMD values (30-32) and several studies

have reported a negative association (33, 34). There are also conflicting reports about the relationship between TG and BMD. Cui et al. (34) results have shown that serum TG levels are positively correlated with hip BMD in postmenopausal women group, which was similar to Adami et al. study (35), Whereas, some reports have found no association (30, 36). Our study also did not find relation between TG and BMD. In addition, studies concerning relationship between HDL levels and BMD is contradictory (28, 29, 37, 38). It seems likely that these different outcomes can be explained by several factors including: different study populations, age distributions, different races and various skeletal sites for BMD measurement. Previous studies also have found a correlation between atherosclerosis and osteoporosis (15, 16, 39, 40). Moreover, results have shown that low BMD and atherosclerosis in postmenopausal women were linked by common risk factors such as: oxidized lipids, leptin, osteoprotegrin and osteocalcin (39-41). Increased oxidized lipids can induce inflammatory responses by artery wall cells that promote the atherosclerosis lesion formation, and also inhibit the differentiation and mineralization of bone cells (19). This mechanism may explain our results that serum TC and LDL, as inflammatory risk factors, are inversely related to BMD and can be involved in the occurrence and severity of osteoporosis in postmenopausal women. However, the main mechanism remain unclear the extent of the relationship between BMD and lipids levels. Several previous studies have shown that Zn and Cu with calcium (Ca) were able to reduce spinal bone loss in postmenopausal women (42, 43). In old individuals, the loss of bone accelerates after menopause with decrease production of estrogen (44, 45). In addition, studies have shown that Zn and Cu levels in serum play an important role in the regulation of bone deposition and resorption (7, 46). Gur et al. results demonstrated that Zn and Cu levels were decreased among patients with postmenopausal women than the control (7) and are consistent with results of Steidl et al. (47). In contrast, Reginster et al. founded that there is no significant difference in Zn and Cu levels in osteoporotic postmenopausal women compare to non-osteoporotic controls (48). Similarly, we found no significant difference in Zn and Cu levels in both groups. Probably, these contradictory results indicate that serum trace elements levels did not directly and correlatively influence BMD. Our data found a strong positive correlation between BMI and BMD valves, which are consistent with previous study (49, 50). However, published data on this theme are still infrequent. For the first time, our study was conducted to explore the association between Zn, Cu and lipid profile in the serum of Iranian postmenopausal osteoporotic and non-osteoporotic women. In the present study, show no significant correlation between serum Zn, Cu and lipid levels in both groups. Our results consistent with previous studies (49, 51). Presumably, the measurement of Zn and Cu in serum alone cannot be a useful criterion to assess the relationship between these parameters with lipids and BMD. Seems to better evaluate the relationship, future studies should measure Zn and Cu levels both serum and erythrocyte. The main limitation of this study was no standardization of the intensity of patients' physical activity that may also influence the levels of serum lipids. Further research involving a large number of patients are necessary to explain the role of trace elements and lipids in the pathogenesis of osteoporosis as well as to characterize the relationship between these parameters with osteoporosis.

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Author's Contribution

Study concept and design: Sahmani, Abbasi and Omidian; analysis and interpretation of data: Sahmani and Sirati Sabet; drafting of the manuscript: Sahmani; critical revision of the manuscript for important intellectual content: Abbasi, Sahmani and Omidian; statistical analysis: Javadi.

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