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Serum Ferritin: Is It an Independent Predictor of Reduced Bone Mineral Density among Elderly Women?

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Abstract

Aim: *In vitro* studies have shown that iron promotes osteoclast differentiation and bone-resorbing activity by enhancing mitochondrial biogenesis, whereas it suppresses osteoblastogenesis. In postmenopausal women, serum ferritin increases by 2 - 3 times due to the lack of a major mechanism of iron excretion, while menstrual blood decreases. Based on this observation, it has been hypothesized that in addition to estrogen deficiency, increased iron as a result of menopause could contribute to bone loss in postmenopausal women. So our aim was to investigate the association between serum ferritin levels and bone mineral density (BMD) in elderly women at various skeletal sites. **Methods:** Retrospective analysis of the medical records of 71 postmenopausal women having a mean age of (66 ± 7) years (range 60 - 83 years) was done. The collected data included age of menopause, past medical history, smoking habits, physical activity, and medication use. BMD was measured at the lumbar spine and femur by dual-energy X-ray absorptiometry, and other biochemical markers including, serum ferritin, 25 hydroxyvitamin D3, serum alkaline phosphatase, and parathyroid hormone were assayed. **Results:** We found that serum ferritin levels are significantly related to BMD of the total hip and lumbar vertebrae [with a p value of (0.01) and (<0.001) respectively] and T scores for the total hip, femur neck and lumber vertebrae [with a p value of (0.004), (0.036) and (<0.001) respectively] and their major determinants are age of menopause, menopause duration, weight, BMI and physical activity. **Conclusion:** This study suggests a positive association between serum ferritin levels and BMD in elderly women without hematologic disorders. Further study is warranted to verify the effects of iron on bone metabolism.

Keywords

Bone Mineral Density, Ferritin, Iron, Osteoporosis, Women

1. Introduction

As women age they lose their bone mass more quickly than men. Estrogen deficiency is the main cause of postmenopausal osteoporosis as it is associated with increased bone turnover rate and remodeling imbalance of bone resorption exceeding bone formation [1]. Additionally, serum ferritin is known to increase by 2 - 3 times during this period due to lack of iron excretion while menstrual blood decreases [2] [3] *In vitro* studies revealed that iron promotes osteoclast differentiation and bone-resorbing activity [4], and suppresses osteoblastogenesis [5] [6]. Based on this observation, it has been hypothesized that in addition to estrogen deficiency, increased iron as a result of menopause could contribute to bone loss in postmenopausal women [7]. Moreover, iron-overloaded mice have increased oxidative stress and bone resorption which leads to changes in bone microarchitecture and material properties and thus bone loss [8].

Several studies revealed that patients with hemochromatosis, thalassemia and sickle cell anemia have reduced Bone Mineral Density (BMD) compared to the general population [9]-[13]. Such findings support the possible negative effect of iron overload expressed in serum ferritin on BMD and bone metabolism.

However the influence of increased serum ferritin levels and, more generally, the effect of iron on BMD in elderly people without hematologic disorders is uncertain.

Therefore, in the present study we investigated the association between serum ferritin levels and BMD in elderly women at various skeletal sites.

2. Methods

A retrospective analysis based on medical records of 71 elderly female patients attending the osteoporosis clinic, Ahmadi Hospital, Kuwait, for osteoporosis screening, from December 2014 to June 2015 was done. The mean age of patients was (66 ± 7) years (range 60 - 83 years). The collected data included age of menopause, past medical history, personal and parental history of fracture, smoking habits, physical activity, and medication use.

All subjects within the determined period were included in the study except those who have chronic diseases that may affect serum ferritin level after reviewing investigations. Exclusion criteria involved chronic kidney disease, chronic liver disease, neoplastic disease, pulmonary or extrapulmonarytuberculosis, history of recent infection, chronic inflammatory diseases as rheumatoid arthritis or inflammatory bowel disease, anemia or history of hereditary anemia, low serum iron, current thyroid disease or treatment for it, history of osteoporosis or history of treatment for osteoporosis, and hormonal replacement therapy. Finally, subjects with exceptionally high serum ferritin levels (>300 ug/L) were excluded in order to rule out those who could potentially have hemochromatosis. [14]

Life style pattern regarding physical activity levels was addressed. It was estimated with a recall of hours of physical activity per week. It was divided into 3 categories, inactive or sedentary (no significant physical activity), slight activity (<30 min/day, less than 3 days/week) and active (>30 min/day more than 3 days/week).

Anthropometric measures as weight and height were collected and body mass index (BMI) was calculated for each subject.

Plasma concentrations of 25-hydroxycholecalciferol, alkaline phosphatase (ALP), parathyroid hormone (PTH), calcium (Ca^{2+}), and iron were collected. Serum ferritin was measured using particle enhanced immunoturbidimetric assay. Human ferritin agglutinates with latex particles coated with anti-ferritin antibodies. The precipitate is determined turbidimetrically at 570/800 nm. BMD (g/cm^2) was measured using dual-energy X-ray absorptiometry (DXA; Discovery w (S/N 83889), Hologic, Waltham, MA, USA), it was performed at the lumbar spine (L1-L4), femur neck, and total hip.

Statistical methodology:

Statistical analyses were performed using SPSS 17.0 (SPSS, Chicago, IL, USA). Inferential analyses were done for quantitative variables using independent t test in cases of two independent groups with parametric data. Inferential analyses were done for qualitative data using Chi-square test for independent variables. For all tests, a two-tailed p-value < 0.05 was considered statistically significant. Relevant variables with statistical significance in univariate analysis were selected for multivariate logistic regression to identify independent risk factors.

3. Results

The characteristics of the studied population are shown in Table 1. Regarding serum ferritin levels, it was observed that they are significantly related to BMD and T scores and their major determinants are age of menopause, menopause duration, weight, and BMI. Serum ferritin was found to be elevated in 8 females of our participants, in whom the lowest BMD for the total hip (0.6872 ± 0.12839), and lumbar vertebrae (0.7550 ± 0.04308) was detected with a p value of (0.01) and (<0.001) respectively. They also got the lowest T score for the total hip (−1.8500 ± 0.92273), femur neck (−2.3500 ± 0.84853), and lumbar vertebrae (−2.6375 ± 0.40333) with a p value of (0.004), (0.036) and (<0.001) respectively. Higher serum ferritin levels were found to be strongly related to the early age of menopause (p = 0.025) and long menopausal periods (p = 0.025) (Table 2). Physical activity which is another important determinant of BMD was found to be strongly related to lower ferritin levels and the higher the ferritin levels are the less the physical activity of a participant (p = 0.003) (Table 3). Correlating serum ferritin values with different quantitative variables proved that serum ferritin has a significant positive correlation with duration of menopause (p = 0.019) and a negative correlation with age of menopause (p = 0.006) and hip T score (p = 0.018) (Table 4). Finally linear regression model of independent factors affecting BMD and T score at different measurement sites proved higher serum ferritin to be an independent risk factor for reduced hip and lumbar T score (p = 0.002) while age and vitamin. D levels were independent risk to reduced BMD and T scores at all measurement sites (Table 5).

4. Discussion

Ferritin is the key control of iron amount in the body. It stores and release iron in a

controlled fashion. It acts as a buffer against iron deficiency and as storage in case of iron excess [15]. Though the fundamental biology of serum ferritin remains unclear, it has growing roles in iron delivery, angiogenesis, inflammation, immunity, signaling and cancer [16].

Serum ferritin also appears to associate aging process. Inflammaging; which is a subclinical inflammatory state that associates aging and thought to be a mechanism of it, is associated with increased levels of serum ferritin [17]. High ferritin levels and excess iron storage exerts its hazards that should be looked for. One of these hazards is reduced BMD. It was found that healthy adults who have elevated serum levels of ferritin have increased rates of bone loss [18].

In a study by Chon and colleagues [19] serum ferritin levels were higher in postmenopausal females compared to premenopausal ones and showed a significant correlation with BMD on lumbar spines. This goes in accordance with our study where our female population who had elevated ferritin levels showed a significant reduction in BMD in both hip and lumbar spines. In contrast Heidari *et al.* [20] in their study to determine factors affecting BMD in postmenopausal women found that high serum ferritin levels are associated with reduced risk of osteoporosis in lumbar spine and femur

Table 1. Characteristics of the studied population.

	Minimum	Maximum	Mean	Std. deviation
Age	60.00	83.00	66.4507	7.01588
Menopause	44.00	58.00	51.4507	3.47969
Weight (kg)	51.00	115.00	78.1915	12.59978
Height (cm)	141.00	165.00	152.7465	5.60476
BMI†	18.73	46.78	33.567	5.489
*Serum ferritin (ug/L)	16.02	290.60	95.8976	69.67446
Hip BMD‡	0.01	1.21	0.8427	0.18497
Hip T score	−3.70	2.20	−0.6803	1.25375
Femur neck BMD	0.38	1.05	0.6827	0.13358
Femur neck T score	−4.20	1.80	−1.4911	1.23854
Lumbar vertebrae BMD	0.63	1.31	0.8790	0.15798
Lumbar vertebrae T score	−3.80	2.40	−1.5048	1.46546
*25-hydroxycholecalciferol (ng/ml)	4.00	64.70	20.3177	12.26267
*PTH§ (pmol/L)	2.98	28.70	6.2210	3.27081
*Serum ALP¶ (U/L)	41.00	202.00	79.2410	24.42734
*Serum iron (umol/L)	1.40	27.80	13.3792	4.63008
*Serum Ca^{2+}†† (mmol/L)	2.08	18.89	2.5656	1.96858

†BMI = Body Mass Index; ‡BMD = Bone Mineral Density; §PTH = Parathyroid Hormone; ¶ALP = Alkaline Phosphatase; ††Ca^{2+} = Calcium. *Reference values: Serum Ferritin (Ref. 15 - 150 ug/L), 25-hydroxycholecalciferol (Ref. 30 - 75 ng/ml), PTH (Ref. 0.5 - 6.89 pmol/L), Serum ALP (Ref. 35 - 104 U/L), Serum Iron (Ref. 6 - 26 umol/L), Serum Ca (Ref. 2.2 to 2.55 mmol/L).

Table 2. Relationship between serum ferritin and different studied variables.

	Serum ferritin*	N	Mean	Std. deviation	p
Age	High	8	69.6250	8.07001	0.18
	Normal	63	66.0476	6.83782	
Menopause	High	8	48.8750	3.94380	0.025
	Normal	63	51.7778	3.30905	
Menopause duration	High	8	20.7500	8.03119	0.025
	Normal	63	14.2698	7.49022	
Weight	High	8	68.2125	9.00261	0.02
	Normal	63	79.4587	12.47428	
Height	High	8	152.6250	3.99777	0.95
	Normal	63	152.7619	5.80174	
BMI†	High	8	29.3775	4.67623	0.021
	Normal	63	34.0990	5.38476	
Hip BMD‡	High	8	0.6872	0.12839	0.01
	Normal	63	0.8624	0.18236	
Hip T score	High	8	−1.8500	0.92273	0.004
	Normal	63	−0.5317	1.21640	
Femur Neck BMD	High	8	0.5981	0.10300	0.06
	Normal	63	0.6934	0.13382	
Femur Neck T score	High	8	−2.3500	0.84853	0.036
	Normal	63	−1.3821	1.24232	
Lumbar vertebrae BMD	High	8	0.7550	0.04308	0.00
	Normal	63	0.8947	0.16042	
Lumbar vertebrae T score	High	8	−2.6375	0.40333	0.000
	Normal	63	−1.3610	1.48988	
25-hydroxychole-calciferol	High	8	15.7125	8.62054	0.26
	Normal	63	20.9025	12.58180	
PTH§	High	8	6.1513	1.82686	0.95
	Normal	63	6.2298	3.42069	
Serum ALP¶	High	8	79.1250	25.92537	0.99
	Normal	63	79.2557	24.44997	
Serum Ca^{2+}††	High	8	2.2962	0.07836	0.7
	Normal	63	2.5998	2.08904	

†BMI = Body Mass Index; ‡BMD = Bone Mineral Density; §PTH = Parathyroid Hormone; ¶ALP = Alkaline Phosphatase; ††Ca^{2+} = Calcium. *Reference values: Serum Ferritin (Ref. low < 15, high >150 ng/ml).

Table 3. Relationship between serum ferritin and physical activity and presence of fractures.

		N	Mean	SD	P
	Physical activity				
Ferritin	Inactive	37	121.5954	82.37090	0.003
	Slight activity	30	70.6853	37.74850	
	Active	4	47.2850	10.32150	
	Fracture				
Ferritin	Yes	8	122.3725	98.55729	0.26
	No	63	92.5357	65.43933	

†SD = Standard Deviation

Table 4. Correlation between serum ferritin and different studied variables.

variable	R	p
Age	0.146	0.225
Age of menopause	−0.325	0.006
Duration of menopause	0.277	0.019
Weight	−0.212	0.076
Height	−0.014	0.907
BMI†	−0.196	0.101
Hip BMD‡	−0.192	0.108
Hip T score	−0.281	0.018
Femur neck BMD	−0.217	0.070
Femur neck T score	−0.234	0.050
Lumbar vertebrae BMD	−0.244	0.040
Lumbar vertebrae T score	−0.227	0.057
25-hydroxychole-calciferol	−0.156	0.193
ALP§	−0.052	0.665
Serum Ca^{2+}¶	−0.133	0.268
Serum iron	0.237	0.046

†BMI = Body Mass Index; ‡BMD = Bone Mineral Density; §ALP = Alkaline Phosphatase; ¶Ca^{2+} = Calcium.

neck. Our selection criteria excluded most of females who has causes for increased serum ferritin levels which resulted in the small sample size and may be responsible for the inability to detect ferritin as an independent variable affecting BMD.

Regarding ferritin levels and other studied variables, we observed that high serum ferritin was significantly related to early menopause and long menopausal duration which is supported by Kim *et al.* [21] who concluded that from premenopause to postmenopause, women experience an increase in their iron stores. Elevated ferritin levels were observed to be higher in participants with the lowest weight (68.21 ± 9) and BMI

Table 5. Linear regression model for independent factors affecting BMD and T score.

Factor	$\beta^{\dagger}$	SE[‡]	P	95% CI[§]
Hip BMD[¶]				
Age	0.011	0.001	<0.001	0.009 – 0.012
25-hydroxychole-calciferol	0.006	0.002	<0.001	0.002 – 0.010
Hip T score				
Age	−0.010	0.005	0.063	−0.020 – 0.001
25-hydroxychole-calciferol	0.021	0.011	0.072	−0.002 – 0.043
Serum ferritin	−0.004	0.002	0.035	−0.009 – 0.000
Femur neck BMD				
Age	0.009	0.001	<0.001	0.008 – 0.010
25-hydroxychole-calciferol	0.004	0.001	0.004	0.001 – 0.007
Femur neck T score				
Age	−0.029	0.004	<0.001	−0.037 – 0.021
25-hydroxychole-calciferol	0.022	0.011	0.056	−0.001 – 0.044
Lumbar BMD				
Age	0.011	0.001	<0.001	0.010 – 0.012
Serum Vit-D	0.006	0.002	<0.001	0.003 – 0.009
Lumbar T score				
Age	−0.024	0.006	<0.001	−0.037 – 0.012
Serum Vit-D	0.027	0.013	0.050	0.000 – 0.053
Serum ferritin	−0.004	0.002	0.093	−0.009 – 0.001

[†]β: Regression coefficient; [‡]SE: Standard error; [§]CI: Confidence interval; [¶]BMD = Body Mass Index.

(29.38 ± 4.68). The relationship between serum ferritin and anthropometric measures was not studied thoroughly, yet it worth mentioning that, the prevalence of obesity in Kuwaiti studies with a nationally representative sample ranged from 24% to 48%, and in adults >50 years was >52%. Rates were significantly higher in women than those in men [22]. Such facts may bias the relationship between serum ferritin and anthropometric measures in this study.

Higher serum ferritin levels were observed to associate poor physical activity. This agrees with Furqan *et al.* [23] and Liu *et al.* [24] who reported that physical activities reduce serum ferritin concentration. Finally serum ferritin was proved by linear regression model to be an independent risk for reduced T score at both hip and lumbar vertebrae. This relation was not evident for BMD in the regression model. It could be attributed to the small sample size of the studied population. More research is needed to address this relation.

5. Conclusion

Serum ferritin plays important roles in different organ function and its related pathology. This study tried to highlight its effect on BMD. Our study suggests a positive asso-

ciation between serum ferritin levels and BMD in elderly women without hematologic disorders. Further study is warranted to verify the effects of iron on bone metabolism.

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