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Original Article

Detection of Some Biochemical Markers in Iraqi Osteoporosis Patients

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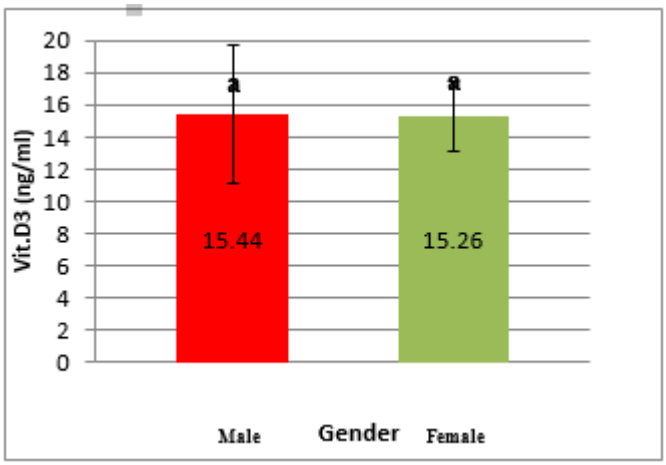
ABSTRACT

Osteoporosis is not limited to women after menopause. It can also afflict men as well and is a hot issue. Men get osteoporotic fractures around ten years later in life than women, although men's life expectancy is growing at a quicker rate than that of women. Consequently, males are living longer than women, and when they do, the repercussions are more severe than those experienced by their female counterparts**.** The aim of our study was to determine the level of CX3CL1, Bone sialoprotein, Gelsolin, Cathepcin K, Vitamin D, Calcium, Phosphorous and Alkaline phosphatase in 100 patients (20 men and 80 women) and 50 as the control group (19 men and 31 women). The results showed that the serum level of CX3CL1, Gelsolin and Cathepcin K increased in female osteoporosis patients and no significant increase was observed in male osteoporosis patients compared with the control group. The results also showed a rise in serum levels of Bone sialoprotein and Alkaline phosphatase in male and female osteoporosis compared with the control group. Further, no significant difference in serum level (vitamin D, Calcium and Phsphorouse) in osteoporosis patientt, both male and female, compared with the control group. In conclusion, the Cathepcin K, Gelsolin and Bone sialoprotein play an essential role in bone metabolism and increase the level in osteoporosis patients.

GRAPHICAL ABSTRACT



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Introduction

In osteoporosis, bone strength, in terms of density and quality, deteriorates over time, and an increased risk of fractures could spontaneously occur due to typical injuries. Osteoporosis is a progressive skeletal disorder in which the bone strength, considering quality and density, is compromised, putting the individual at increased risk of fractures [1]. In addition to low boen mineral density (BMD), it is accompanied by the loss of biomechanical and structural properties, which are essential for bone homeostasis maintenance [1]. Osteoporosis is a common syndrome and causes significant health problems worldwide [2]. Broken bones caused by osteoporosis are related to an increased death risk [3]. More importantly, fractures are leading to disability, low quality of life, and decreased physical functions [4]. In the year 2000, it was anticipated that around 9 million new osteoporotic fractures cases occurred, with a total of 56 million prevalent cases [5]. Between 2001 and 2011, the prevalence of osteoporosis in Taiwan grew by around 7.6 %, according to World Health Organization (WHO). BMD is a powerful clinical diagnostic measure for osteoporosis and a better test for predicting osteoporotic fractures [5]. The condition known as osteoporosis is related to many hereditary and nongenetic causes, some of which include age [6], sex [2], menopausal status [7], educational level [8], coffee drinking [6], smoking, not exercising, alcohol consumption, diet [1], and body mass index (BMI) [9]. The purpose of this study was accordingly to find new biomarkers of Iraqi patients with osteoporosis and its association with physiological status that help in early diagnosis of cases of osteoporosis to prevent development of complication.

Materials and Methods

This study was carried out with patients who attended the Bone Density unit in a hospital in Marjan Medical City in Babylon Governorate. This study included 150 females and males. They were divided into two groups; the first group comprised 100 patients (80 females and 20 males) with OP, and the second group included 50 relatively healthy (females and males). The age of both groups was matched and ranged between 20-80 years. Venous blood was taken from patients using disposable syringes to determine their haemoglobin levels. Each patient provided five millilitres of blood, of which two millilitres were deposited into EDTA tubes, and the other three millilitres were pushed gently into disposable gel-containing tubes. Similarly, blood in the EDTA tubes was stored at -20 degrees Celsius in order to be used later in the genetic portion of the study. In contrast, blood in the gel-containing tubes made clotting at room temperature for 15 minutes before being separated by centrifuge at 3000 rpm for 10-15 minutes. Sera were obtained and stored at -20 degrees Celsius.

Biomarkers analysis

In serum, the quantitative detection of CX3CL1, gelsolin, cathepcin K, and bone sialoprotein was carried out (BTL company, China), which relied on the technique of ELISA, and vitamin D was examined by AccuBind company, USA, which also relied on the ELISA. According to the industrial business BIOLABO, the enzymes calcium and alkaline phosphatase were measured in serum.

Statistical analysis

Analysis of study data was carried out by (SPSS) software (V20). The results were expressed as mean ± S.E.

Results and Discussion

What follows are the levels of biochemical parameters in osteoporosis patients and healthy groups according to gender (mean ± S.E.).

Table 1 demonstrates the levels of biochemical parameters showing that in osteoporosis, patients markedly rise in level biochemical parameters measured in this study, where the significant increase ($p \leq 0.05$) in CX3CL1 in females, and a significant increase in bone sialoprotein concentration for both genders can be observed when compared with healthy control group and there was insignificant increase ($p \leq 0.05$) in gelsolin and cathepsin K level in female osteoporosis and no significant difference in male. Our results did not show a marked difference in vitamin D level, calcium and phosphorous in both

genders, while there was a significant increase at ($p \leq 0.05$) in alkaline phosphatase in both genders. Vijayakumar and Bu sselberg (2016) [10] found that gender is a risk factor for osteoporosis. Women are at higher risk of developing osteoporosis than men are (Ivanova *et al*., 2015). In Taiwan (2006-2008), data of NNHS found the occurrence of osteoporosis in males and females by 23.9 % and 38.3 %, respectively [11]. Menopause, according to Vijayakumar and Bu sselberg (2016), is a key contributing factor to differences in osteoporosis prevalence between men and women. Menopausal women are oestrogen deficient and thus are more prone than premenopausal women to bone loss, fractures, and osteoporosis than males. According to the findings of this research, women are more adversely impacted than men, as shown in Table 1.

Women are more susceptible to osteoporosis than males, mostly due to the consequences of menopause. CX3CL1 (fractalkine) is a member of the CX3C family identified so far [12]. CX3CL1/FKN is unique among chemokines in that it occurs as both a soluble chemoattractant and transmembrane protein, which is produced by the natural killer cells, T. cell, and monocytes in contrast to all other chemokines [13]. So far, just a few studies have looked at the possibility of CX3CL1/FKN being involved in bone remodelling processes, although the results are promising. Following these findings, Han *et al*., hypothesized that a critical role in bone resorption and osteoclast recruitment is played by the CX3CL1–CX3CR1 axis [14]. As previously mentioned, disruption of the CX3CL1-CX3CR1 axis by using an antibody against the protein CX3CL1 has been shown to suppress osteoblast-guided development of osteoclasts in vitro [15].

Table 1: levels some of biochemical parameters in osteoporosis patients and healthy according to gender

Groups / Parameters	Gender	Male	Female
		Mean±S.E	
CX3CL1 (ng/mL)	Patient	10.16±1.3	11.53±2.6
	Healthy	9.76±1.5	3.46±0.6
p-value		0.121	0.02*
Bone sialoprotein (ng/mL)	Patient	47.53±6.7	45.36±12.4
	Healthy	31.45±5.1	19.32±9.8
p-value		0.005*	0.008*
Gelsolin (ng/MLS)	Patient	50.06±10.2	75.61±12.5
	Healthy	48.13±8.1	42.46±10.5
p-value		0.09	0.02*
Cathepsin K (ng/mL)	Patient	3.07±0.2	4.77±0.6
	Healthy	2.99±0.1	1.25±0.8
p-value		0.410	0.04*
Vit. D3 (ng/mL)	Patient	18.44±4.3	15.26±2.2
	Healthy	20.48±4.4	20.66±3.4
p-value		0.215	0.06
Ca (mg/dL)	Patient	8.46±1.3	8.22±0.8
	Healthy	8.43±1.4	9.38±2.2
p-value		0.687	0.311
PO_4 (mg/dL)	Patient	4.74±0.8	4.70±0.9
	Healthy	3.77±0.7	4.18±1.1
p-value		0.567	0.244
ALP (Iu/L)	Patient	93.07±15.2	114.5±17.8
	Healthy	79.00±11.7	69.85±12.1
p-value		0.06*	0.002*

*significant difference at ($p \leq 0.05$).

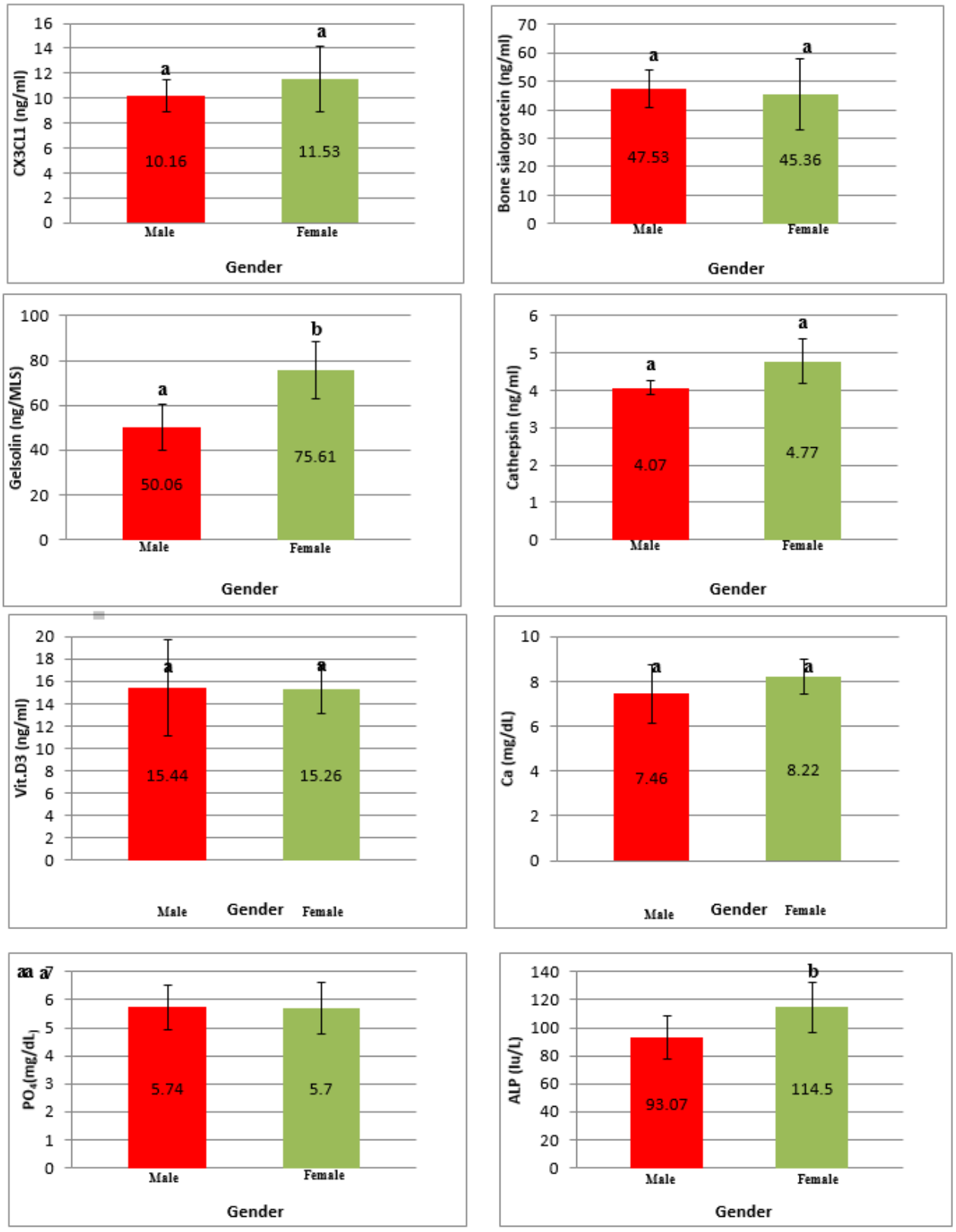

Figure 1: Level of biochemical parameters in osteoporosis patients according to gender

Also, it has been discovered that the CX3CR1–CX3CL1 axis is critical in preserving osteoclastic precursor cells. This is the first time that this issue has been reported [16]. Our findings reveal a significant increase in CXC3L1 level in female osteoporosis patients compared with the control group, similar to the results of Yi-Ding Chen *et al.*,2016 [17], who found that FKN level was rose

after menopause in osteoporotic patients when compared with postmenopausal non-osteoporotic females after the menopause period. Higher FKN levels in osteoporosis cases were shown to be associated with lower bone mineral density (BMD), high bone turnover indicators, and increased inflammatory markers. The CX3CL1/CX3CR1 axis is important in osteoclast development and in binding osteoclasts with immune cells to the bone tissue, among other things. It contributes to the development of infection and the generation of various inflammatory cytokines (TNF-a, IL-1a, and IL-6), which are detrimental to bone health. Increasing levels of CX3CL1 are related to increased levels of bone turnover and inflammatory markers in human blood serum (IL-1, IL-6, NTx, and TRACP-5b), as well as increased levels of CX3CL1 in serum [18]. Bone sialoprotein is a new metric of bone metabolism. Bone sialoprotein is generated by osteoblasts and is a unique parameter of bone metabolism [19].

However, it is unknown that bone sialoprotein levels are indicative of bone production or bone resorption, as is the case in humans, even though it has been hypothesized that sialoprotein levels reflect mechanisms that are more closely associated with bone resorption [20]. When comparing male and female osteoporosis individuals to the control group, our findings revealed greater significant differences. Shaarwy and Hasan (2001) [21] demonstrated that serum BSP levels were significantly higher in postmenopausal osteoporosis patients compared with healthy perimenopausal control group. As a result of different antiresorptive treatments, serum BSP decreased, and this decrease coincided with the decrease in bone resorption markers. The circulating BSP reveals a good marker of bone resorption and is a useful tool for monitoring antiresorptive therapy in postmenopausal osteoporosis. Pietschmann *et al*. (2001) [22] discovered that the amount of BSP in males with idiopathic osteoporosis decreased dramatically. In men with osteoporosis, sialoprotein is expressed during the first stages of bone deposition, and inferred with parts of bone, but there seems to be a malfunction at discrete stages of osteoblastic in the males with osteoporosis.

It is also necessary to examine the likelihood of a distinct metabolic of BSP in men and females as participants in this study. GSN is critical in the severing and capping of actin filaments, which is essential in the structure of the actin cytoskeleton [23]. It was required for a variety of tasks, including podosome assembly, rapid cell migration, and signalling pathways, among others [24]. According to Aciksaka and colleagues (2001) [25], podosomes are cytoskeletal structures in which actin polymerization and depolymerization occur at a fast rate. When it comes to osteoclasts, enhanced dendritic cells, macrophage, and endothelial cells, podosomes are crucial for adhesion, physical sensing, and matrix remodelling, among other things [26].

Along with bone matrix degradation, osteoclasts may also degrade extracellular matrix, and specific mineral content, both of which are required for bone healing and the Ca balance maintenance [27]. It is necessary to have stable cytoskeletal and adhesion and motility activities in podosomes in order for osteoclasts to be activated during the bone turnover phase [28]. The inability to generate podosomes, unusual actin cytoskeletal architecture, and lower fees of osteoclast motility, as well as blocked podosome-related signal transduction, have been demonstrated in previous research, and it was shown to result in reduced bone resorption, increased bone strength, and increased bone mass [29].

There was no statistical difference in GSN concentration between males and females in this study. On the other hand, significant differences in GSN were seen between persons with high and low BMD, with the latter being especially true in female participants. Compared with the healthy group, female osteoporosis patients had a considerable rise in GSN concentration, according to the present research results. This result is consistent with that of Wen-Yu Wang (2018) [30], who discovered that plasma GSN levels were higher in extremely low BMD subjects than in high BMD in Chinese women after menopause and that there were significant differences in plasma GSN levels between high and low BMD in both genders.

The results suggest that the function of the GSN is likely regulated by elements that are distinct to each gender, such as sex hormones. The findings of a previous study has revealed that GSN might function as an important regulator in the regulation of androgen-mediated impacts on osteoclastogenesis and bone resorption [28]. It is currently unclear if GSN interacts with oestrogen to impact bone metabolism and bone mineral density (BMD), which can be further researched in the future.

In bone development, osteoclasts create and release cathepsin K, which is one of the essential catalytic enzymes. Cathepsin K is created by osteoclasts and has an important role in bone growth. Due to its well-established involvement in bone type I collagen degradation, it has gained attention as a possible therapeutic target in osteoporosis. [See full bio for more information] [31]. When synthesized as a procathepsin K, procathepsin K is then activated in the lysosomes by an enzyme-dependent process that includes hydrolytic breakage at low pH before releasing into the ducts [32]. This suggests that a portion of the cathepsin K is released into the blood and may function as a specific marker of osteoclast activity. Although many assays have been devised, it is not apparent if they are intended to detect the proenzyme. When comparing the osteoporosis patients to the healthy group, the results of the present investigation demonstrated a statistically significant rise in cathepcin K level with the disease. This discovery, which is similar to the results of Meier (2006) [33], indicated that cathepsin K level is elevated in individuals with osteoporosis and Paget's disease and patients with Paget's disease.

After completing this trial, the researchers discovered that there was no significant difference in Ca concentration between individuals with osteoporosis and the control group. There was no remarkable discrepancy in Ca concentration between osteoporotic women and the control. Our results also agreed with those of Najlaa *et al*. (2018) [35], who reported no statistically significant difference in calcium levels between osteoporotic males and females and the control group. As previously reported by Selvapandian *et al*. (2018) [36], serum phosphorus showed no statistically significant difference between women with osteoporosis and the control group. This could be because serum calcium and phosphorus phosphorus levels were regulated, and homeostasis was maintained regardless of the amount of calcium and phosphorus stored in the bone [37]. The results of this inquiry also concur with those of Muhammad *et al*. (2018) [34], who discovered that there was no statistically significant difference in blood phosphorus levels between osteoporotic men and women and the control group. This is in line with the results by Ramesh *et al*. (2013) [38], who found that serum alkaline phosphatase was greater in osteoporotic groups than in the control group. According to Muhammad *et al*. (2018), ALP can be excreted from osteoblasts, which are high in ALP, and it can also be found in the plasma membrane of cells in the liver, small bowel, and fetal membranes, all of which may contribute to the total quantity of alkaline phosphatase. This is in agreement with Muhammad *et al*.'s (2018) research, reporting a statistically significant difference in ALP levels between osteoporotic men and women and the control group. According to the results of this study, there was a variation in vitamin D concentration between the osteoporosis cases. In addition to gender, environmental conditions, nutrition, stressors and disorders of calcium and enzymes and other diseases can be a risk factor in exacerbating musculoskeletal diseases, especially osteoporosis [39-41].

Conclusion

In sum, our findings are in tanedem with those of Ramesh *et al*. (2013), reporting that decline of outdoor activities among women, as well as reduced exposure to sunshine, along with our culture of dressing in long dresses, would limit the production of vitamin D in the skin and its conversion to the active form, which is the most important form of vitamin D storage in the body. The absorption of calcium and phosphorus is dependent on vitamin D levels, and when these levels are inadequate, it produces a rise in parathyroid hormone, resulting in calcium and phosphorus shortage.

The percentage of the distribution of disease in women higher than men in Iraq.
Indicators cannot be adopted (Vit.D, Ca and po4) as biological markers for osteoporosis disease because these indicators depending on the age and gender.
Obesity or increase in body mass index BMI have large association with osteoporosis disease.
Vital signs (CX3CL, bone sialoprotein, gelsolin and cathepcin K) consider positive indicators for osteoporosis disease.

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Authors' contributions

All authors contributed to data analysis, drafting, and revising of the paper and agreed to be responsible for all the aspects of this work.

Conflict of Interest

We have no conflicts of interest to disclose.

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