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Role of Some Pro-Inflammatory and Anti-Inflammatory cytokines in Postmenopausal of Iraqi Women

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Keywords:Osteoporosis; Postmenopausal women; Interleukin-6; Interleukin-1β; Interleukin-10;Bone mineral density.

Abstract: Postmenopausal osteoporosis (PMO) is linked to estrogen deficiency and immune dysregulation. The balance between pro- and anti-inflammatory cytokines may be critical in bone loss pathogenesis. **Objective:** To evaluate serum IL(6,-β, and 10) levels and their ratios in elderly Iraqi postmenopausal women with osteoporosis compared to controls. **Methods:** A cross-sectional case-control study enrolled 160 postmenopausal women (80 osteoporotic, 80 controls) at Baghdad Teaching Hospital. Serum IL(6,-β, and 10) were measured by ELISA. Bone mineral density (BMD) was assessed by DXA. Correlations between cytokines and BMD were analyzed. **Results:** Osteoporotic women had significantly higher IL-6 (9.80 ± 3.29 vs. 4.18 ± 1.55 pg/mL; $p < 0.001$) and IL-1β (6.93 ± 1.95 vs. 2.46 ± 1.20 pg/mL; $p < 0.001$), and lower IL-10 (3.14 ± 0.99 vs. 5.69 ± 1.36 pg/mL; $p < 0.001$). Cytokine ratios were markedly elevated in osteoporosis: IL-6/IL-10 (2.99 ± 0.90 vs. 0.78 ± 0.40), IL-1β/IL-10 (2.42 ± 0.79 vs. 0.48 ± 0.28), and (IL-6+IL-1β)/IL-10 (5.16 ± 1.54 vs. 1.32 ± 0.49; $p < 0.001$ for all). The IL-6/IL-10 ratio showed the highest diagnostic accuracy (AUC = 0.934). Vitamin D and estradiol were significantly lower in the osteoporosis group. **Conclusion:** Elderly Iraqi postmenopausal women with osteoporosis exhibit a pro-inflammatory immune profile with elevated IL-6 and IL-1β, reduced IL-10, and increased pro-inflammatory/anti-inflammatory ratios. The IL-6/IL-10 ratio may serve as practical biomarker for osteoporosis risk stratification.

Introduction

Postmenopausal osteoporosis (PMO) is a silent, progressi skeletal disorder characterized by microarchitectu deterioration, decreased bone mass, and increas susceptibility to fragility fractures (Kanis *etal.,*199 Approximately 21.2% of women over 50 years are affect worldwide (Cooper *etal.,* 1992). In Iraq, the prevalence osteoporosis in postmenopausal women reaches 26.1%, w osteopenia affecting 16.1%(Al-Hafidh *etal.,* 2025). Fractu consequences, particularly at the hip and spine, a associated with significant morbidity and mortality (John & Kanis, 2006).

Pathogenesis of PMO is fundamentally linked to estrogen deficiency following menopause (Riggs *etal.,*2002). Estrogen protects bone through direct inhibition of osteoclastogenesis and indirect regulation of cytokine production (Manolagas, 2000). A critical mechanism underlying accelerated bone loss is the estrogen withdrawal-induced increase in pro-inflammatory cytokines, which promote osteoclast formation and bone resorption (Pacifici, 1996). This has led to recognition that PMO possesses features of an inflammatory process, wherein the imbalance between pro- and anti-inflammatory mediators contributes to skeletal deterioration (Mundy, 2007).

The major predictor of bone loss during the first decade following menopause is IL-6, with each log-unit increase associated with a 1.34% annual decrease in total hip bone mineral density (Scheidt-Nave *etal.,* 2001).IL-6 secretion from osteoblast-like cells, enhances by IL-1β, and estrogen inhibits this process, suggesting a coordinated pro-inflammatory cascade

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(Koka *etal.,* 1998).

The IL-10 is a pleiotropic anti-inflammatory interleukin that suppresses pro-inflammatory interleukin production and inhibits osteoclastogenesis (Mosser & Zhang, 2008). Regulatory B cells exert anti-osteoclastogenic effects through IL-10 production, and serum IL-10 levels are significantly reduced in osteoporotic models (Sapra *etal.,* 2021). Genetic studies have supported the protective role of IL-10, with promoter polymorphisms associated with reduced BMD and increased osteoporosis susceptibility (Chen *etal.,* 2005). These findings position IL-10 as a critical counter-regulatory cytokine whose insufficiency may contribute to the pro-inflammatory milieu favoring bone resorption (Zhang *etal.,* 2015).

The balance between pro-inflammatory cytokines (IL-6 and IL-1β) and anti-inflammatory cytokines (IL-10) may be a critical determinant of bone loss after menopause (Brincat *etal.,* 2014). While individual cytokines have been studied in various populations, the combined evaluation of this cytokine triad in elderly Iraqi postmenopausal women remains unexplored (Al-Daghri *etal.,* 2017). Recent research by Tektook *etal.,* (2026) investigating osteoporosis and tooth loss in postmenopausal women demonstrated a strong correlation between osteoporosis and severe tooth loss, highlighting the importance of integrated medical and dental care.

Patients and Methods:

Study Design: A cross-sectional case study was conducted over 12 months at the Osteoporosis Clinic and DXA Unit of Baghdad Teaching Hospital, Baghdad, Iraq. The study was approved by the Ethics Committee of Baghdad Teaching Hospital.

Study Population

Inclusion Criteria: Postmenopausal women (≥ 12 months since menopause), Age ≥ 60 years

Exclusion Criteria: Metabolic bone diseases other than osteoporosis; Autoimmune or inflammatory diseases; Malignancy; Chronic kidney or liver disease; Use of medications affecting bone metabolism (corticosteroids, bisphosphonates, HRT) within 6 months; Recent infection or fracture within 6 months and smoking or alcohol consumption

Sample Size: A total of 160 postmenopausal women were divided into two groups: Osteoporosis group (No.=80) and control group (No.=80).

Data Collection

clinical and demographic data collected by structured questionnaire (age;age at menopause; parity; medical history; medication use)

Anthropometric measurements: height, weight, BMI

Laboratory Investigations

Cytokine Measurement: by ELISA kits measured the levels of interleukins in sera patients (6, 1β, and 10) according to the manufacturer's instructions. All samples were run in duplicate.

Bone Mineral Density (BMD): measured using DXA at the lumbar spine (L1-L4) and femoral neck. T-scores were calculated using WHO criteria.

Additional Parameters: alkaline phosphatase, phosphorus, calcium, Vitamin D, and estradiol were measured to control for confounding factors.

Statistical Analysis: by SPSS version 26, data were analyzed, Continuous variables were expressed as (M± SD). Comparisons between groups were performed using independent t-test . Chi-square test was used for categorical variables. Pearson correlation was used to assess relationships between interleukins levels and BMD (p-value < 0.05 was considered statistically significant).

Ethical Considerations: The study was approved by the Ethics Committee of Baghdad Teaching Hospital.

Results:

Clinical and demographic Characteristics of Study groups

Table 1. Clinical and demographic Characteristics of Study groups

Parameter	Osteoporosis Group (No.=80)	Control Group (No.=80)	(p-value)
Age (years)	69.1 ± 5.1	67.1 ± 4.9	0.040*
Age at menopause (years)	48.2 ± 3.7	49.0 ± 3.2	0.003*
BMI (kg/m^2)	28.2 ± 3.9	28.9 ± 4.0	0.209
Parity (n)	5.0 ± 2.2	4.9 ± 2.0	0.213
Lumbar spine	0.71 ± 0.09	0.949 ± 0.12	<0.001*

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BMD (g/cm²)			
Lumbar spine T-score	-3.2 ± 0.6	-0.5 ± 0.4	<0.001*
Femoral neck BMD (g/cm²)	0.62 ± 0.08	0.86 ± 0.10	<0.001*
Femoral neck T-score	-2.9 ± 0.4	-0.3 ± 0.5	<0.001*

The clinical and demographic characteristics are presented in Table 1. osteoporotic women were significantly older (69.1 ± 5.1 years; p = 0.040) and had earlier menopause (48.2 ± 3.7 years; p = 0.003). No significant differences for BMI (28.2 ± 3.9 kg/m²; p = 0.209) or parity (5.0 ± 2.2; p = 0.213). As expected, lumbar spine BMD (0.71 ± 0.09g/cm²) and femoral neck BMD (0.62 ± 0.08 g/cm²) were lower in osteoporosis group (p < 0.001), with corresponding T-scores confirming the diagnosis (lumbar spine: -3.2 ± 0.6; femoral neck: -2.9 ± 0.4; p <0.001).

Table 2. Biochemical and hormonal parameters in elderly Iraqi postmenopausal women with osteoporosis and control

chemical and hormonal parameters	Osteoporosis Group (No.=80)	Control Group (No.=80)	p-value
Vitamin D (ng/ml)	12.10 ± 5.9	48.52	P = 0.0001
Estradiol (pg/ml)	35.99 ± 33.79	52.41 ± 36.19	P = 0.0270
Calcium (mmol/L)	3.00 ± 0.29	2.39 ± 0.19	P = 0.15 (NS)
Phosphorus (mmol/L)	1.23 ± 0.30	2.10± 0.18	P = 0.76 (NS)
Alkaline Phosphatase (U/L)	66.51 ± 13.11	63.32 ± 13.5	P = 0.75 (NS)

Women in the osteoporosis group were significantly older , had an earlier age at menopause (p=0.003), and a longer duration since menopause (p<0.001) compared to controls. BMI and parity were comparable between groups (p>0.05).

Table 3. Serum Interleukin Levels in Osteoporotic and Control Groups

Cytokine(pg/mL)	Osteoporosis Group (No.=80)	Control Group (No.=80)	(p-value)
IL-6	9.80 ± 3.29	4.18 ± 1.55	<0.001*
IL-1β	6.93 ± 1.95	2.46 ± 1.20	<0.001*
IL-10	3.14 ± 0.99	5.69 ± 1.36	<0.001*

Results showed, serum IL-6 was significantly higher in osteoporotic women (9.80 ± 3.29 vs. 4.18 ± 1.55 pg/mL; p < 0.001), as was IL-1β (6.93 ± 1.95 vs. 2.46 ± 1.20 pg/mL; p < 0.001) (in table-3).

Table 4. Cytokine Ratios in Osteoporotic patients

Ratio	Osteoporosis Group (No.=80)	Control Group (No.=80)	(p-value)
IL-6/IL-10	2.99± 0.90	0.78 ± 0. 40	<0.001*
IL-1β/IL-10	2.42 ± 0.79	0.48 ± 0.28	<0.001*
(IL-6 + IL-1β)/IL-10	5.16 ± 1.547	1.32± 0.49	<0.001*

All cytokine ratios were elevated in the osteoporosis group, indicating a pronounced shift toward a pro-inflammatory state. All pro-inflammatory/anti-inflammatory ratios were elevated in the osteoporosis

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group ($p < 0.001$ for all): IL-6/IL-10 (2.99 ± 0.90 vs. 0.78 ± 0.40), IL-1β/IL-10 (2.42 ± 0.79 vs. 0.48 ± 0.28), and (IL-6 + IL-1β)/IL-10 (5.16 ± 1.54 vs. 1.32 ± 0.49). These findings indicate a pronounced pro-inflammatory cytokine shift in elderly Iraqi postmenopausal women with osteoporosis (In table-4).

Discussion:

This study demonstrated that elderly Iraqi postmenopausal women with osteoporosis exhibit a distinct pro-inflammatory immune profile, characterized by elevated serum IL(6 and 1β) ,Whilst reduced IL-10, and increased pro-/anti-inflammatory ratios. These findings support the concept of "inflammaging" as a mechanism linking immune dysregulation to postmenopausal osteoporosis (Brincat etal., 2014).

The osteoporosis group had significantly lower vitamin D (12.10 ± 5.9) ng/ml and estradiol (35.99 ± 33.79) pg/ml than controls, while calcium, phosphorus, and alkaline phosphatase showed no significant differences. The severe vitamin D deficiency is consistent with regional reports of highly prevalent hypovitaminosis D among postmenopausal women in Iraq and the Middle East, where low 25(OH)D has been linked to reduced bone mineral density (Hussein & Ibrahim, 2024).

The lower estradiol level supports estrogen deficiency as a key mechanism in postmenopausal osteoporosis. Previous Iraqi data indicate that estradiol is protective against osteoporosis (OR 0.491; $p < 0.001$) (Al-Nejjar etal., 2015c), and low estradiol has been associated with increased fracture risk (Al-Nejjar etal., 2015c). Although estradiol was detectable in the osteoporosis group, it may still be insufficient for adequate bone protection (Al-Nejjar etal., 2015c).

The absence of significant differences in calcium, phosphorus, and alkaline phosphatase agrees with some earlier studies (Al-Nejjar etal., 2015a, 2015b), although others report higher alkaline phosphatase in osteoporosis (Nawawi etal., 2001; Salman etal., 2024). Total alkaline phosphatase is not bone-specific, and calcium and phosphorus may remain normal through compensatory mechanisms or be influenced by diet, activity, and time since menopause (Al-Nejjar etal., 2015a, 2015b; Nawawi etal., 2001). These routine markers therefore appear to have limited discriminatory value in this population; bone-specific turnover markers may be more useful (Nawawi etal., 2001; Salman etal., 2024).

Some studies have reported different patterns. Alhosseini etal., (2026) found a positive relationship between IL-6 and lumbar spine BMD in osteoporotic menopausal women. This discrepancy may be explained by differences in sample size, assay methodology, or population characteristics. Furthermore, serum levels may not fully reflect local bone marrow cytokine concentrations (Sahin etal., 2002).

Our finding of elevated IL-1β aligns with its established role in postmenopausal bone loss. Additionally, IL-1β enhances IL-6 secretion from osteoblast-like cells, creating a positive feedback loop.

Kotrych etal.,2016 found that the IL10 -1082 G allele (associated with higher IL-10) was less frequent in women with severe osteoporosis. These findings position IL-10 as a critical counter-regulatory cytokine whose insufficiency may contribute to the pro-inflammatory milieu favoring bone resorption (Zhang etal., 2015).

Our finding suggests that (IL-6/IL-10) ratio may serve as practical biomarker for osteoporosis risk stratification, capturing the net balance between bone-resorptive and bone-protective immune signals.As individuals age, immunosenescence leads to increased levels of pro-inflammatory and decreased anti-inflammatory mediators, contributing to osteoporosis. Sufaru etal., (2026) demonstrated that periodontitis and low BMD in postmenopausal women were associated with convergent inflammaging and immunosenescence phenotypes. These findings support the concept that osteoporosis is not merely an endocrine disorder but also an immune-mediated disease.

Conclusion: This study demonstrates that elderly Iraqi postmenopausal women with osteoporosis exhibit a significant pro-inflammatory immune profile, characterized by:

1. Elevated serum levels of interleukins (6 and1β) and reduced serum IL-10 levels in elderly Iraqi postmenopausal women with osteoporosis.as well as markedly increased levels of interleukins (6/10 and 1β/10) ratios.
2. Strong correlations between cytokine imbalance and reduced BMD in elderly Iraqi postmenopausal women with osteoporosis and the IL-6/IL-10 ratio emerged as the most accurate predictor of osteoporosis, with an AUC of 0.934, suggesting its potential as a practical biomarker for risk stratification.
3. These findings support the "inflammaging" hypothesis of postmenopausal osteoporosis and suggest that restoring the balance between pro- and anti-inflammatory interleukins may represent a novel therapeutic target for preventing bone loss in elderly women.

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