Serum interleukin-17 expression in postmenopausal women and its relation to osteoporosis and risk of fractures

Samar G. Soliman, Samah S. Youssef, Amira K. Mohammed, Dalia S. Saif

Department of Rheumatology, Rehabilitation and Physical Medicine, Faculty of Medicine, Menoufia University, Shebin EL-Kom, Menoufia, Egypt

Correspondence to Amira K. Mohammed, MSc, Department of Rheumatology, Rehabilitation and Physical Medicine, Faculty of Medicine, Shebin EL-Kom, Yassin Abdel Ghaffar Street from Gamal Abdel Anasar Street 32511, Menoufia, Egypt. Tel: +201060554928; e-mail: amirakmohamed2@gmail.com

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Background/Aim
Osteoporosis is a musculoskeletal disorder that is characterized by low bone mineral density (BMD) as well as an elevated risk of fractures. We aim to investigate the expression of interleukin-17 (IL-17) in postmenopausal women and to assess its relation to BMD and fracture risk.

Patients and methods
A case-control study included sixty postmenopausal female Patients were gathered from the Outpatient Clinic of the Rheumatology, Rehabilitation and Physical Medicine Department, Faculty of Medicine, Menoufia University, Egypt. All participants were divided into two groups; patients group, which enrolled 30 Postmenopausal females diagnosed as having osteoporosis, and control group, which included 30 Postmenopausal females without osteoporosis. All participants were exposed to clinical, anthropometric, and radiological examinations, as well as assessments of serum levels of total and ionized calcium by the colorimetric methods, 25 hydroxy vitamin D, parathyroid hormone, Estradiol level (E2) by chemiluminescent immunoassay, in addition to the serum level of IL-17 using ELISA technique.

Results
The present study exhibited significant increase ($P<0.05$) in IL-17 level and significant decrease ($P<0.05$) in estradiol level in patients group compared with controls. Moreover, significant differences were found in fracture risk assessment instrument tool analysis for the 10 year probability of major osteoporotic fractures ($P>0.05$) and hip fracture ($P>0.05$). Osteoporotic group demonstrated higher mean probabilities for both types of fractures compared with normal group. IL17 level exhibited negative correlations with DEXA score and serum estrogen level but exhibited positive correlation with fracture risk assessment instrument tool.

Conclusion
This study demonstrated a comprehensive evidence for the complex interactions among IL-17, BMD, and fracture risk in postmenopausal women. The elevated IL-17 levels in osteoporotic women and their correlation with fracture risk probabilities suggest a potential role for this cytokine in osteoporosis pathogenesis and risk assessment.

Keywords:
estradiol, osteoporosis, postmenopausal women, serum interleukin-17

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Introduction

Osteoporosis presents as a chronic skeletal disorder marked by reduction in bone mineral density (BMD) as well as in the structural integrity of the underlying bone tissue or bone mass which makes it prone to fracture. It may be either acquired or secondary to a specific agent or substance, infectious, parasitic, neoplastic, or of other etiology. Trabecular bone is the primary characteristic of Type I osteoporosis, which typically manifests during menopause. Type 1 osteoporosis is caused by low estrogen levels after the menopause, whereas type II osteoporosis is defined by a gradual loss of trabecular and cortical bone and begins at a later age. Predominantly, it is attributed to diminished bone formation [1,2].

Clinical criteria for osteoporosis and inadequate bone mass have been defined by the WHO using T-scores, which compare BMD values to those of a young adult reference. Loss of bone mass is seen in most postmenopausal osteoporotic women in correlation with estrogen insufficiency and/or advanced age [3].

Osteoporosis does not exhibit any clinical symptoms until a fracture occurs [3]. Over 50% of postmenopausal women are expected to sustain an

osteoporotic fracture during their lifetime inclusively vertebral deformity and hip fractures. Even though osteoporosis affects both sexes, the health and economic costs associated with osteoporosis are borne by women ~80%; fracture rates are significantly greater in elderly women than in similarly aged men [4].

There are probably many reasons for the sexes difference in fractures incidence; however, one factor that has been found is that after the menopausal period, women lose estrogen with subsequent bone mass loss. Loss of bone mass during the first year of menopause plays an important role in the progression of fractures later in life, as a lack of estrogen leads to accelerated bone density loss [5].

T-helper (Th) 17 cells generate interleukin-17 (IL-17), a proinflammatory cytokine. It improves bone degradation by increasing RANKL expression on synoviocytes and osteoblasts by enhancing signaling of RANK in osteoclasts. In animal studies, it has been recognized as a critical regulator of osteoclastogenesis in the context of estrogen deficiency, and it is a contributing factor to bone deterioration in long-standing autoimmune disorders that are associated with bone loss and numerous inflammatory disorders [6,7].

Estrogen (E2) guard against bone loss by two mechanisms, the first mechanism is promoting osteoprotegerin expression in osteoblasts which binds to RANK thus preventing RANKL-RANK binding resulting in blocking osteoclast differentiation, while the second mechanism is initiation of osteoclast apoptosis via Fas-ligand signaling [7].

This study aims to investigate serum IL-17 expression in postmenopausal women and to assess its association to BMD and risk of fracture.

Patients and methods

Patients

The present study is a case–control study that was conducted on 60 female patients in postmenopausal period. Patients were recruited from the Outpatient Clinic of the Rheumatology, Rehabilitation, and Physical Medicine Department, Faculty of Medicine, Menoufia University, Egypt. The inclusion criteria included only postmenopausal women were involved in the current study. However patients with systemic diseases that affect BMD like renal failure, gastro-intestinal abnormalities, malignancy, diabetes mellitus, auto immune diseases, inflammatory arthritis, thyroid and parathyroid diseases, smokers, patients on medications that affect bone mineral density as corticosteroids, chemotherapy and hormonal therapy. Patients with a history of or present use of medicine for the treatment of osteoporosis were excluded from the present investigation while only those treated with calcium and vitamin D were involved.

Study design

All postmenopausal female enrolled in this study were allocated into two groups, patient group that included 30 postmenopausal females diagnosed as having osteoporosis and control group that encompassed 30 postmenopausal females who do not have osteoporosis in accordance to the WHO criteria for definition and calcification of osteoporosis [8].

Ethical consideration

The present study was conducted with the Code of Ethics of the World Medical Association, according to the principles expressed in the Declaration of Helsinki. This study has been approved by the local Ethics Committee of Menoufia University, Menoufia Governorate, Egypt with approval number 2/2023PMRR28, a written informed consent was provided by each participant before their inclusion in the study.

Methods

Clinical and anthropometric examinations

All participants were exposed to demographic data (including name, age, and occupation), menstrual history (regarding: early menopause, late menarche, history of oligomenorrhea, and years of menstruation), medical history (including current smoking, inadequate physical activity, recurrent falls, previous fractures, shortening over time, Activities of daily living) and drug history. General examination (as regards blood pressure, temperature, pulse), body height (in Meter), weight (in Kilogram), and BMI (BMI was calculated by dividing the weight of an adult in kilograms by height in meters squared) was performed [9]. Local examinations were also conducted, with a particular emphasis on the back. They comprised: Tenderness: height decrement: Vertebral fracture – kyphosis, scoliosis or lordosis. Furthermore, the hip was also checked for any sign of tenderness, shortening or external rotation, or muscle weakness; that may cause falls.

Collection of blood samples

Five ml of venous blood were extracted from all subjects by sterile venipuncture from the cubital vein and

collected in plain vacutainer tubes without additives and allowed to clot at 37°C for 30 min. Serum was separated after centrifugation at the speed of 2000–3000 r. p. m and then stored at -20°C until used for biochemical and immunoassays analysis.

Biochemical measurements

The biochemical tests were performed for all participants in serum including the levels of total and ionized calcium, 25 hydroxy vitamin D, parathyroid hormone (PTH), serum Estradiol level (E2) and IL-17.

Serum total or ionized calcium levels were assayed using an ARCHITECT c4000 clinical chemistry analyzer (Abbott Diagnostics, USA). The chemiluminescent immunoassay techniques were used to determine serum levels of 25 hydroxy vitamin D, PTH, and E2 using a cobas-e601 fully automated analyzer for immunoassay analysis (Roche Diagnostics, Germany). According to the manufacturer instruction, the serum level of human IL-17 was estimated using the ELISA kit of Bioassay Technology Laboratory (BT LAB, Shanghai, China).

Radiological methods

Imaging workup to rule out any pathology or fracture in all the patients went through normal radiography of the spine in anterior-posterior and lateral positions. BMD of L1-4 of the lumbar spine was determined using a DEXA Scan with the T score measurement. Osteoporosis is classified into the following categories based on T score, as defined by WHO and derived from DEXA measurements: Normal -1.0 and above, osteoporosis -2.5 and below, osteopenia -1.0–-2.5, and severe 'established' osteoporosis -2.5 and below plus one or more osteoporotic fracture(s) [3]. Major osteoporotic fractures of the hip, spine, or wrist were predicted for both groups during the following decade using the fracture risk assessment instrument (FRAX) [10].

Sample size

The sample size was calculated using Epi Info, STATCalc version 7, to determine serum level of IL-17 in postmenopausal women at 80% power and 95% CI. A sample size of 60 participants divided into equal groups (osteoporotic group and nonosteoporotic group) was calculated from rheumatology and

Table 1 Demographic and laboratory investigations among all female postmenopausal participants

Variables	Control group (*n*=30)	Patients group (*n*=30)	Test value	*P* value
Age (year)				
Mean±SD	62.13±6.43	66.7±7.2	t=2.59	0.012*
Range	52–75	53–78		
BMI (kg/m^2)				
Mean±SD	32.45±6.7	29.37±4.58	t=2.08	0.042*
Range	20.7–45.1	20.1–42.7		
Duration of menopause (year)				
Mean±SD	13.87±6.77	17.7±6.27	t=2.28	0.027*
Range	5–26	6–26		
Serum total calcium (mg/dl)				
M±SD	9.48±0.53	7.91±0.71	t=9.63	<0.001*
Range	8.5–10.4	6.7–9.1		
Serum ionized calcium (mg/dl)				
Mean±SD	4.93±0.28	3.93±0.47	t=9.97	<0.001*
Range	4.5–5.3	3.3–4.7		
Serum 25 OH Vitamin D (ng/ml)				
Mean±SD	30.57±10.18	25.02±9.72	t=2.16	0.035*
Range	13.4–49.9	9.23–38.9		
PTH (pg/ml)				
Mean±SD	34.37±14.2	38.14±13.29	t=1.06	0.293
Range	14.8-54.8	12.5-54.4		
Estradiol (pg/ml)				
Mean±SD	16.07±4.89	13.83±3.26	t=2.08	0.042*
Range	10–24	9–22		
Interleukin 17 (ng/ml)				
Mean±SD	69.09±50.54	133.37±93.74	t=3.31	0.002*
Range	36.64–323.04	40.37–549.35		

BMI, body mass index; PTH, parathyroid hormone. *Significant difference among two groups at *P*value less than 0.05 using independent *t*-test.

Table 2 Serum levels of interleukin-17 in patients' group with different grades of osteoporosis

	Osteoporosis group (*n*=19)	Established osteoporosis (*n*=11)	Test value	*P* value
Serum IL-17 (ng/ml)				
Mean±SD	101.96±45.7	187.62±128.88	t=2.65	0.013*
Range	40.37–199.58	63.15–549.35		

*Significant difference among two groups at *P* value less than 0.05 using independent *t*-test.

rehabilitation outpatient clinics at Menoufia university hospital.

Statistical analysis

An analysis was performed on the recorded data using SPSS Inc.'s (Chicago, Illinois, USA) statistical software for the social sciences, version 23.0. The standard deviation and ranges were used to depict parametric (normal) quantitative data. The tests of Kolmogorov–Smirnov and Shapiro–Wilk were used to ensure that the data was normal. A *t*-test with a significance level of independent sampling was used for mean comparisons. Spearman correlation coefficient was used to correlate between different parameters. Our study utilized a confidence interval with a significance level of 0.05, so, the *P* value lower than 0.05 was deemed statistically significant, and vice versa. To determine sensitivity and specificity, receiver operating characteristic curves were used [11].

Results

This was a case–control study that was conducted on 60 female patients in postmenopausal period; it showed that patients with osteoporosis differed significantly from those without in terms of BMI, age, and duration of menopause. The serum levels of IL17 was significantly greater in cases versus controls. In contrast, serum calcium (total and ionized), 25 OH vitamin D, and Estradiol were significantly greater in controls compared with cases, with insignificant differences regarding to PTH among the two groups, as shown in Table 1.

The levels of serum IL-17 rise significantly as osteoporosis grades progress, with a significantly greater level in patients with established osteoporosis in comparison to those with osteoporosis (187.62 ±128.88 vs. 101.96±45.7), at *P* value equal to 0.013, as demonstrated in Table 2.

The data represented in Table 3 exhibited that there is a positive relationship between IL-17 level and both patients age (r=0.255, P<0.05) and duration of menopause (r=0.293, P<0.05), with negative correlation among the level of IL-17 and BMI (r=–0.303, P<0.05), serum levels of total (r=–0.433, P<0.01) or ionized (r=–0.445, P<0.01) calcium, 25 OH Vitamin D (r=–0.353, P<0.01) and Estradiol (r=–0.259, P<0.05).

A significant negative correlation was noticed among IL-17 levels, with grades of DEXA scores (P<0.05), as it increases with advanced grades of osteoporosis regarding dual energy X-ray absorptiometry (DEXA) score. While, IL-17 was positively associated with FRAX tool (P<0.05), indicating a potential role of IL-17 in osteoporosis fracture risk prediction, as shown in Table 4.

Table 3 Correlation between serum interleukin-17 level and both clinical and laboratory data

	IL-17	
	R	*P* value
Age	0.255	**0.049***
BMI	–0.303	**0.018***
Duration of menopause	0.293	**0.023***
Serum Calcium Level (total)	–0.433	**0.006****
Serum Calcium Level (Ionized)	–0.445	**0.004****
Serum 25 OH Vitamin D	–0.353	**0.006****
PTH	0.077	0.560
Estradiol (E2)	–0.259	**0.031***

BMI, body mass index; PTH, parathyroid hormone. *Significant correlation at *P* less than 0.05. **Highly significant correlation at *P* less than 0.01, using Spearman correlation coefficient (r).

Table 4 Correlation between DEXA Score, fracture risk assessment instrument tool and interleukin-17

	DEXA score							
	A-P spine		Left femur neck		Left femur total		Left forearm	
	r	*P* value	r	*P* value	r	*P* value	r	*P* value
IL-17	–0.344	0.007*	–0.468	0.002*	–0.403	0.001*	–0.341	0.008*
	FRAX tool							
	10 years Probability of major osteoporotic fracture (%)				10 years Probability of Hip fracture (%)			
	r		*P* value		r		*P* value	
IL-17	0.389		0.002*		0.504		<0.001*	

*Highly Significant correlation at *P* value less than 0.01, using Spearman correlation coefficient (r).

Table 5 Validity of serum interleukin-17 level among postmenopausal women with and without osteoporosis

	AUC	*P* value	95% CI	Cutoff point	Sensitivity (%)	Specificity (%)	PPV (%)	NPV (%)
Serum IL-17	0.859	<**0.001***	0.745–0.935	>80.12	83.33	90.00	89.3	84.4

AUC, area under the curve; NPV, negative predictive value; PPV, positive predictive value.

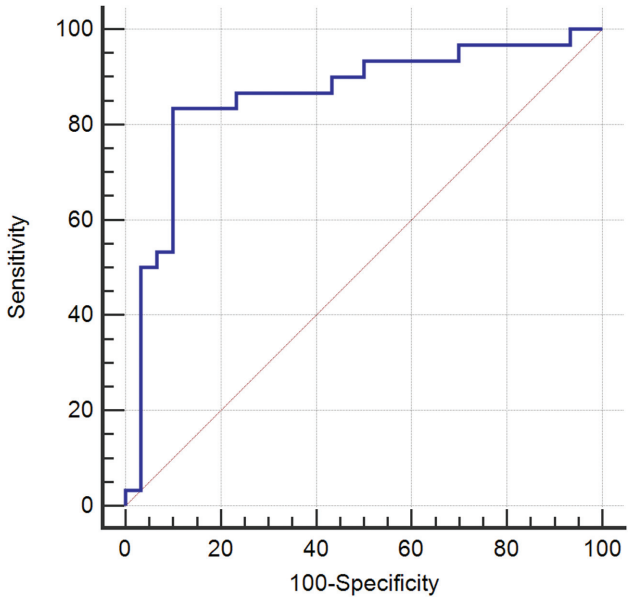
Regarding to the blood level of IL-17, the results showed that, at cutoff point 80.12, it could distinguish between postmenopausal woman with osteoporosis and those without, with 83.33% sensitivity, 90% specificity, area under the curve=0.859, 89.3% positive predictive value, and 84.4% negative predictive value, as reported in Table 5, and illustrated in Fig. 1.

Discussion

In long-standing autoimmune disorders that are associated with bone loss, IL-17 is one of the factors that increase bone loss [7]. We aim to investigate the expression of serum IL-17 in postmenopausal women and to assess its relation to BMD and risk of fracture.

The present study revealed significant differences among the osteoporotic group versus non-osteoporotic in relation to age, BMI, menopause duration, serum level of calcium (total and ionized), 25 OH vitamin D, and estradiol. These results are in agreement with the research conducted by Lips and van Schoor [12], as they documented lower levels of vitamin D in cases of osteoporosis compared with nonosteoporotic subjects.

Figure 1



Receiver operating characteristic curve of Serum levels of interleukin-17 in prediction of osteoporosis.

Interestingly, our study found significantly higher IL-17 levels in osteoporotic post-menopausal females compared with controls, and that the level of IL-17 increases with the advancement of osteoporosis grades. In agreement with our results, El-Mallah *et al.* [13] and Molnar *et al.* [14] reported in their study an elevated level of IL-17 in postmenopausal women having osteoporosis, suggesting its involvement in the bone resorption process. Additionally, they exhibited an association between deficiency of estrogen and elevated levels of IL-17 in postmenopausal females.

In harmony with our results, Molnar *et al.* [15], Zhang *et al.* [16], and Waliullah *et al.* [17], reported that serum levels of IL-17A were greater in postmenopausal patients suffering from osteoporosis. In the same way, Al-Tai [18], and Zhao and co-authors [19] reported that Postmenopausal osteoporotic women's had higher levels of IL-17, IL-17-producing clusters of differentiation 4 ($CD4^+$) T cells and mRNA levels of IL-17 in $CD4^+$ T cells compared with healthy postmenopausal women.

Other research has shown that IL-17 can induce chronic inflammatory events, such as bone loss, and that it is situated at the very top of the cascade of inflammatory cytokine, where it induces fibroblasts, synoviocytes, and macrophages to generate additional proinflammatory cytokines [20,21].

Similar to our results, Th 17 cells and IL-17A mRNA levels are greater in healthy older people compared with younger ones [22,23]. Furthermore, Bhadricha and his colleagues [24] found that postmenopausal women with low BMD had increased IL-17 levels, and the frequency of Th 17 was associated with their T-scores. Postmenopausal women may have a decline in BMD due to an increase in the frequency of Th 17 cells and higher levels of IL-17, as proposed by these researchers. Moreover, the bone spring effect of IL-17 inhibitors could serve as the foundation for the use of humanized IL-17 inhibitors in postmenopausal osteoporosis treatment [25].

Recent research has demonstrated that IL-17 can enhance bone loss by boosting osteoclast formation and lowering osteoblast differentiation, highlighting the critical function of the immune system in regulating bone turnover. Psoriasis, rheumatoid arthritis, systemic

sclerosis, and systemic lupus erythematosus are among the long-term autoimmune diseases associated with bone loss, and IL-17 plays a role in their deterioration [26–29].

In our research, the E2 levels of the studied groups exhibit a statistically significant difference, with the normal group exhibiting higher mean E2 levels than the osteoporotic group suggesting that lower E2 levels are associated with osteoporosis. This agrees with El-Mallah *et al*. [13], Molnár *et al*. [14], and Waliullah *et al*. [17], as they reported that, the osteoporotic group exhibited significantly lower estradiol levels than the nonosteoporotic group. In postmenopausal females with estrogen deficiency, they also delivered a higher concentration of IL-17.

This could be attributed to the fact that E2 enhances osteoclast apoptosis, caused by increased assembly of TGF-β, thereby preserving bone. Proinflammatory cytokines including IL-1, IL-17, TNF-α and IL-6 are amplified in a shortage of estrogen, which increases osteoclast activity, as estrogen adversely affects these cytokines [30].

De Selm *et al*. [31], found that blocking the signaling of IL-17 in an animal model stops osteoclastogenesis, which in turn stops estrogen deprivation from causing osteoporosis. Furthermore, the analysis of the FRAX tool revealed that the osteoporotic group had significantly greater 10 years probabilities of major osteoporotic fracture and fracture of the hip. These findings underscore the utility of the tool of FRAX in assessment of fracture risk, as demonstrated by Kanis *et al*. [32] and Kripa *et al*. [33] in their large-scale validation study.

In our study, IL-17 levels exhibited significant negative correlations with DEXA scores and serum estradiol levels, with a positive correlation with the FRAX tool ($P<0.05$) indicating a potential role of IL-17 in osteoporosis fracture risk prediction. This result implies IL-17 potential role in fracture risk prediction and warrants further investigation. While our results are preliminary, they align with the growing body of evidence linking inflammatory cytokines to bone metabolism, as discussed by Weitzmann [34].

El-Mallah *et al*. [13], and Scheffler *et al*. [7] studies, also showed that a strong negative association was observed between IL-17 and both BMD as measured by DEXA score and estrogen levels, in addition to a strong positive association among IL-17 with the index of FRAX.

In our study, serum IL-17 levels were able to significantly predict the presence of osteoporosis, with an area under the curve of 0.859, a cutoff value of greater than 80.12 ng/ml, 83.33% sensitivity, and 90.00% specificity. In a harmony with our study, El-Mallah and co-authors [13], demonstrated that the diagnosis of osteoporosis was performed with 100% positive predictive value, 100% specificity, 100% negative predictive value, and 100% sensitivity when the IL-17 serum level exceeded 80 pg/ml.

Conclusion

The present study demonstrated a comprehensive evidence for the complex interactions among IL-17, fracture risk in postmenopausal women, and BMD. The elevated IL-17 levels in osteoporotic women and their correlation with fracture risk probabilities suggest a potential role for this cytokine in osteoporosis pathogenesis and risk assessment. These results contribute to the knowledge growing body on the involvement of inflammatory mediators in bone metabolism and may have implications for future diagnostic and therapeutic approaches in osteoporosis management.

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Authors' contributions: S.G.S. was responsible for conceptualization, data curation, methodology, project administration, supervision, reviewing, and editing. D.S.S. aided in reviewing, editing, formal analysis, validation, and statistical analysis in addition to the manuscript revision. S.S.Y. helped in data curation, visualization, reviewing, and editing. A.K.M. was responsible for clinical history taking, data entry, laboratory investigation, and interpretation, in addition to submission of the manuscript to the journal.

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Conflicts of interest

There are no conflicts of interest.

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