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Serum interleukin-17 and estradiol levels in postmenopausal women in relation to osteoporosis

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Abstract

Background: In post-menopausal women, estrogen deficiency leads to instability between bone formation and resorption which is regulated by osteoclastogenic cytokines leading to resorption. Interleukin-17 (IL-17) a proinflammatory cytokine has been found as an important regulator of osteoclast-genesis induced by estrogen deficiency in favor of bone loss in animal studies.
The study aimed to evaluate levels of IL-17 and estrogen (E2) in relation to bone mineral density (BMD) and risk of fracture in postmenopausal women with and without osteoporosis.

Results: IL-17 levels were significantly higher and E2 levels were significantly lower in the osteoporotic group compared to the non-osteoporotic group (*P* value ≤ 0.01). There was a highly significant difference in DEXA score and FRAX index between two groups: with higher values of FRAX and lower values of DEXA score among osteoporotic group (*P* value ≤ 0.01). IL-17 was inversely correlated to estrogen level and highly significant negative correlation with DEXA as well as a highly significant positive one with FRAX index. IL-17 serum level was able to diagnose osteoporosis at a cutoff level of > 80 pg/mL with 100% sensitivity, 100% specificity, 100% positive predictive value (PPV), and 100% negative predictive value (NPV).

Conclusions: Serum IL-17 was significantly elevated in osteoporotic postmenopausal women when compared to healthy postmenopausal ones and was inversely correlated with estrogen level and DEXA.

Keywords: Interleukin-17, Osteoporosis, Serum estradiol, DEXA

Background

Osteoporosis is a complex skeletal disease distinguished by low bone mineral density (BMD) and micro-architectural decay of bone tissue with subsequent fragility [1].

Osteoporosis is either primary or secondary to an identifiable cause as drug, or disease. The primary type includes either type I (postmenopausal) or type II (senile) osteoporosis. The first starts at menopause and occurs predominantly in trabecular bone. It is a consequence of estrogen shortage after menopause. The second type starts 4–8 years later and shows signs of a continual loss of both trabecular and cortical bone. It is predominantly credited to downgraded bone formation [2].

With an escalating aging population, osteoporosis and related fractures are an imperative community health issue that put a huge economic burden on health service supplies.

Bone undergoes endless remodeling which is a fundamental process for healthy bone development. This remodeling is founded on an equilibrium between osteoclastogenic bone resorption and osteoblastogenic bone formation. Mesenchymal stem cells form osteoblast to deliver extracellular bone matrix while monocytic lineage is the source of osteoclasts secreting bone resorptive factors. In post-menopausal women, bone resorption surge, with a drop of bone mineral density (BMD) [3].

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The pathogenesis of bone loss provoked by estrogen shortage is controlled by osteoclastogenic cytokines secreted by bone marrow stromal cells, osteoblasts, or activated T cells.

These include receptor activator of nuclear factor k-B ligand (RANKL), TNFα, IL-6, and IL-17, and contribute to osteoclast differentiation, proliferation, and maturation [4].

Estrogen (E2) guards bone via two core processes: firstly, it provokes osteoprotegerin (OPG) expression in osteoblasts with an anti-osteoclastogenesis role by binding to RANK, the primary differentiation factor for osteoclasts, thus blocking RANKL-RANK binding through it, and secondly, by initiation of osteoclast apoptosis through Fas-ligand signaling. Furthermore, E2 alters the bone marrow leading to a decrease in the number of B lymphocytes, the manufacturer of RANKL [5].

Interleukin-17 (IL-17) a proinflammatory cytokine formed by Th17 cells [6] and promotes the expression of RANKL on osteoblasts and synoviocytes and potentiates RANK signaling in osteoclasts thereby promoting bone destruction [7]. IL-17 is one of the contributor of bone worsening in long-established auto-immune disorders associated with bone loss [8], many inflammatory disorders [9], and has been found as a crucial regulator of osteoclastogenesis associated with estrogen deficiency in animal studies [5].

This study aimed to evaluate the levels of IL-17 and estrogen in relation to bone mineral density and risk of fracture in postmenopausal women with and without osteoporosis.

Methods

This study included sixty postmenopausal females: 30 diagnosed as having primary post-menopausal osteoporosis and 30 without osteoporosis. According to the World Health Organization (WHO) definition of osteoporosis for post-menopausal women based on DEXA measurements [10]. Patients were engaged in the study from January 2020 to June 2020.

Exclusion criteria included patients with secondary osteoporosis such as renal failure, malignancy, gastrointestinal abnormalities, thyroid, and parathyroid diseases, osteomalacia, and patients on treatment of osteoporosis. Other causes that may affect the level of IL-17 such as inflammatory autoimmune diseases were also excluded. Written informed consent was taken from all patients and approval from the ethical committee was obtained.

All participants underwent the following:

Full medical history taking

Full medical history taking with consideration to the following: current cigarette smoking, early menopause, low intake of diet rich in calcium and vitamin D, shortening over time, recurrent falls, previous fractures, inadequate physical activity, medical history of drugs, and activities of daily living (ADL) using the Katz ADL. This index ranks adequacy of performance of six functional domains (bathing, dressing, toileting, transferring, continence, and feeding). Patients were scored yes/no for independence in each of the six functions. A score of 6 indicates full function, 4 indicates moderate impairment, and 2 or less indicates severe functional impairment [11].

Clinical examination

A. General examination: including body weight and body height. Body mass index (BMI) defined as: BMI = WEIGHT (in kg)/height (in m^2).
B. Local examination with emphasis on the following:

- Back examination as tenderness, loss of height, and kyphosis (vertebral fracture), scoliosis, or lordosis
- Hip examination as tenderness, shortening, or external rotation of hip (hip fracture)
- Weakness of the lower extremity muscles that might lead to falls

Radiological investigations

A. Bone densitometry (using DEXA scan): BMD in the lumbar spine (L1-4) by dual energy X-ray absorptiometry (DEXA). T score was assessed. According to the World Health Organization (WHO) definition of osteoporosis based on DEXA measurements, osteoporosis is categorized according to T score into as follows: Normal −1.0 and above, Osteopenia −1.0 to −2.5, Osteoporosis −2.5 and below, Severe "established" osteoporosis −2.5 and below plus one or more osteoporotic fracture(s) [12].

According to T score patients were split into two groups as follow: Group A: 30 postmenopausal with osteoporosis (T score less than −2.5), group B: 30 postmenopausal without osteoporosis (T score greater than −1).

B. Fracture assessment by FRAX: Fracture assessment was done for both groups using fracture risk assessment tool (FRAX), to assess the10-year probability of a major osteoporotic fracture either in the hip, spine, or wrist [13]. FRAX is a permitted, internet-based computer algorithm that can be retrieved through (http://www.shef.ac.uk/FRAX) [13].

C. Plain X-ray over spine antero-posterior and lateral view to exclude any pathology or fracture

Laboratory investigations

Ten milliliters of venous blood were withdrawn from each subject under complete aseptic condition. Erythrocyte sedimentation rate (ESR) (standard Westergren method), C-reactive protein (CRP) (nephelometric assay), liver and kidney functions, thyroid-stimulating hormone (TSH), and parathyroid hormone (PTH) were measured to exclude secondary causes. Estradiol (E2) was measured by electrochemiluminescence on the Cobas system by Roche Diagnostics, GMBH, Sandhofer Str. 116, 68305 Mannheim, Germany. Interleukin-17A concentration was measured using Invitrogen™ e Bioscience™ IL-17 Platinum ELISA Kit (Catalog Number BMS 2017) supplied by Thermo Fisher Scientific (Thermo-Scientific, 168 Third Avenue, Waltham, MA, USA) according to the manufacturer instructions.

Statistical analysis

The data were analyzed by SPSS program version 20. Data were displayed using mean, standard deviation, and range for quantitative variables that are normally distributed and as median and IQR (percentiles) in case of skewed data. Comparison between two groups is performed using independent *t* test, ANOVA for comparing more than two variables, and Chi-square test for comparison of qualitative data. Pearson's correlation was used to test the relation between two numeric variables. *P* value ≤ 0.05 is statistically significant and *P* ≤ 0.01 is highly significant.

Results

This cross-sectional study was conveyed on 60 postmenopausal women. Their age ranged between 46.6 and 68.1 years with mean ± SD of 59.31± 6.38 years. The duration of menopause ranged between 5 and 22 years with mean of 11.27 ± 4.92 years while BMI ranged between 21.5 and 40.9 with mean ± SD of 32.2 ± 5.15. Twenty percent of post-menopausal osteoporotic group had history of fracture, while 40.0% of cases had history of fracture in the non-osteoporotic group. Activities of daily living (ADL) ranged between 4 and 6 with mean ± SD of 5.07 ± 0.70 in both groups. Patients were divided into two groups based on DEXA measurements: group A, 30 postmenopausal females with osteoporosis (T score less than −2.5); group B, 30 postmenopausal females without osteoporosis (T score greater than −1).

On comparing between the osteoporotic group and non-osteoporotic group regarding demographic data (age, menopause duration and BMI, history of fracture and ADL), there was no statistical difference between both groups. A non-significant statistical difference was also found when comparing each of vertebral examination (tenderness, deformity as scoliosis, and kyphosis) and hip examination (pain, tenderness, limitation of movement) between the two groups (Table 1).

On comparing between osteoporotic and non-osteoporotic subjects regarding DEXA score and FRAX index, there was a highly significant statistical difference between the two groups: with higher values of FRAX and lower values of DEXA score among the osteoporotic group (Table 2).

Regarding laboratory data, no statistically significant difference was found between the 2 groups as regards each of ESR, CRP, and PTH. On the other hand, IL17 levels were significantly higher and estradiol levels were significantly inferior in the osteoporotic group compared to the non-osteoporotic group (*P* value ≤ 0.01) (Table 3).

On performing correlation study between each of E2, IL-17, DEXA score, and FRAX in relation to the clinical

Table 1 Comparison between osteoporotic group and non-osteoporotic group regarding demographic data

		Non-osteoporotic group No. = 30	Osteoporotic group No. = 30	Test value	*P* value	Sig.
Age (years)	Mean ± SD	57.19 ± 6.86	61.44 ± 5.24	−1.909•	0.067	NS
	Range	46.6-68.1	51.4-69.9			
Duration of menopause	Mean ± SD	10.00 ± 5.41	12.53 ± 4.17	−1.436•	0.162	NS
	Range	5-22	6-19			
BMI	Mean ± SD	32.80 ± 5.87	31.60 ± 4.36	0.636•	0.530	NS
	Range	21.5-40.9	23.8-36.7			
History of fracture	No	18 (60.0%)	24 (80.0%)	1.429*	0.232	NS
	Yes	12 (40.0%)	6 (20.0%)			
ADL	Mean ± SD	5.27 ± 0.80	5.07 ± 0.70	0.728•	0.473	NS
	Range	4-6	4-6			

P value > 0.05, non-significant; *P* value ≤ 0.05, significant; *P* value ≤ 0.01, highly significant independent *t* test *Chi-square test
BMI body mass index, *ADL* activities of daily living

Table 2 Comparative statistics between the 2 groups regarding radiological data

Radiological data		Non-osteoporotic group No. = 30	Osteoporotic group No. = 30	Test value	*P* value	Sig.
DEXA score	Mean ± SD	−0.8 ± 0.07	−1.26 ± 0.18	9.545•	0.000	HS
	Range	−0.62-0.88	−1.07-1.7			
FRAX	Median (IQR)	1.1 (0.6-1.6)	0.3 (0.2-0.4)	−3.934$^{\mp}$	0.000	HS
	Range	0.4-1.9	0.1-1.5			

P value ≤ 0.05, non-significant; *P* value ≤ 0.05, significant; *P* value ≤ 0.01, highly significant
•Independent *t* test; $^{\mp}$Mann-Whitney test
DEXA dual energy X-ray absorptiometry, FRAX fracture risk assessment tool

and laboratory data of participant cases, there was a significant negative correlation between E2 level, age, and menopause duration, while there was a highly significant positive correlation between FRAX and each of age and duration of menopause as shown in Table 4.

Conversely, IL-17 had a highly significant statistical negative correlation with bone mineral density (DEXA score), as well as a highly significant positive one with FRAX index. On the contrary, E2 levels showed a highly significant positive correlation with DEXA scores and a negative one with FRAX index. A highly significant negative correlation between IL-17and E2 serum levels in all postmenopausal participants was found (Table 5) (Fig. 1a, b, c, d).

Receiver operating characteristic (ROC) curve was applied to determine the best cutoff level of IL-17 that discriminates between osteoporotic and non-osteoporotic group was 80 pg/mL at which sensitivity was 100%, specificity 100%, positive predictive value (PPV) 100%, negative predictive value (NPV) 100%, with an area under the curve 1.00. On performing ROC curve, DEXA score diagnosed osteoporosis at a cutoff level of ≤ 0.875 with 100% sensitivity, 100% specificity, 100% positive predictive value (PPV), and 100% negative predictive value (NPV), with an area under the curve of 1.00, whereas FRAX diagnosed osteoporosis at a cutoff level of > 0.4, with 93.33% sensitivity, 80% specificity, 82.4% PPV, and 92.3% NPV with an AUC of 0.92.

Discussion

Postmenopausal osteoporosis represents an interaction between estrogen scarcity and augmented immune reactivity. T cells are the IL-17 source, while its receptor is expressed on fibroblasts, osteoblasts, chondrocytes, macrophages, dendritic, as well as on endothelial, and most parenchymal cells [14]. IL-17 is one of contributor of bone deterioration in long-established auto-immune inflammatory disorders associated with bone loss including psoriasis, rheumatoid arthritis, systemic sclerosis, and systemic lupus erythematosus [6, 9, 15].

This study aimed to evaluate the levels of IL-17 and estrogen in relation to bone mineral density and risk of fracture in postmenopausal women with and without osteoporosis.

In the present study, IL-17 levels were significantly higher and estradiol levels were significantly lower in the osteoporotic group compared to the non-osteoporotic group (*P* value ≤ 0.01).

Table 3 Comparative statistics between the 2 groups regarding laboratory data

Investigations		Non-osteoporotic group No. = 30	Osteoporotic group No. = 30	Test value	*P* value	Sig.
ESR	Mean ± SD	10.71 ± 3.14	9.66 ± 2.55	1.002•	0.325	NS
	Range	5.2-14.6	5.7-14			
CRP	Mean ± SD	1.97 ± 0.65	1.90 ± 0.72	0.294•	0.771	NS
	Range	1-2.9	1-2.9			
PTH	Mean ± SD	43.77 ± 14.27	40.60 ± 15.85	0.576•	0.569	NS
	Range	17.9-64.1	13.4-63.9			
Estradiol (E2)	Median (IQR)	240 (150-300)	20 (5-25)	4.635$^{\mp}$	0.000	**HS**
	Range	75-500	4-100			
IL-17	Median (IQR)	60 (50-60)	280 (240-300)	4.696$^{\mp}$	0.000	**HS**
	Range	45-80	160-480			

P value ≤ 0.05, non-significant; *P* value ≤ 0.05, significant; *P* value ≤ 0.01, highly significant
•Independent *t* test
$^{\mp}$Mann-Whitney test
ESR erythrocyte sedimentation rate, *CRP* C-reactive protein, *PTH* parathyroid hormone, IL-17 interleukin-17

Table 4 Correlation study between IL-17, E2, radiological data, and different studied variables in postmenopausal women

	Estrogen		IL-17		DEXA score		FRAX	
	r	*P* value	*r*	*P* value	*r*	*P* value	*r*	*P* value
Age (years)	**−0.407***	**0.026**	0.254	0.176	−0.232	0.217	**0.584****	**0.001**
Duration of menopause	**−0.394***	**0.031**	0.212	0.262	−0.193	0.308	**0.553****	**0.002**
BMI	0.192	0.309	−0.100	0.598	0.083	0.663	−0.298	0.110
ADL	0.164	0.387	−0.121	0.523	0.069	0.716	−0.051	0.790
ESR	0.076	0.690	−0.259	0.166	0.236	0.209	−0.109	0.568
CRP	−0.014	0.940	−0.051	0.790	−0.075	0.693	−0.066	0.728
PTH	−0.004	0.982	−0.157	0.407	−0.007	0.969	−0.163	0.389

P value ≤ 0.05, non-significant; *P* value ≤ 0.05, significant; *P* value ≤ 0.01, highly significant
r Spearman correlation coefficient, *BMI* body mass index, *ADL* activities of daily living, *ESR* erythrocyte sedimentation rate, *CRP* C-reactive protein, *PTH* parathyroid hormone, *IL-17* interleukin-17, *DEXA* dual energy X-ray absorptiometry, *FRAX* fracture risk assessment tool

Our results agree with Molnar et al. [16, 17] who investigated serum IL-17A, rank ligand, OPG levels and (BMDs) in 18 pre- and 72 postmenopausal women and reported that IL-17A were elevated in osteoporotic women than in osteopenic ones. They also conveyed the connection between estrogen deficiency and elevated IL-17 level in post-menopausal females.

Same results were also reported by AL-Tai [18] who evaluated IL-17 in 84 postmenopausal females and concluded that serum IL-17 was significantly high-up in osteoporotic postmenopausal when compared to healthy postmenopausal women. Furthermore, Zhao et al. [19] reported higher serum concentrations of IL-17, with increased IL-17-producing CD4+ T cells, as well as mRNA levels of IL-17 in CD4+ T cells in osteoporotic postmenopausal women than postmenopausal healthy controls. Similarly, Waliullah et al. [20] also conveyed a higher level of IL-17 in postmenopausal females with estrogen deficiency.

This is because E2 preserves bone by boosting osteoclasts apoptosis attributed by increased assembly of TGF-β. In an estrogen shortage, the osteoclasts are enhanced by amplified action of proinflammatory cytokines, as IL-1, IL-6, IL-17, and TNF-α, which are adversely operated by estrogen [21]. IL-17 bone loss effect is triggered through RANK ligand-mediated osteoclastogenesis, to generate MCSF and RANKL in osteoblasts and mesenchymal stem cells to boost the growth of bone-resorbing osteoclasts from monocyte/macrophage precursors. Moreover, Th17 cells (RANKL-expressing T cells) reinforce osteoclastogenesis [22].

Table 5 Correlation study between IL-17, E2, and radiological data in postmenopausal women

	Estrogen			IL-17		
	r	*p* value	Sig.	*r*	*p*	Sig.
DEXA score	0.584	0.001	**HS**	−0.661	0.001	**HS**
FRAX index	−0.679	0.001	**HS**	0.639	0.001	**HS**
Estradiol (E2)				−0.665	0.001	**HS**

DEXA dual energy X-ray absorptiometry, *FRAX* fracture risk assessment tool

De Selm et al. [23] observed that blocking IL-17 signaling prevents estrogen deficiency-mediated osteoporosis by inhibiting osteoclastogenesis in an animal model. Additionally, there was an upsurge in IL-17A producing T helper 17 cells in BM after ovariectomy of mice, and on providing them with neutralizing IL-17 antibodies; bone loss was no longer deteriorating. While another study established that mice missing the core IL-17 receptor (IL-17RA) or its downstream effector protein, Act1, were guarded from the skeletal impacts of ovariectomy [5].

In our study, IL-17was inversely correlated to estrogen level and had a highly significant statistical negative correlation with bone mineral density (DEXA score) as well as a highly significant positive one with FRAX index. These results are in harmony with Molnar et al. [17], Zhang et al. [24], and Waliullah et al. [20], who stated that serum IL-17A levels were higher in postmenopausal patients with osteoporosis, with a significant negative correlation between IL-17A levels and BMD further highlighting the influential role of IL-17 in the pathogenesis of postmenopausal OP.

On performing ROC statistical analysis, IL-17 serum level was able to diagnose osteoporosis at a cutoff level of > 80 pg/mL with 100% sensitivity, 100% specificity, 100% PPV, and 100% NPV. To our limited knowledge, this is the earliest study to investigate the diagnostic performance of IL-17 using ROC curve to discriminate osteoporotic from non-osteoporotic postmenopausal females.

In the present study, DEXA score diagnosed osteoporosis at a cutoff level of ≤ 0.875, with 100% sensitivity, 100% specificity, 100% PPV, and 100% NPV and an AUC of 1.0.

As for the FRAX, it can be used to diagnose osteoporosis at a cutoff level of > 0.4, with 93.33% sensitivity, 80% specificity, 82.4% PPV, and 92.3% NPV and an AUC of 0.92.

Kripa et al. [25] in their study evaluate various screening tools in determining the risk of osteoporosis in 2000

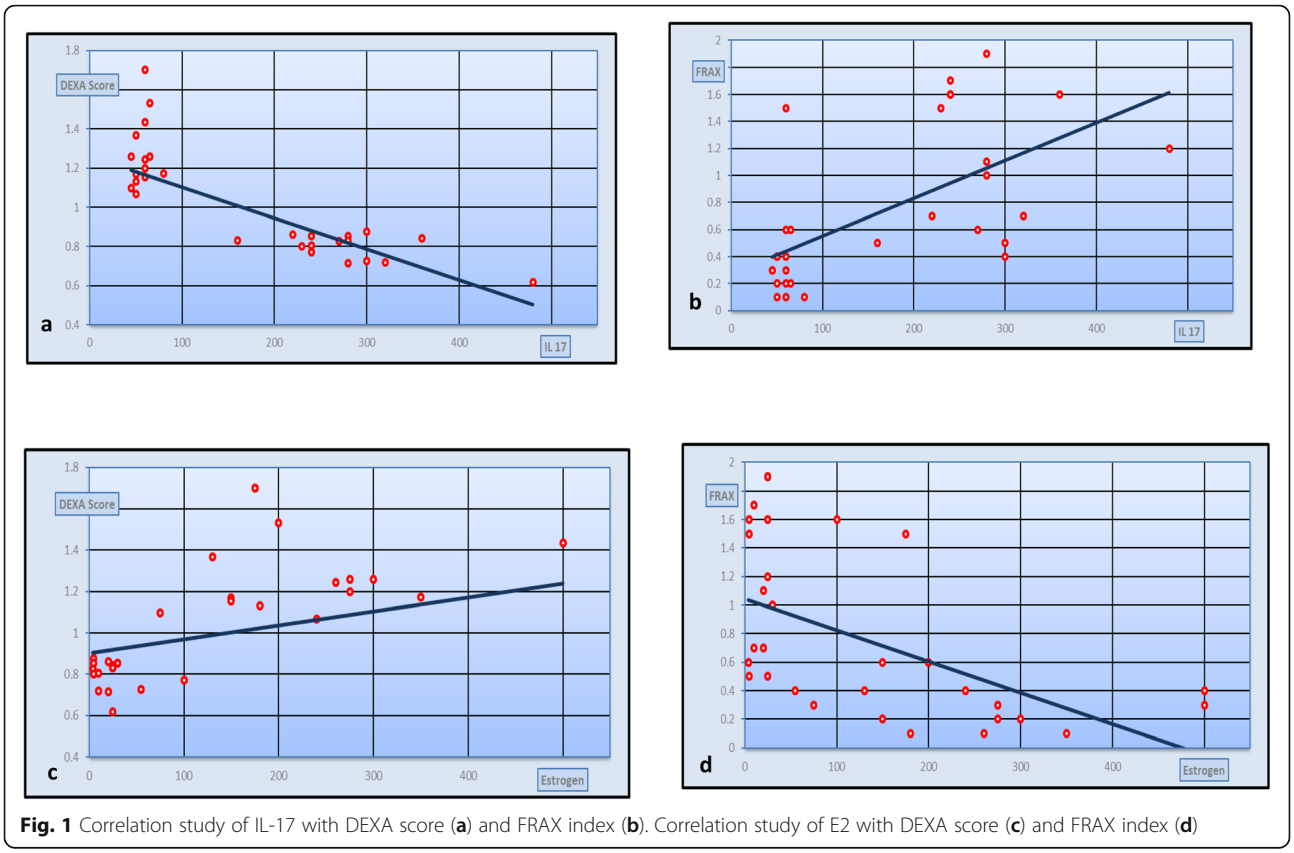

Fig. 1 Correlation study of IL-17 with DEXA score (**a**) and FRAX index (**b**). Correlation study of E2 with DEXA score (**c**) and FRAX index (**d**)

postmenopausal women concluded that the performance of FRAX® was suboptimal as it was devised to foresee fractures not osteoporosis. They found that at a cutoff level of ≥ 0.7%, AUC of 0.736, FRAX® had a sensitivity of 72.7% and an acceptable specificity 60.5%. Thus, the utilization of straightforward evaluating methods for the spotting of osteoporosis helps in the early distinguishing of women in danger of fracture.

Conclusions

In conclusion, serum IL-17 was significantly elevated in osteoporotic postmenopausal women when compared to healthy postmenopausal ones. It was also inversely correlated with estrogen level and bone mineral density in these patients. However, our study was limited by disregarding the osteopenic patient, the small population number and narrow geographical scale. So, further studies with enrollment of these limitations are essential to emphasize our conclusion. The results of the present study together with the impact on bone loss witnessed with anti-IL-17A therapies in postmenopausal osteoporosis animal models raise the issue of a distinctive effect of this cytokine on bone. A potential consequence of IL-17A blocking therapies in postmenopausal osteoporosis will be an appealing focus to investigate in future studies.

Abbreviations

BMD: Bone mineral density; RANKL: Nuclear factor k-B ligand; E2: Estrogen; OPG: Osteoprotegerin; IL-17: Interleukin-17; ADL: Activities of daily living; BMI: Body mineral index; DEXA: Dual energy X-ray absorptiometry; FRAX: Fracture risk assessment tool; ESR: Erythrocyte sedimentation rate; CRP: C-reactive protein; TSH: Thyroid-stimulating hormone; PTH: Parathyroid hormone; ROC: Receiver operating characteristic; PPV: Positive predictive value; NPV: Negative predictive value

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Authors' contributions

NN gave idea and put study design. ER and SA collected the patients' data and analyze them. ER wrote the paper with revision. They all approved the final version of the manuscript.

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Availability of data and materials

The datasets used and/or analyzed during the current study are available from the corresponding author on reasonable request.

Declarations

Ethics approval and consent to participate

This study was approved by the Ethical Committee of the Faculty of Medicine, Ain Shams University, 29 September 2019; number of approval, MS 318/2019.

All patients included in this study gave written informed consent to participate in this research.

Consent for publication
All patients included in this research gave written informed consent to publish the data contained within this study. If the patient was less than 16 years old, deceased, or unconscious when consent for publication was requested, written informed consent for the publication of this data was given by their parent or legal guardian.

Competing interests
The authors declare that they have no competing interests.

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