"Assessment of STAT3, IL-6, IL-11 Levels and Their Association with Osteoporosis in Premenopausal Women In Tikrit, Iraq"

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Abstract:

Background: Osteoporosis is a progressive bone disease characterized by decreased bone density and increased fragility, leading to a higher risk of fractures. Thyroid hormones and cytokines like IL-6, IL-11, and STAT3 may play a role in bone metabolism and early bone loss**. Objectives:** To assess the levels of T4, T3, TSH, STAT3, IL-6, and IL-11 and investigate their association with osteoporosis in premenopausal women in Tikrit Province, Iraq. **Method and material:** A case-control study was conducted in Tikrit Teaching Hospital, Tikrit Province, Iraq. Extended from July 2024 to the end of July 2025. Which include 90 females as follows: 60 females with osteoporosis and 30 healthy females as a control group. Sandwich ELISA kits (Sunlong-China) were used to detect target antigens, with HRP-labeled antibodies for signal detection. Optical density was measured at 450 nm using a spectrophotometer. **Result:** The mean±SD of T4 for the study group and control was 74.94±15.08, 96.70±18.81, respectively with highly significant P value was <0.0001**, and the mean±SD of T3 for the study group and control was 1.904±0.4082, 2.265±0.3468, respectively with highly significant P value was <0.0001**, and the mean±SD of TSH for the study group and control was 2.066±0.3812, 2.252±0.3887, respectively with significant P value was 0.0326*. and the mean±SD of STAT3for the study group and control was 15.59±3.331, 14.49±2.134, respectively non-significant P value was 0.1017NS. The mean±SD of IL 6 for the study group and control was 49.83±6.573, 46.62±8.192, respectively with significant P value was 0.0478*. The mean±SD of IL 11 for the study group and control was 138.4±28.30, 152.0± 29.04, respectively with significant P value was 0.351N. **Conclusion**: Compared to healthy controls, women with osteoporosis exhibited much decreased T3, T4, and TSH levels as well as greater IL-6 levels. These results imply that the development of osteoporosis could be influenced by thyroid dysfunction and chronic inflammation. There were no notable variations in IL-11 or STAT3 levels.

Key words: Osteoporosis, Premenopausal women, Cytokines, STAT3, Thyroid hormones.

"تقييم مستويات STAT3 و IL-6و IL-11وعلاقتها بهشاشة العظام لدى النساء ما قبل سن اليأس في تكريت، العراق"

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الخلاصة

الخلفية: تُعد هشاشة العظام من الأمراض المزمنة الشائعة التي تتصف بانخفاض تدريجي في كثافة العظام وارتفاع قابليتها للتعرض للكسور. ويُعتقد أن للهرمونات الدرقية وبعض السيتوكينات الالتهابية، مثل IL-6 و IL-11وبروتينSTAT3 ، دورًا مهمًا في تنظيم أيض العظام والمراحل المبكرة من فقدان الكتلة العظمية. ومن هذا المنطلق، أصبح فهم العلاقة بين هذه المؤشرات الحيوية وخطر الإصابة بهشاشة العظام ذا أهمية سريرية كبيرة، خصوصًا لدى النساء قبل سن اليأس.

الهدف من الدراسة: هدفت هذه الدراسة إلى تقييم مستويات كل من T4 و T3و TSHو STAT3و IL-6وIL-11، واستقصاء علاقتها بحدوث هشاشة العظام لدى النساء قبل سن اليأس في محافظة تكريت، العراق. **المواد وطرق العمل:** أُجريت هذه الدراسة في مستشفى تكريت التعليمي بمحافظة تكريت خلال الفترة الممتدة من يوليو 2024 وحتى نهاية يوليو 2025. شملت الدراسة 90 امرأة، منهن 60 امرأة مشخصة بهشاشة العظام و30 امرأة سليمة كمجموعة سيطرة. تم استخدام تقنية Sandwich ELISA للكشف عن المستضدات الحيوية المستهدفة. **النتائج:** أظهرت النتائج انخفاضًا ذا دلالة إحصائية عالية في مستويات هرموني T4وT3 لدى مجموعة المصابات مقارنة بمجموعة السيطرة .($P < 0.0001$) كما لوحظ انخفاض ذو دلالة إحصائية في مستوى TSHلدى مجموعة الدراسة($P = 0.0326$) .أما مستوى بروتين STAT3 فلم يُظهر فروقًا ذات دلالة إحصائية بين المجموعتين ($P = 0.1017$). وبالنسبة للسيتوكينات، بيّنت الدراسة ارتفاعًا ذا دلالة إحصائية في مستويات IL-6لدى النساء المصابات بهشاشة العظام ($P = 0.0478$)، في حين لم تُسجّل أي فروق ذات دلالة إحصائية في مستويات ($P = 0.351$) IL-11. **الاستنتاج:** تشير نتائج الدراسة إلى تأثير محتمل لاضطراب وظائف الغدة الدرقية، ممثلًا بانخفاض مستويات T3 و T4وTSH، إضافة إلى ارتفاع مستويات IL-6الدالة على وجود حالة التهابية مزمنة، في زيادة خطر الإصابة بهشاشة العظام لدى النساء قبل سن اليأس. كما توضح النتائج عدم وجود علاقة واضحة لكل من STAT3 و IL-11مع هشاشة العظام في هذه الفئة من النساء. وتبرز هذه المعطيات أهمية إجراء فحوصات دورية لوظائف الغدة الدرقية والواسمات الالتهابية لدى النساء المعرضات لخطر هشاشة العظام، مما قد يسهم في الكشف المبكر والوقاية من المضاعفات المرتبطة بها.

الكلمات المفتاحية: هشاشة العظام، النساء ماقبل سن اليأس، السايتوكينات،STAT3 ، **هرمونات الغدة الدرقية.**

Introduction

Osteoporosis is a significant public health problem in women, especially after menopause. Therefore, achieving high bone mass during late adolescence and minimizing bone loss during the reproductive years is critical to reducing the risk of fragility fractures later in life [1]. Osteoporosis is a prevalent illness associated with considerable morbidity, affecting over 50% of women who are at risk of sustaining an osteoporosis-related fracture during their lifetime and resulting in over 10 million hip fractures worldwide among individuals over the age of 55 [2]. An estimated 200 million people worldwide suffer from osteoporosis, primarily women. Approximately one-third of women over 50 have fractures associated with osteoporosis, with a sex ratio of roughly one male to six females [3]. For numerous women, these hazards commence far in advance of the phase of heightened bone loss associated with menopause. Screening rates and treatment initiation for osteoporosis frequently do not meet recommended standards for women across all age groups, attributable to several causes, including healthcare disparities related to access to screening and treatment [4]. Bone mass can be enhanced with adequate consumption of calcium and vitamin D, coupled with increased physical activity in premenopausal women diagnosed with osteoporosis [5]. The thyroid-stimulating hormone (TSH) regulates the production and secretion of thyroxine (T4) and thyronine (T3), the two primary thyroid hormones in humans [6]. Overt hypothyroidism decreases bone turnover by diminishing both osteoclastic resorption and osteoblastic activity [7]. women with overt hypothyroidism experience a protracted bone remodeling cycle and low bone turnover due to diminished osteoblastic activity and osteoclastic bone resorption. Conversely, hyperthyroidism is associated with a shorter rebuilding period and a higher bone turnover rate [8]. Osteocytes engage with immune cells in both normal and pathological contexts [9]. The effects of IL-6 on bone metabolism are highly diverse. A particularly noteworthy response is the recognition of IL-6 as a pro-osteoclastic factor that supports osteoclastic processes[10]. IL-11, a member of the IL-6 family, regulates bone metabolism, focusing on osteogenesis and osteoclasis. IL-11's role and mechanisms in bone metabolism have been studied in recent years, and some research has shown that it could be used to treat bone disorders, IL-11 can stimulate osteoclastogenesis via the Jak/STAT pathway, MAPK/PI3K pathway, phosphorylation of Yes-associated protein 1 (YAP1), and a RANKL-independent mechanism [11]. IL-11 modulates osteoblasts, osteoclasts, bone marrow stromal cells, adipose tissue-derived mesenchymal stem cells, and chondrocytes. It participates in bone homeostasis, encompassing osteogenesis, osteolysis, bone marrow hematopoiesis, bone marrow adipogenesis, and bone metastasis [12] .The aim of study is to assess the levels of T4, T3, TSH, STAT3, IL-6, and IL-11 and investigate their association with osteoporosis in premenopausal women.

Method and material

Sample conducted and collection

A case-control study was conducted in Tikrit Teaching Hospital, Tikrit Province, Iraq. Extended from July 2024 to the end of July 2025. Which include 90 females as follows: 60 females with osteoporosis and 30 healthy females as a control group. Five milliliters of blood were drawn from all females and

maintained in the gel tube until they clotted, then centrifuged at 2500 rpm for 15 minutes. The serum was collected and kept at -20 °C until being utilised for T4, T3, TSH, IL-6, IL-11, and STAT3 concentration.

Estimation the T4, T3, TSH, IL-6, IL-11, and STAT3 concentration

ELISA kits (Sunlong-China) were used in the sandwich ELISA system (which is a system that relies on the antigen being sandwiched between antibodies that have been pre-coated on the plate and the HRP enzyme extracted from horseradish peroxidase). Optical density was measured spectrophotometrically at a wavelength of 450 nm. The T4, T3, TSH, IL-6, IL-11, and STAT3 concentration in the samples was calculated by comparing the OD value to the standard curve. Based on the concentrations of standard solutions, which are on the horizontal axis (X), and the absorbance values on the vertical axis (Y), a standard curve was drawn. The absorbance values are then projected onto the curve to determine the concentration of T4 and TSH, measured in pg/ml, and T3, measured in pg/ml. The IL 6, STAT3 measured in ng/ml, IL 11 measured in pg/ml.

Statistical analysis: The statistical study was performed using GraphPad Prism 9.0 and Microsoft Excel 2010 software. P value less than 0.05 were considered significant.

Results:

1. Measurement of T4 levels in women with osteoporosis and the control group

The results for T4 showed that the lowest value was 40.70 ng/ml in the study group and 70.65 ng/ml in the control group. Furthermore, the mean±SD was **74.94±15.08** in the study group, smaller than the control group, with a coefficient of variation of 20.13%, and the mean±SD was **96.70±18.81** in the control group with a coefficient of variation of 19.45%. The result with a highly significant *P* value was <0.0001**, as show in **Figure 1**.

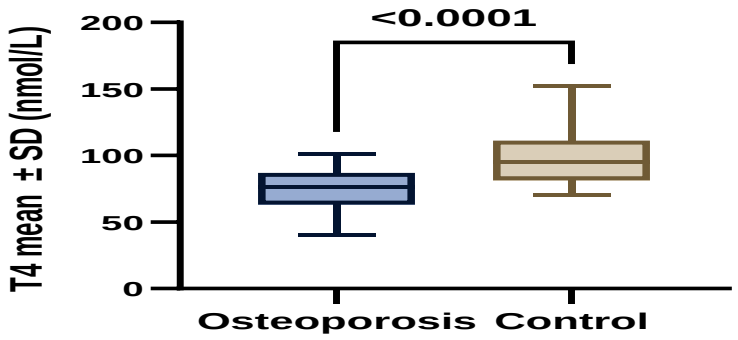

Figure 1: Show the mean ± SD of T4 for women with osteoporosis and the control group, where the result indicates the presence of a significant statistical difference (*P* value < 0.0001**).

2. Measurement of T3 levels in women with osteoporosis and the control group

Figure 2 revealed the results for T3 showed that the lowest result was 1.111 pg/ml in the study group and 1.1711 pg/ml in the control group. Furthermore, the mean±SD was **1.904±0.4082** in the study group, smaller than the control group, with a coefficient of variation of 21.44%, and the mean±SD was **2.265±0.3468** in the control group, with a coefficient of variation of 15.31%. The result with a highly significant *P* value was <0.0001**.

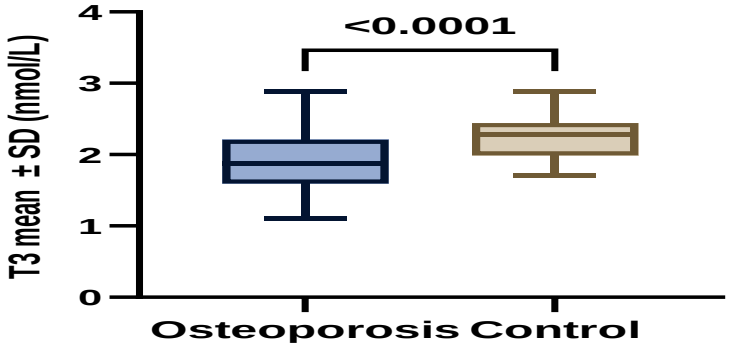

Figure 2: Show the mean ± SD of T3 for women with osteoporosis and the control group, where the result indicates the presence of a significant statistical difference (*P* value < 0.0001**).

3. Measurement of TSH levels in women with osteoporosis and the control group

Figure 3 indicated TSH that the low result was 2.085 pg/ml in the study group and 2.230 pg/ml in the control group. The study group exhibited a mean±SD of **2.066±0.3812**, with a coefficient of variation of 18.45%, whereas the control group demonstrated a mean±SD of **2.252±0.3887**, accompanied by a coefficient of variation of 17.26%. The result a significant *P* value was 0.0326*.

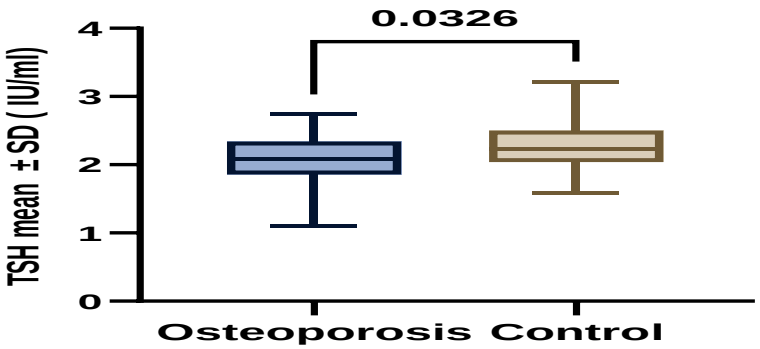

Figure 3: Show the mean ± SD of TSH for women with osteoporosis and the control group, where the result indicates the presence of a significant statistical difference (*P* value < 0.0326*).

4. **Pearson Correlation Coefficient of T4, T3, and TSH for study group and control**

Show the result of the Pearson correlation coefficient between serum T4, T3, and TSH concentrations with osteoporotic patients, where the 95% confidence interval was -0.03223 to 0.4518, -0.5011 to -0.03157, and -0.4692 to 0.01017, respectively, with probabilities of (P value: 0.0860, 0.0283*, and 0.0599, respectively. As shown in **Table 1**.

Table 1: Pearson Correlation Coefficient of T4, T3, and TSH Serum Concentration in Female Patients with Osteoporosis (n=60).

T4	**0.2235**	-0.03223 to 0.4518	0.04996	0.0860 NS
T3	-0.2832	-0.5011 to -0.03157	0.08022	**0.0283***
TSH	-0.2444	-0.4692 to 0.01017	0.05972	0.0599 NS

*:Significant, NS: non-Significant

5. Measurement of STAT3 levels in women with osteoporosis and the control group and sensitivity and specificity.

Figure 4 show the results STAT3 that the lowest result was 10.64 ng/ml in the study group and 11.64 ng/ml in the control group. Also, the mean±SD was **15.59±3.331** in the study group, more than the control group, with a coefficient of variation of 21.36%, and the mean±SD was **14.49±2.134** in the control group with a coefficient of variation of 14.73%. The result was non-significant *P* value was 0.1017NS. The ROC curve for the STAT3 revealed the sensitivity was 59.11%, the specificity was 48.57%, the confidence interval was 0.4422 to 0.6805, the area under curve (AUC) was 0.5614, and the cutoff value was <16.11 ng/ml, with non-significant difference (P=0.3443 NS). As show in **Figure 5.**

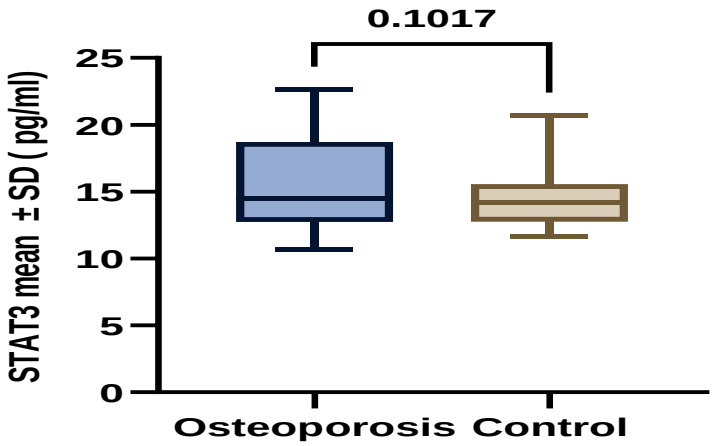

Figure 4: Show the mean ± SD of STAT3 for women with osteoporosis and the control group, the result was non-significant P value was 0.351NS.

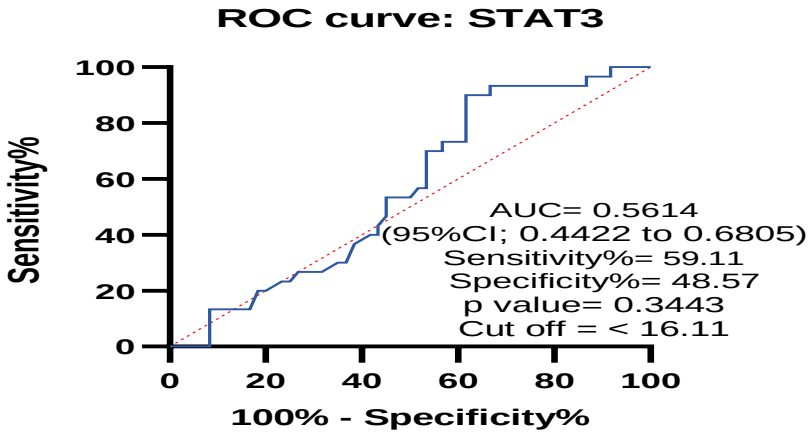

Figure 5: Show the mean ± SD of STAT3 for women with osteoporosis and the control group, the result was non-significant *P* value was 0.3443 NS.

11-Measurement of IL 6 levels in women with osteoporosis and the control group and sensitivity and specificity.

Figure 6 show the results IL6 that the lowest result was 33.47 ng/ml in the study group and 29.93 ng/ml in the control group. Also, the mean±SD was **49.83±6.573** in the study group, higher than the control group, and mean±SD was **46.62±8.192** in the control. The result significant *P* value was 0.0478*. The ROC curve revealed that the IL6 revealed the sensitivity was 57.53%, the specificity was 52.40%, the confidence interval was 0.4992 to 0.7475, the area under curve (AUC) was 0.6233, and the cutoff value was <50.85 ng/ml, with a significant difference (*P*=0.0436). as show in **Figure 7.**

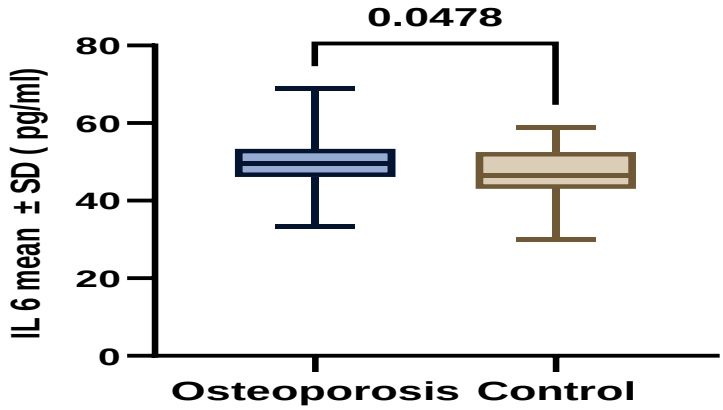

Figure 6: Show the mean ± SD of IL 6 for women with osteoporosis and the control group, the result was a significant *P* value was 0.0478*.

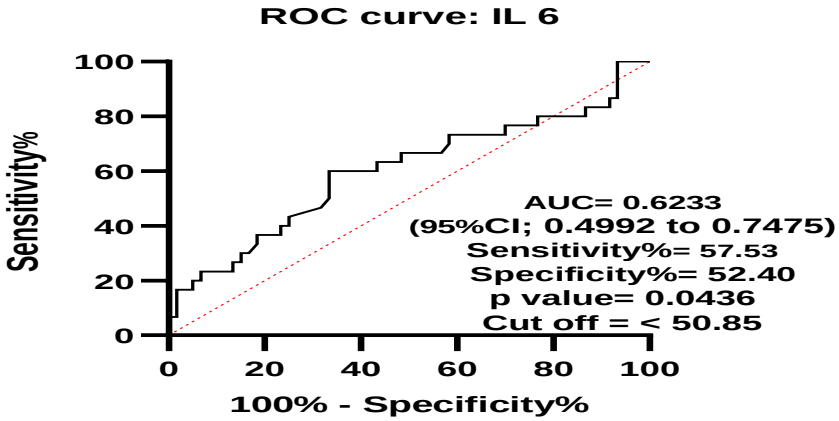

Figure 7 : ROC curve analysis (Wilson/Brown method) Sensitivity% and 1-Specificity %, for IL 6.

6. Measurement of IL11 levels in women with osteoporosis and the control group.

Figure 8 show the results IL11 that the lowest result was 94.92 pg/ml in the study group and 116.7 pg/ml in the control group. Also, the mean±SD was **138.4±28.30** in the study group, smaller than the control group, and mean±SD was **152.0± 29.04** in the control. The result non-significant *P* value was 0.351NS. The ROC curve revealed that the IL11 revealed the sensitivity was 46.79%, the specificity was 58.43%, the confidence interval was 0.5534 to 0.7782, the area under curve (AUC) was 0,6658, and the cutoff value was > 135.6 pg/ml, with a significant difference (*P*=0.0106***). as show in **Figure 9.**

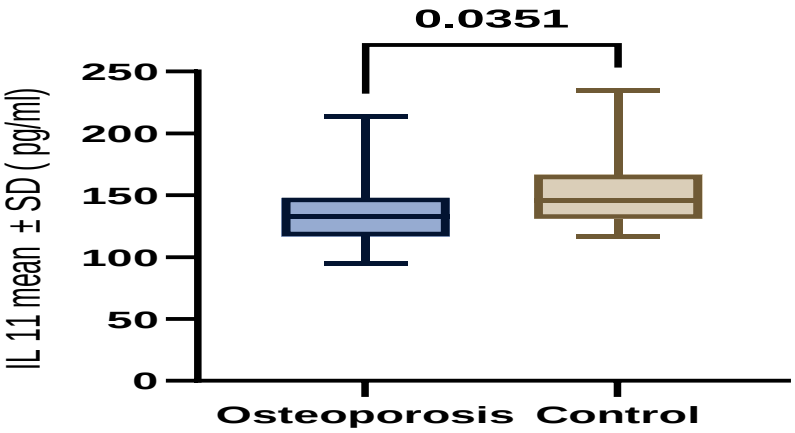

Figure 8: Show the mean ± SD of IL 11 for women with osteoporosis and the control group, the result was non-significant *P* value was 0.351NS.

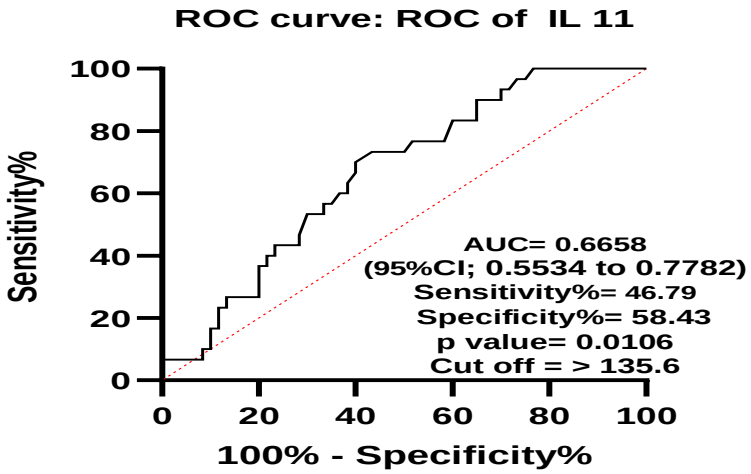

Figure 9 : ROC curve analysis (Wilson/Brown method) Sensitivity% and 1-Specificity %, for IL11.

7. Pearson Correlation Coefficient of STAT3, IL6 and IL11 with patient and control group.

Table 3 shows the Pearson correlation coefficient between serum STAT3, IL6 and IL11 concentrations with bone mineral density in osteoporotic patients, where the 95% confidence interval was -0.3264 to 0.1785, -0.2017 to 0.3047, -0.3808 to 0.1177, respectively, with probability of (*P* value: 0.5485NS, 0.6764NS, 0.2844NS) respectively.

Table 2: Pearson Correlation Coefficient of STAT3, IL6 and IL11 serum concentration with BMD in female patients with osteoporosis (n=60).

STAT3	-0.07901	-0.3264 to 0.1785	0.006242	0.5485 NS
IL 6	**0.05499**	-0.2017 to 0.3047	0.003024	0.6764 NS
IL 11	-0.1405	-0.3808 to 0.1177	0.01973	0.2844 NS

NS: non-Significant

Discussion:

In our current study, we obtained different average results between the study group and the control group, as it was shown that the mean of T4 and T3 in the study group was lower than the mean of the control group, and this difference was highly statistically significant. Also, the mean for TSH in the study group was higher than the mean for the control group. In a study documented by Delitala et al, thyroid hormones are crucial for proper skeletal development and bone metabolism in adults; however, they can adversely affect bone structures in cases of thyroid failure. Untreated severe hyperthyroidism affects bone mass and elevates the risk of high bone turnover osteoporosis. These results were highly statistically significant, indicating that this increase in average weight has a close association with the incidence of osteoporosis in women. The relation between thyroid hormones and bone metabolism is well documented in children with hypothyroidism [7]. Another study conducted that the mean for TSH, T4, and T3 were 1.7 (±1.0) mIU/L, 7.8 (±1.5) µg/dl, and 115.2 (±22.4) ng/dl, respectively [13]. A supplementary function in bone metabolism has been suggested for TSH, as the TSH receptor, primarily found in thyroid follicular cells, has also been identified in other tissues, such as osteoblasts and osteoclasts [14]. Patients with hyperthyroidism, hypothyroidism, autoimmune thyroid disease, or abnormal peripheral thyroid sensitivity should focus on osteoporosis prevention [3]. Normal bone development, bone metabolism, and the formation of peak bone mass all depend on thyroid hormone (T3, T4), an amino acid derivative released by thyroid follicular epithelial cells that promotes human growth and development. The thyroid-stimulating hormone (TSH) axis and associated protein antibodies control the production and secretion of thyroid hormone, and in cases of thyroid dysfunction, aberrant synthesis and secretion of thyroid hormone may have a negative impact on the skeletal system [7]. A study documented that thyroid hormone and pancreatic function were important factors associated with bone metabolism in patients with type 2 diabetes and low T3 syndrome, which may increase the risk of osteoporosis[15]. Through the above studies that focused on the role of thyroid and pituitary hormones, they had a role in bone metabolism and osteoporosis. Our study focused on measuring some interleukins, such as 6 and 11. Our results revealed a discrepancy and difference in the concentration of these interleukins between the study group and the control group. The concentration of interleukin 6 was higher in the study group and statistically significant, and the ROC curve revealed the area under curve (AUC) was 0.6233. As for interleukin 11, the concentration was lower than in the control group, and the ROC curve shows the area under curve (AUC) was 0,6658, and the results were statistically significant. Regarding the results we reached for STAT3, its concentration was higher than in the control group, and ROC curve showed the area under curve (AUC) was 0.5614, but without statistical significance.Interleukin-6 (IL-6) and interleukin-11 (IL-11) are to osteoclast formation and bone resorption. IL-6 and IL-11, which are thought to play a role in several osteolytic bone disorders, are directly capable of inducing osteoclast formation by a RANKL-independent mechanism [16]. IL-11 measurements may serve as biomarkers for evaluating bone turnover and monitoring antiresorptive treatment in postmenopausal osteoporosis [17]. The role of IL-11 in bone metabolism has been discovered earlier, mainly focusing on the regulation of osteogenesis and osteoclasis [12]. Signal transducer and activator of transcription 3 (STAT3) is integral to the interaction between cytokines and kinases, since it binds to downstream gene promoters and participates in various physiologic and pathological processes. Recent data

indicates that STAT3 and its associated network are involved in bone remodeling and the pathogenesis of osteoporosis, suggesting that this factor may serve as a significant target for osteoporosis therapy [18]. These results indicate that these cytokines play a prominent role in osteoporosis.

Conclusion: With very significant p-values (<0.0001), the findings revealed that women with osteoporosis had far lower levels of the thyroid hormones T4 (74.94±15.08 vs. 96.70±18.81) and T3 (1.904±0.4082 vs. 2.265±0.3468) than healthy controls. These results imply that low thyroid hormone levels could be linked to compromised bone metabolism and help to cause osteoporosis. The osteoporotic group also had notably lower TSH values (2.066±0.3812 vs. 2.252±0.3887, P=0.0326), which could suggest changed thyroid function in these individuals. Concerning inflammatory markers, women with osteoporosis had much greater IL-6 levels (49.83±6.573 vs. 46.62±8.192, P=0.0478), hence supporting the influence of chronic inflammation on bone resorption and osteoporosis progression. Though IL-11 levels were not statistically different between groups (P=0.351), STAT3 levels were also not significantly different (P=0.1017), indicating a more constrained relevance for these markers in the setting of osteoporosis in this sample. Ultimately, the findings point to a possible involvement in the development of osteoporosis in women via lower thyroid hormone levels and higher IL-6.

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