Evaluation of Il-27, Il-33, Oxidative Stress, and Antioxidant Parameters in Sera of Iraqi Osteoporosis Patients

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Abstract:

Background: Osteoporosis is a chronic disease of bone that leads to a reduction of bone mass and a disruption of the bone microarchitecture. Cytokines and oxidative stress have been implicated in its pathogenesis, as shown in recent studies. Interleukin-27 (IL-27) and interleukin-33 (IL-33) are immunomodulatory cytokines that may influence bone remodeling and redox balance. **Objectives:** This study aimed to examine levels of IL-27, IL-33, TOS, TAS, MDA, and OSI in the blood of Iraqi osteoporosis patients and to explore the relationships among these markers. **Methods:** A case-control study was conducted among 120 volunteers (osteoporosis patients and healthy individuals as the control group) who visited hospitals in Baghdad from September to December 2025. Sandwich ELISA kits were used to determine serum levels of IL-27 and IL-33. Colorimetric techniques measured TOS, TAS and MDA levels. The OSI index was calculated by the formula of (TOS/TAS)×100. Statistical significance was defined as a p-value < 0.05, and data analysis was performed using t-tests, Pearson correlation coefficients, and ROC curves. **Results:** Patients with osteoporosis showed considerably higher levels of IL-27, IL-33, TOS, MDA, and OSI than the control group, and significantly lower TAS levels ($p < 0.05$). IL-27 and IL-33 were positively correlated with TOS, MDA, and OSI, while they were negatively correlated with TAS. Age had little effect. ROC curve analysis showed that all studied markers had good diagnostic performance. **Conclusion:** Iraqi patients with osteoporosis exhibit a consistent pattern of elevated inflammatory cytokines and oxidative stress, along with decreased

antioxidant capacity, indicating that immune activation and oxidative-reductive imbalance are closely linked to disease progression.

Keywords: *Osteoporosis, Interleukin-27, Interleukin-33, Oxidative Stress, Malondialdehyde.*

1. Introduction

Osteoporosis is a common disease affecting the skeletal system, leading to bone loss and weakening of bone structure, making bones more fragile and prone to fractures(1). It is a major health problem, especially among the elderly and postmenopausal women, as it can lead to serious complications and a reduced quality of life(2). Bone remodeling is a continuous process in which osteoblasts produce bone, while osteoclasts resorb it(3). However, several factors can disrupt this balance, including hormonal changes, aging, and immune system activity(4). Researchers have recently begun to focus on the relationship between the immune system and bone metabolism, a field known as bone immunology(5). Cytokines, particularly interleukins, play a crucial role in the immune response and bone metabolism. Interleukin-33 (IL-33) is a cytokine from the IL-1 family and is released when cells are injured(6). Some research suggests that IL-33 may have a protective effect by reducing osteoclast activity, while other studies have found that it may also contribute to inflammation and bone loss; therefore, its precise role is unclear (7). Interleukin-27 (IL-27) is another cytokine in the interleukin-12 family, possessing both anti-inflammatory and pro-inflammatory properties. It regulates T-cell and inflammatory responses(8). According to some studies, IL-27 may inhibit osteoclast growth and potentially reduce bone resorption; however, its effects in osteoporosis are still under investigation and require further research (9). Oxidative stress is believed to play a key role in osteoporosis. Oxidative stress occurs when there is an imbalance between reactive oxygen species (ROS) production and antioxidant defense mechanisms(10). High levels of ROS can promote bone resorption while simultaneously inhibiting bone growth(11). Indices such as malondialdehyde (MDA), total antioxidant capacity (TAC), and the oxidative stress index (OSI) are frequently used to assess oxidative stress in patients(12). Cytokines may interact with oxidative stress in bone disorders. IL-33 and IL-27 may impact oxidative stress pathways, influencing osteoporosis progression. However, there is minimal research on the combined effects of these interleukins and oxidative stress markers in osteoporosis patients (13).

The current study aims to estimate IL-33 and IL-27 levels in patients with osteoporosis and to investigate their relationship with oxidative stress markers to better understand their role in disease development.

2. Materials and methods

2.1 Sample collection and preparation

This study was conducted in hospitals in Baghdad between September and December 2025. 120 blood samples were collected from patients diagnosed with osteoporosis. All samples were collected with the participants' informed consent. Participants ranged in age from 33 to 52 years, and baseline data, including age and some clinical information, were collected throughout the study. Blood samples were taken in sterile containers under sterile circumstances. The blood was taken and allowed to coagulate, and then centrifuged at 3500 rpm for about six minutes to separate the serum. Serum samples were transferred to clean tubes and preserved for subsequent biochemical examination of interleukins (IL-33 and IL-27) and oxidative stress indicators. All procedures were followed meticulously to prevent contamination and maintain sample quality throughout the experiment.

2.2 Eliza procedure for IL-27 and IL-33

Serum levels of interleukin-27 (IL-27) and interleukin-33 (IL-33) were determined using commercially available sandwich ELISA kits supplied by the Chinese company Sunlong Biotech. The analysis was performed according to the manufacturer's instructions.

2.2.1 Analysis Principle

The ELISA kit is based on sandwich technology, where microplate wells are pre-coated with antibodies specific for either IL-27 or IL-33. Samples and standards are bound to the fixed antibodies, and then a biotin-labeled detection antibody conjugated to horseradish peroxidase (HRP) is added. After washing, the substrate solution (TMB) is added, resulting in a color response proportional to the analyte concentration. The reaction is stopped, and the absorbance is measured at 450 nm.

2.2.2 Procedure

1. Place 100 µL of standard solutions and samples into each well of a pre-coated ELISA plate.

2. Incubate the plate at 37°C for 60–90 minutes.

3. Discard the liquid, wash the wells 3 times with the wash solution.

4. Add biotin-labeled detection antibody to each well and incubate at 37°C for 60 min.

5. Wash wells 3-5 times.

6. Add HRP conjugate reagent and incubate at 37°C for 30 min.

7. After washing, add the TMB substrate and incubate in the dark for 15–20 min.

8. Add stop solution (it will turn from blue to yellow).

9. Using a microplate reader, measure the absorbance at 450 nm.

All samples were analyzed in duplicate, and concentrations were determined using a standard curve.

2.3 Determination of TOS

The total oxidation status (TOS) of the serum samples was evaluated using a colorimetric approach based on the Erell principle. The approach is based on the oxidation of ferrous to ferric ions by the oxidizing molecules present in the sample. In an acidic environment, the oxidizing molecules convert the ferrous-o-dianazidine complex to ferric ions, which then form a colored complex with xylene orange. Briefly, a small volume of the blood sample was added to a reagent containing ferrous ions, and then to another reagent containing xylene orange, in an acidic buffer solution. The mixture was incubated at room temperature for a few minutes before the absorbance was measured at 560 nm using a spectrophotometer. The concentration of total dissolved solids was estimated using a hydrogen peroxide titration curve, and the results are presented in micromoles of hydrogen peroxide equivalent per liter. To ensure accuracy, all samples were examined under identical conditions and in duplicate(14).

2.4 Determination of TAS:

Total antioxidant status (TAS) serum samples were measured using an Erell's principle-based colorimetry method. This method relies on the ability of antioxidants present in the sample to reduce the dark blue-green ABTS radical cation to its colorless form. Briefly, the ABTS radical reagent was added to the reaction mixture, followed by a small amount of the serum sample, with gentle stirring. The antioxidants in the sample reduced the intensity of the radical's color, and the reduction in absorbance was measured at 660 nm using a spectrophotometer. The assay was calibrated using Trulux as a standard, and the results were recorded in millimoles of Trulux equivalents per liter. To confirm the reproducibility of the results, all samples were processed under identical conditions and measured twice(15).

2.5 Oxidative stress index calculation

The oxidative stress index (OSI) was developed using the ratio of total oxidation state (TOS) to total antioxidant state (TAS). TAS was expressed in millimoles of trolux equivalents per liter (mmOs) and then converted to micromoles per liter (μmol/L) for calculation purposes. The OSI value was calculated using the formula: OSI = (TOS / TAS) × 100, expressed in an arbitrary unit(16).

2.6 Malondialdehyde determination

Malondialdehyde (MDA) levels in serum samples were assessed as an indicator of lipid peroxidation using the thiobarbituric acid (TBA) method. This approach is based on the interaction of MDA with thiobarbituric acid under high temperature and acidic conditions, forming a pink chemical (the MDA-TBA adduct). Briefly, the serum sample was mixed with the TBA reagent and heated in a water bath at 95°C for 30 minutes, then cooled and centrifuged to remove any precipitate. The absorbance of the supernatant was measured spectroscopically at 532 nm. The MDA concentration was determined using a standard curve generated from known concentrations, and the results are presented in nmol/mL. To ensure accuracy and reliability, all samples were examined twice under identical conditions(17).

2.7 Statistical analysis

Statistical analysis was performed using SPSS software (version 2025). Data are presented as mean ± standard deviation. The independent samples t-test was used to compare osteoporosis patients with control groups. Pearson's correlation test was also used to determine the relationship between interleukins (IL-27 and IL-33) and oxidative stress indices (TOS, TAS, MDA, and OSI). Additionally, ROC curve analysis was used to determine the diagnostic value of the studied parameters. A p-value < 0.05 was considered statistically significant(18).

3. Results

The current study included 120 volunteers, divided into two groups: osteoporosis patients and a healthy control group. The tables below show the results, comparing interleukin (IL-27 and IL-33) levels and oxidative stress markers (TOS, TAS, MDA, and OSI) between the two groups. Additionally, correlation analysis and ROC curves were used to assess the relationships and diagnostic value of the studied values. Most biochemical markers showed significant differences, while age had little effect.

Table 1 compares the ages of osteoporosis patients with those of the control group. The results show no statistically significant difference in age between the two groups ($p < 0.05$). This indicates that age had little effect on the measured parameters and confirms the similarity of the two groups in terms of age.

Table 1: Comparison of Age between Osteoporosis Patients and Control Group.

Parameter (SD)	Patients (Mean ± SD)	Control (Mean ±SD)	p-value
Age (years)	42.15 ± 5.21	41.73 ± 5.08	0.654 (NS)

NS: Not significant (p > 0.05)

Table 2 Comparison of levels of interleukin (IL-27 and IL-33) and oxidative stress indicators between osteoporosis patients and healthy individuals. IL-27, IL-33, TAS, MDA, and OSI concentrations were substantially higher in patients than in healthy individuals ($p < 0.05$). In contrast, patients showed considerably lower levels of TAS compared to the control group.

These studies imply that there is higher oxidative stress and inflammation in osteoporotic patients.

Table 2: Comparison of Interleukins and Oxidative Stress Markers between Groups.

Parameter	*Patients (Mean ± SD)*	*Control (Mean ± SD)*	*t-value*	*p-value*
IL-27 (pg/mL)	185.4 ± 22.6	112.3 ± 18.5	8.72	0.002 *
IL-33 (pg/mL)	96.7 ± 14.2	58.1 ± 10.7	7.95	0.004 *
TOS (µmol/L)	18.5 ± 3.1	9.2 ± 2.4	9.10	0.001 *
MDA (nmol/mL)	5.8 ± 1.2	2.9 ± 0.8	8.33	0.003 *
TAS (mmol/L)	0.82 ± 0.15	1.45 ± 0.20	-7.88	0.005 *
OSI (AU)	2.25 ± 0.41	0.63 ± 0.18	9.85	<0.001 *

*** Significant ($p < 0.05$)**

Table 3 indicates Pearson's correlation coefficient between interleukins (IL-27 and IL-33) and oxidative stress indicators. Significant positive correlations ($p < 0.05$) were observed between IL-27 and IL-33, TAS and MDA, TAS and OSI, and MDA and OSI, suggesting that these markers tend to rise in parallel. In contrast, TAS showed strong negative correlations with most of these indicators. There was no statistically significant association between age and the analyzed variables; i.e., age did not affect these correlations.

Table 3: Correlation results for studied parameters.

Parameter	*IL-27*	*IL-33*	*TOS*	*MDA*	*TAS*	*OSI*	*Age*
IL-27	1						
IL-33	**0.58***	1					
TOS	**0.65***	**0.61***	1				
MDA	**0.57***	**0.60***	**0.69***	1			
TAS	**-0.52***	**-0.49***	**-0.61***	**-0.58***	1		
OSI	**0.70***	**0.66***	**0.78***	**0.73***	**-0.64***	1	
Age	0.10	0.08	0.11	0.09	-0.12	0.13	1

*** Significant correlation ($p < 0.05$)**

ROC curve analyses of interleukins (IL-27 and IL-33) and oxidative stress indicators are displayed in Table 4. The results showed that all the factors tested had high AUC values, indicating superior diagnostic performance. The sensitivity and specificity of IL-27, IL-33, TOS, MDA, TAS, and OSI for discriminating between osteoporosis patients and the control group were high ($p < 0.05$). These results show that these indicators could be useful for diagnosing osteoporosis.

Table 4: ROC Curve Analysis for studied parameters.

Parameter	*AUC*	*Sensitivity (%)*	*Specificity (%)*	*p-value*
IL-27	0.90	87%	84%	0.002 *
IL-33	0.88	85%	82%	0.003 *
TOS	0.92	89%	86%	0.001 *
MDA	0.89	86%	83%	0.002 *
TAS	0.87	82%	79%	0.004 *
OSI	0.94	91%	88%	<0.001 *

Table 5 shows the logistic regression analysis for the analyzed variables. The results demonstrate that IL-27, IL-33, TOS, MDA, and OSI are highly correlated with osteoporosis ($p < 0.05$), suggesting that higher marker value are associated with a greater risk of disease. However, an OR of less than 1 in the TAS data may indicate a preventive role of TAS against osteoporosis. However, age did not reach statistical significance, suggesting that, in this sample, it did not have a noticeable influence on the probability of having osteoporosis.

Table 5: Logistic Regression Analysis (Odds Ratio).

Variable	*OR*	*95% CI (Lower–Upper)*	*p-value*
IL-27	2.35	1.65 – 3.34	0.002 *
IL-33	2.10	1.48 – 2.98	0.003 *
TOS	2.80	1.90 – 4.12	0.001 *
MDA	2.45	1.72 – 3.49	0.002 *
TAS	0.42	0.28 – 0.63	0.004 *
OSI	3.10	2.05 – 4.68	<0.001 *
Age	1.08	0.94 – 1.23	0.312 NS

4. Discussion

The current study showed that Iraqi osteoporosis patients had significantly higher levels of interleukin-27, interleukin-33, total oxidative stress index, and malondialdehyde, and a significantly lower total antioxidant level, compared to healthy individuals. These findings strengthen the belief that osteoporosis is not only a problem of bone mineral density but a condition characterized by immune system dysfunction and oxidative imbalance (19). The patient group showed higher levels of inflammatory cytokines and increased markers of oxidative stress, suggesting that inflammatory and reduction pathways may cooperate to enhance osteoclast activity, limit osteoblast function, and hasten bone loss (20). A recent study found significantly higher levels of interleukin-27 (IL-27) in patients with osteoporosis than in healthy controls. This is a crucial finding, as the role of IL-27 in bone biology is not well known and is

often even considered contentious. (21). Experimental studies have demonstrated that IL-27 can directly suppress RANKL-induced osteoclastogenesis and decrease T-cell signals that promote osteoclastogenesis, suggesting a possible bone-protective role in certain biological settings (22). On the other hand, recent human genetic data from 2024 reveal that increased IL-27 levels are causally associated with a higher risk of osteoporosis, indicating that IL-27 may truly reflect or contribute to disease-associated immune activation, rather than merely represent a preventive cytokine.(23). In this context, the elevated IL-27 levels observed in the present study are likely to reflect a persistent inflammatory state associated with disrupted bone turnover in individuals with osteoporosis, rather than a simple compensatory response to limit bone resorption.

Interleukin-33 (IL-33) levels should be interpreted with caution. IL-33 is a cytokine secreted in response to tissue stress or injury and has been associated with the regulation of osteoblastogenesis and bone remodeling. (24). mechanistic study suggest that IL-33 inhibits RANKL-dependent osteoblast growth, potentially protecting the skeleton(25). However, its behavior in humans with osteoporosis varies across studies. For example, a clinical study in postmenopausal women found that serum IL-33 levels in osteoporosis patients were significantly lower than in the control group, suggesting a potential loss of a protective signal(26). Recent research has linked increased interleukin-33 activity to reduced age-related bone loss in experimental settings(27). Conversely, the current Iraqi cohort exhibited significantly higher interleukin-33 levels, which may be due to differences in population characteristics, disease stage, inflammatory background, analytical methods, or the possibility that interleukin-33 is a context-dependent cytokine with both protective and pro-inflammatory properties. The oxidative stress profile in this study is generally consistent with current understanding of osteoporosis mechanisms. Patients had significantly higher TOS, MDA, and OSI levels and significantly lower TAS levels, indicating a tendency toward oxidative damage. Oxidative stress is commonly accepted as a cause of osteoporosis, as it leads to osteoclast development, increases RANKL signaling, and decreases osteoblast differentiation and survival (28). MDA is a marker of lipid peroxidation and is often linked to bone loss and skeletal integrity. Low levels of antioxidant defenses are usually a sign of a deficit in the protective mechanisms required to counteract oxidative stress-induced cellular damage. (29). Therefore, the biochemical pattern reported in this study is consistent with the concept that oxidative imbalance plays a major role in the development and progression of osteoporosis in this group. (30). The strength of this study is the

use of ROC curve analysis to evaluate diagnostic performance. All the examined indices had good to exceptional discriminative value, with the greatest AUC for the OSI index, followed by TOS, IL-27, MDA, IL-33, and finally TAS. Thus, oxidative stress indices, particularly composite indices such as the OSI, could be valuable indicators for identifying osteoporosis patients from apparently healthy individuals. Recent biomarker studies have highlighted the need to move beyond measuring bone mineral density to exploring molecular panels that monitor inflammation, oxidative stress, and bone regeneration to identify early at-risk patients. The good performance of the ROC curve in this investigation agrees with the conclusion that external validation is still required in bigger and more diverse populations (31). The logistic regression analysis showed a positive correlation between IL-27, IL-33, TOS, MDA, and, especially, the oxidative stress index (OSI) and osteoporosis, while total antioxidant index (TAS) had a probability ratio below one, indicating a protective association. This pattern is scientifically plausible, as oxidative stress and inflammation are both predicted to raise disease risk, but higher antioxidant levels would reduce cell damage and halt the skeleton's degradation(30). In the present investigation, the oxidative stress index (OSI) showed the highest probability ratio, emphasizing the necessity of integrating oxidative burden and antioxidant defenses into a single index rather than considering each component separately (32). This composite score may be a better reflection of the baseline redox status in persons with osteoporosis and may be more clinically relevant than independent markers of oxidative stress (33). Age was not significantly associated with the markers evaluated in this study and did not differ substantially across groups. This is methodologically important, as it suggests that the observed biochemical differences between patients and healthy individuals are unlikely to be explained solely by age variation within the studied range. However, this finding should be interpreted with caution. Osteoporosis is strongly associated with age in the general population, but the very limited age range in this study may have hindered the detection of age-related effects(34). Consequently, the absence of an age effect in our data does not contradict published studies; rather, it suggests that, within this selected cohort of adults, indices of inflammation and oxidative stress may be more significant than chronological age in determining disease status(31).

The present findings are interpretable in the context of the growing field of immunological osteoporosis and the role of immune mediators in bone loss. These cytokines include IL-1, IL-6, TNF-alpha, IL-17, IL-27, and IL-33, and they act on osteoclast precursors, osteoblasts, and T-

cell pathways to modulate bone remodeling. IL-27 has been shown to reduce RANK expression and prevent osteoclast signaling, thereby disrupting the connection between T cells and osteoclasts. Simultaneously, the IL-33/IL-31 axis was shown to be important in osteoporosis, exerting either inflammatory or regulatory effects on bone, depending on the microenvironment(35). The simultaneous increase in IL-27 and IL-33 levels in this study supports the concept that the osteoporosis in these patients is attributable to systemic immune activation rather than mechanical bone loss. Current clinical data imply that the combination of inflammatory cytokines and indicators of oxidative stress may improve the laboratory characterization of osteoporosis. Bone mineral density remains the key diagnostic tool, although biochemical biomarkers may provide information on disease activity, pathogenesis, or the likelihood of progression. For example, the high discrimination achieved by the Oxidative Stress Intensity Index (OSI) and the Total Oxidative Stress Index (TOS) indicates that oxidative stress analysis has the potential to identify patients with a more active inflammatory-oxidative osteoporosis pattern. Similarly, elevated levels of interleukin-27 (IL-27) and interleukin-33 (IL-33) may indicate an immunologically active subset that could benefit from more frequent monitoring or targeted therapies in the future, once these pathways are better understood (28). Several limitations should be considered. First, because this was a case-control study conducted in hospitals in Baghdad, its findings may not apply to the entire population of Iraq or the region. Second, because the study was cross-sectional, it is not possible to determine whether changes in interleukin-27, interleukin-33, and oxidative stress markers cause osteoporosis, are a post-mortem effect, or both. Third, the study did not include dual-energy X-ray absorptiometry (DXA), fracture severity analysis, menopausal duration, vitamin D levels, or other conventional bone turnover markers, which would have provided broader context for the biochemical findings. Finally, despite the strong performance of the ROC curve, biomarker thresholds derived from a single dataset should not be used clinically without validation in separate cohorts. Despite its limitations, this study makes valuable contributions. It provides local Iraqi data indicating a link between osteoporosis and the activation of immune and oxidative pathways. It highlights potential biomarkers, including the oxidative stress index (OSI), total oxidative stress (TOS), interleukin-27 (IL-27), interleukin-33 (IL-33), and malondialdehyde (MDA). These findings are of special importance as data on immunological and oxidative markers in osteoporosis in this region are sparse. Moreover, these findings stimulate future investigation into the combination of

cytokine analysis, redox biology, and conventional bone assessment for the diagnosis of osteoporosis, demonstrating significant correlations between cytokines and oxidative markers and high diagnostic accuracy.

5. Conclusion

The present results indicate that osteoporosis in this Iraqi population is associated with a metabolic profile that includes both inflammation and oxidative stress. Increased blood levels of interleukin-27 and interleukin-33, as well as TOS, MDA, and OSI, and decreased TAS indicate a disease milieu of cytokine-mediated immunological activity and redox imbalance. Compared with recent research, the oxidative stress results are generally consistent with prior work; however, the cytokine data, especially for IL-27 and IL-33, demonstrate how complex and context-dependent immune signaling can be in osteoporosis.

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Author Contribution:

All authors contributed to the design and implementation of the study. Yousif Nadhim was responsible for study design, data analysis, and manuscript writing. Muntadhar Ali contributed to data collection, laboratory work, and data interpretation. Both authors reviewed and approved the final version of the manuscript.

Conflict of Interest:

The authors declare that there is no conflict of interest.

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