# A comparative study of biochemical variables among obese women with and without osteoporosis

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## Abstract

**Background and aims:** Osteoporosis is a global health priority characterized by low bone mineral density. While historically associated with aging, its rising prevalence suggests a complex multifactorial origin. This study aimed to evaluate specific biochemical variables in obese women to determine if increased body mass provides protection against bone loss. The research compared bone metabolism markers across three categories: obese women with osteoporosis, those with osteopenia, and healthy obese controls. **Methods:** The study involved 120 obese women (Mean BMI: 31.02–33.55), categorized into three groups based on DEXA scan results. Researchers analyzed various biochemical markers, including Osteoprotegerin (OPG), Aromatase (ARO), Progesterone (P4), Testosterone (T), and Alkaline Phosphatase (ALP). Additionally, serum levels of Calcium (Ca), Magnesium (Mg), and Phosphorus (P) were measured alongside their respective ratios. **Results and Conclusions:** Significant findings included a sharp decline in OPG levels in the osteoporosis group ($p<0.001$). Aromatase and Progesterone also showed highly significant variances between healthy controls and those with bone density loss ($p<0.001$). While T, ALP, and Ca differed between the control and osteoporosis groups, Mg and P levels remained stable across all subjects. The study concludes that osteoporosis is increasingly prevalent and independent of age-related decline alone. Crucially, the results show that osteoporosis and osteopenia can occur in women despite increased body mass, suggesting that obesity alone may not be enough to prevent decreased bone mineral density, thus highlighting the need for regular and thorough screenings for this age group.

***Keywords:*** *Bone Mineral Density, Osteoporosis, Osteopenia, OPG, ARO, P4.*

## 1. Introduction

As a systemic skeletal disorder, osteoporosis is defined by a decline in bone mass and the structural degradation of bone tissue, which substantially elevates fracture risk (1, 2).Driven by dysfunctional bone cell activity, this chronic and progressive metabolic condition is often termed the "silent epidemic" because it typically remains asymptomatic until clinical complications arise (3). Current World Health Organization data underscores the severity of this public health challenge, indicating that osteoporosis affects roughly 21.2% of women and 6.3% of men over the age of 50 (4). The pathogenesis of osteoporosis is rooted in a metabolic imbalance where osteoclast-mediated bone resorption outpaces osteoblast-driven bone formation, disrupting the dynamic equilibrium necessary for skeletal maintenance (5). Etiologically, the disease is categorized into primary and secondary forms; primary osteoporosis is typically associated with aging in individuals over 50, with its most frequent manifestation being postmenopausal osteoporosis triggered by the physiological depletion of estrogen. In contrast, secondary osteoporosis arises from specific underlying medical conditions or pharmacological interventions that adversely affect bone mineral density (3, 6). Osteoprotegerin (OPG), a secreted glycoprotein within the tumor necrosis factor receptor (TNFSF) superfamily, serves as a pivotal regulator of bone homeostasis, inflammation, and cellular differentiation (7, 8). Encoded on chromosome 8q23-24 and lacking a transmembrane domain, OPG is synthesized by various bone marrow cells, including osteoblasts, and functions primarily to prevent excessive bone resorption (9, 10). It maintains skeletal integrity by acting as a decoy receptor that binds to the receptor activator of nuclear factor-kappa B ligand (RANKL), thereby neutralizing the RANK/RANKL signaling pathway; this interaction effectively inhibits osteoclast maturation and activation while promoting bone formation (9, 11). Beyond its role in bone remodeling, OPG also interacts with the TNF-related apoptosis-inducing ligand (TRAIL), blocking its binding to death receptors and subsequently suppressing TRAIL-mediated apoptosis (9). Aromatase is a pivotal enzyme in the biosynthetic pathway of estrogen, facilitating the conversion of C19 androgens into C18 phenolic estrogens through the demethylation of the C19 carbon atom (12). Supported by the flavin-dependent enzyme cytochrome P450 NADPH reductase, aromatase eliminates the methyl group from substrates such as testosterone to produce estradiol and estrone (13, 14). This enzymatic process is

essential for reproductive health and is a primary therapeutic target in managing estrogen-dependent pathologies, such as endometriosis, uterine fibroids, and certain cancers. The expression of aromatase is widespread, occurring in various tissues including the brain, endocrine glands, and the placenta during pregnancy, and its activity fluctuates throughout puberty and developmental growth stages (12).

Progesterone, chemically identified as pregn-4-ene-3,20-dione or P4, is a principal steroid hormone synthesized naturally within the human body. As one of the most prevalent hormones released by the gonads, it is primarily secreted by the ovaries, testes, and adrenal cortex, though it is also produced within the central nervous system, including the brain and spinal cord. The biosynthesis of progesterone from cholesterol is mediated by specific enzymes located in microglia, neurons, and glial cells (15, 16). Functioning as the physiological partner to estradiol, progesterone plays an essential role in skeletal maintenance by activating osteoblasts and progesterone receptors to stimulate the synthesis of new bone tissue. While estradiol primarily serves to suppress bone resorption, progesterone facilitates bone formation; thus, the synergy between these two hormones is fundamental to maintaining bone homeostasis and long-term skeletal integrity (17). The primary objective of this research was to examine specific biochemical variables in obese women to determine if elevated body mass serves as a protective factor against the depletion of bone mineral density. To investigate this, the study compared various bone metabolism markers specifically Osteoprotegerin (OPG), Aromatase (ARO), Progesterone (P4), Testosterone (T), and Alkaline Phosphatase (ALP) across three cohorts: obese women with osteoporosis, those with osteopenia, and healthy obese controls. By analyzing these hormonal and enzymatic profiles alongside essential minerals like Calcium, Magnesium, and Phosphorus, the study aimed to clarify the complex relationship between obesity and bone health.

## 2. Materials and methods

### 2.1 Patients and Controls

To investigate the research hypotheses, 120 women were included and divided into three distinct groups of 40 participants each: an osteoporosis group (ages 37–65), an osteopenia group (ages 30–65), and a healthy control group (ages 30–63). The study included both premenopausal and postmenopausal women the hormonal and reproductive status of the study participants was determined, and age and medical history were used to classify the participants. In premenopausal women, the phase of their menstrual cycle was considered when blood

samples were drawn to minimize the influence of hormonal changes. Stringent exclusion criteria were applied to eliminate confounding factors, disqualifying individuals with thyroid dysfunction, malignancy, autoimmune disorders (such as rheumatoid arthritis or systemic lupus erythematosus), chronic respiratory or renal failure, and those with a history of alcohol consumption or smoking. Furthermore, pregnant women and patients receiving hormone therapy were excluded from the study. Prior to participation, all participants provided informed consent, and the study protocol received ethical clearance from the Ethics Committee of the College of Science at Al-Mustansiriya University. Biological samples were obtained at Al-Wasiti Hospital in Baghdad during a two-month window beginning in October 2025.

### 2.2 Bone Condition Assessment

According to the DEXA scan, this is the most accurate method for determining bone mineral density. It is considered the gold standard for diagnosis and an indicator of fracture risk. Bone mineral density (BMD) was assessed using a STRATOS Dual-Energy X-ray Absorptiometry (DEXA) scanner. Measurements were performed at the lumbar spine region. Samples were divided into three groups based on the World Health Organization classification: (1) Normal: BMD greater than -1 SD (T-score), (2) Osteopenia: BMD between -1 and -2.5 SD (T-score), and (3) Osteoporosis: BMD less than -2.5 SD (T-score) (3).

### 2.3 Blood Analysis

To analyze the biochemical markers, venous blood was collected from all participants and separated to obtain serum, which was used to investigate the effects of osteoprotegerin (OPG) and aromatase (ARO) using a sandwich ELISA kit (SUNLONG BIOTECH, China). Testosterone (T) was analyzed using the competitive ELISA (DRG, Germany). All ELISA measurements were performed according to the manufacturer's instructions. Additionally, progesterone (P4) was analyzed using automated spectrophotometry (Abbott Diagnostics, USA, using the Architect Plus i1000SR). This is a one-step immunoassay to detect the presence of progesterone in human serum using CMIA micro-immunoassay technology. ALP was analyzed using automated spectrophotometry (Abbott Diagnostics, USA, Architect Plus C4000 Analyzer). Furthermore, ionization (calcium (Ca), magnesium (Mg), phosphorus (P), calcium/magnesium ratio (Ca/Mg), and calcium/phosphorus ratio (Ca/P)) was analyzed using automated spectrophotometry (Abbott Diagnostics, USA, Architect Plus C4000 Analyzer). The tests were conducted according to the manufacturer's instructions, and the results were

expressed in their standard units approved for each test. Serum samples stored in aliquots at -20°C prior to analysis.

### 2.4 Statistical Analysis

All analyses were performed using SPSS version 26. Statistical analysis was performed between the control group, the osteoporosis group, and the osteopenia group using one-way ANOVA and Pearson's correlation coefficient (r) to find the relationship between all the study variables.

## 3. Results

Analysis data revealed that age differed significantly across the three study cohorts. While hip circumference also showed statistical significance, other physical metrics including body mass index (BMI), waist circumference, and the waist-to-hip ratio demonstrated no significant differences between the groups (Table 1).

**Table 1: Distribution of mean age, BMI, and anthropometric measurements.**

| Parameter | Control | Osteopenia | Osteoporosis | P-Value |
|---|---|---|---|---|
| **Age (year)** | 43.87 ± 8.159 | 49.57 ± 11.21 | 59.13 ± 9.63 | $< 0.05^{*\#\alpha}$ |
| **BMI (kg/m²)** | 33.55 ± 5.547 | 31.64 ± 5.54 | 31.02 ±13.38 | $NS^{*\#\alpha}$ |
| **Waist (cm)** | 106.57 ± 11.94 | 103.42 ± 13.07 | 106.45 ± 12.05 | $NS^{*\#\alpha}$ |
| **Hip (cm)** | 116.95 ± 10.19 | 111.17 ± 17.014 | 110.47 ± 11.59 | $< 0.05^{\#}$ |
| **Waist/Hip** | 0.912 ± 0.071 | 0.9462 ± 0.144 | 0.96 ± .079 | $NS^{*\#\alpha}$ |

**All values are mean ± SD. * p-value for control versus osteopenia cases. #p-value control versus osteoporosis cases. α p-value for osteopenia versus osteoporosis cases. NS; Nonsignificant. BMI (Bone Mass Index)**

Biochemical analysis revealed that OPG concentrations were significantly reduced in both the osteoporosis and osteopenia groups relative to the healthy controls ($p<0.001$). While significant variances were observed between the control and each of the bone-loss groups, OPG levels did not differ significantly between patients with osteopenia and those with osteoporosis. Similarly, P4 levels were markedly lower in both affected groups compared to controls ($p<0.001$). Although ARO levels appeared higher in the osteoporosis group than in

the control group, this increase did not reach statistical significance. Furthermore, a marginal decline in T levels was noted in the osteoporosis and osteopenia cohorts compared to the control group.

Regarding enzymatic and ionic markers, ALP activity was elevated in the osteopenia and osteoporosis groups; statistical significance was confirmed between the control and osteoporosis groups, as well as between the two bone-loss categories. Serum levels of Ca, Mg, and P were also higher in the osteopenia and osteoporosis groups than in the controls. However, while Ca concentrations showed a statistically significant increase in both affected groups ($p<0.05$), the fluctuations in Mg and P levels across the three cohorts were not statistically significant.

**Table 2: Statistical distribution of studied biochemical parameters level in serum.**

| Parameter | Control | Osteopenia | Osteoporosis | P-value |
|---|---|---|---|---|
| **Number** | 40 | 40 | 40 | - |
| **OPG (pg/ml)** | 603.36 ± 133.4 | 506.98 ± 99.59 | 498.49 ± 58.86 | $< 0.001^{*\#}$ |
| **ARO (ng/ml)** | 3.102 ± 0.413 | 2.782 ± 0.305 | 3.15 ± 1.136 | $< 0.05^{*\alpha}$ |
| **P4 (nmol/L)** | 0.91 ± 0.776 | 0.423 ± 0.28 | 0.345 ± 0.113 | $< 0.001^{*\#}$ |
| **T (ng/ml)** | 0.386 ± 0.144 | 0.38 ± 0.097 | 0.325 ± 0.084 | $< 0.05^{\#\alpha}$ |
| **ALP (U/L)** | 95.9 ± 31.52 | 96.9 ± 22.8 | 111.31 ± 27.58 | $< 0.05^{\#\alpha}$ |
| **Ca (mg/dl)** | 8.98 ± 0.268 | 9.21 ± 0.398 | 9.29 ± 0.502 | $< 0.05^{*\#}$ |
| **Mg (mg/dl)** | 1.866 ± 0.143 | 1.923 ± 0.145 | 1.901 ± 0.148 | $NS^{*\#\alpha}$ |
| **P (mg/dl)** | 3.213 ± 0.424 | 3.305 ± 0.519 | 3.34 ± 0.47 | $NS^{*\#\alpha}$ |
| **Ca/Mg** | 4.840 ± 0.397 | 4.809 ± 0.339 | 4.914 ± 0.443 | $NS^{*\#\alpha}$ |
| **Ca/P** | 2.847 ± 0.421 | 2.845 ± 0.396 | 2.840 ± 0.480 | $NS^{*\#\alpha}$ |

**All values are mean ± SD. * p-value for control versus osteopenia cases. #p-value control versus osteoporosis cases. α p-value for osteopenia versus osteoporosis cases. NS; Osteoprotegerin (OPG), Aromatase (ARO), Progesterone (P4), Testosterone (T), and Alkaline Phosphatase (ALP), Calcium (Ca), Magnesium (Mg), and Phosphorus (P). Nonsignificant.**

Using Pearson's correlation coefficient, OPG showed a positive correlation with ARO. Furthermore, ARO showed a negative correlation with T. P4 showed a negative correlation with Ca and P (Table 3). In Table 4, OPG showed no correlation with the variables. Moreover, ARO showed a positive correlation with P4 and Ca. P4 showed a positive correlation with Ca and ARO.

**Table 3: Correlation of parameters in osteopenia patients.**

| *Parameter* | **OPG** | | **ARO** | | **P4** | |
|---|---|---|---|---|---|---|
| | r | p | r | p | r | p |
| **Age** | -0.24 | 0.134 | -0.005 | 0.977 | -0.242 | 0.132 |
| **Waist/Hip** | 0.165 | 0.31 | -0.272 | 0.09 | -0.276 | 0.085 |
| **BMD** | -0.265 | 0.099 | -0.236 | 0.143 | 0.282 | 0.078 |
| **OPG** | - | - | **0.47** | **0.002** | 0.204 | 0.206 |
| **ARO** | **0.47** | **0.002** | - | - | 0.176 | 0.277 |
| **P4** | 0.204 | 0.206 | 0.176 | 0.277 | - | - |
| **T** | 0.015 | 0.929 | **-0.33** | **0.037** | 0.058 | 0.723 |
| **ALP** | 0.043 | 0.792 | 0.16 | 0.325 | 0.037 | 0.819 |
| **Ca** | -0.172 | 0.29 | -0.103 | 0.526 | **-0.374** | **0.017** |
| **Mg** | 0.2 | 0.215 | 0.03 | 0.854 | 0.023 | 0.889 |
| **P** | -0.216 | 0.182 | -0.039 | 0.813 | **-0.318** | **0.046** |

**Bone Mineral Density (BMD), Osteoprotegerin (OPG), Aromatase (ARO), Progesterone (P4), Testosterone (T), and Alkaline Phosphatase (ALP), Calcium (Ca), Magnesium (Mg), and Phosphorus (P).**

**Table 4: Correlation of parameters in osteoporosis patients.**

| *Parameter* | **OPG** | | **ARO** | | **P4** | |
|---|---|---|---|---|---|---|
| | r | p | r | p | r | p |
| **Age** | 0.135 | 0.405 | 0.181 | 0.264 | 0.2 | 0.217 |
| **Waist/Hip** | -0.204 | 0.206 | -0.250 | 0.119 | 0.048 | 0.77 |
| **BMD** | -0.013 | 0.936 | -0.006 | 0.969 | 0.032 | 0.844 |
| **OPG** | - | - | 0.224 | 0.165 | -0.057 | 0.728 |
| **ARO** | 0.224 | 0.165 | - | - | **0.525** | **0.001** |
| **P4** | -0.057 | 0.728 | **0.525** | **0.001** | - | - |
| **T** | -0.239 | 0.138 | 0.146 | 0.367 | 0.13 | 0.425 |
| **ALP** | -0.018 | 0.914 | 0.067 | 0.68 | -0.106 | 0.515 |
| **Ca** | -0.021 | 0.9 | **0.474** | **0.002** | **0.446** | **0.004** |

| | | | | | | |
|---|---|---|---|---|---|---|
| **Mg** | 0.202 | 0.211 | 0.125 | 0.442 | 0.146 | 0.368 |
| **P** | 0. 11 | 0.498 | -0.106 | 0.516 | -0.187 | 0.249 |

Table 5 shows the ROC curve analysis for osteoporosis and its diagnostic power, highlighting that BMD is the most accurate diagnostic indicator. OPG also proved to be a good diagnostic tool. ARO emerged as a statistically significant factor, and P4 and Ca demonstrated diagnostic power. Table 6 shows that the analysis confirms that BMD is the best and most accurate diagnostic indicator. OPG demonstrated good diagnostic power, and ARO emerged as a moderately strong indicator. P4 also demonstrated good diagnostic power, and Ca demonstrated moderate diagnostic power.

**Table 5: Osteopenia Parameters ROC Outcomes.**

| Parameters | AUC | P-value | Cut-off value | Sensitivity | Specificity |
|---|---|---|---|---|---|
| **Age** | 0.657 | 0.012 | 54 | 40 % | 92.5 % |
| **BMI** | 0.604 | 0.104 | 33.06 | 70 % | 57.5 % |
| **BMD** | **0.999** | **<0.001** | **0.968** | **100 %** | **97.5 %** |
| **Waist/Hip** | 0.669 | 0.3 | 0.95 | 50 % | 75 % |
| **OPG** | **0.763** | **<0.001** | **544.19** | **85 %** | **65 %** |
| **ARO** | **0.738** | **<0.001** | **2.96** | **82.5 %** | **67.5 %** |
| **P4** | **0.729** | **<0.001** | **0.39** | **70%** | **67.5 %** |
| **T** | 0.511 | 0.869 | 0.29 | 82.5 % | 30 % |
| **ALP** | 0.558 | 0.378 | 96 | 55 % | 62 % |
| **Ca** | **0.658** | **0.002** | **9.2** | **55 %** | **80 %** |
| **Mg** | 0.611 | 0.081 | 1.83 | 77.5 | 45 |
| **P** | 0.547 | 0.476 | 3.5 | 40 % | 77.5 |

**Table 6: Osteoporosis Parameters ROC Outcomes.**

| Parameters | AUC | P-value | Cut-off value | Sensitivity | Specificity |
|---|---|---|---|---|---|
| **Age** | **0.887** | **<0.001** | **49** | **85%** | **77.5%** |
| **BMI** | 0.614 | 0.072 | 30.6 | 72.5% | 72.5% |
| **BMD** | **1** | **<0.001** | **0.78** | **100%** | **100%** |
| **Waist/Hip** | 0.686 | 0.002 | 0.95 | 62.5% | 75% |

| | | | | | |
|---|---|---|---|---|---|
| **OPG** | **0.752** | **<0.001** | **560.93** | **82.5%** | **65%** |
| **ARO** | 0.633 | 0.04 | 3.06 | 72.5% | 62.5% |
| **P4** | **0.776** | **<0.001** | **0.3** | **82.5%** | **67.5%** |
| **T** | 0.62 | 0.059 | 0.39 | 80% | 45% |
| **ALP** | **0.677** | **0.004** | **99** | **65%** | **67.5%** |
| **Ca** | **0.698** | **<0.001** | **9.1** | **60%** | **72.5%** |
| **Mg** | 0.233 | 0.577 | 1.75 | 87.5% | 30% |
| **P** | 0.586 | 0.183 | 3.2 | 62.5% | 57.5% |

## 4. Discussion

Given its rising global prevalence, osteoporosis has emerged as a major international health concern and is currently recognized as the most common bone disorder worldwide. In this study, osteoprotegerin (OPG) emerged it is related to bone health, with concentrations being significantly lower in patients (osteoporosis and osteopenia) compared to the control group. Synthesized and secreted primarily by osteoblasts, OPG plays a fundamental role in maintaining skeletal integrity by acting as an inhibitory decoy receptor for RANKL; this interaction suppresses osteoclast activation, thereby preventing excessive bone resorption. The findings of this investigation demonstrate that the marked reduction of OPG in osteoporotic patients is closely linked to diminished bone mineral density (18). Furthermore, these results suggest an inverse relationship between OPG levels and disease severity, indicating that the risk of osteoporosis escalates as serum OPG concentrations decline (19). Consequently, OPG is related to monitoring bone metabolism and identifying accelerated bone loss in women. Aromatase expression is widely distributed across extragonadal tissues in both sexes, including the brain, adipose tissue, mammary glands, and skeletal system. This tissue-specific distribution ensures precise localized regulation of estrogen synthesis and its subsequent biological actions (20). By facilitating the conversion of androgens into estrogens, aromatase plays a fundamental role in maintaining hormonal balance. Consequently, the pharmacological inhibition of this enzyme can lead to estrogen deficiency and various pathological outcomes. Estrogen is recognized as the primary steroid responsible for skeletal integrity (21), as it regulates the equilibrium between bone formation and resorption via osteoblast and osteoclast activity. Research indicates that aromatase inhibitors can impair bone remodeling and diminish density by blocking the androgen-to-estrogen conversion necessary for bone preservation (22). Furthermore, this enzymatic conversion within bone cells is vital for

maintaining skeletal health post-menopause, with individual and collective variations in aromatase activity directly correlating with differences in bone mineral density (23).

Progesterone has shown a secondary role, as the low progesterone levels observed in patients with osteoporosis and osteopenia suggest that while both conditions are associated with low progesterone levels, osteoporosis is linked to a more severe hormonal deficiency, which exacerbates bone fragility. The decrease from the control group to patients with osteoporosis may reflect bone density loss resulting from hormonal changes. Progesterone, the physiological companion of estradiol, functions in bone by gradually increasing the formation of new bone through the action of osteoblasts and progesterone receptors. Additionally, progesterone is crucial for the acquisition of optimal bone mineral density during adolescence and maturity, as well as for the prevention of bone loss during the premenopausal and potentially perimenopausal periods (17). The hormonal deficiency that is linked to bone deterioration is underscored by the low progesterone levels observed in osteoporosis patients (24). The relationship between serum testosterone levels and skeletal health in women has gained significant research traction due to the critical role of androgens in female physiology. Findings indicate an inverse correlation between testosterone concentrations and the presence of osteoporosis, as patients with the condition exhibit lower hormone levels compared to healthy controls. Testosterone profoundly impacts bone formation by interacting with androgen receptors on osteoblasts, promoting their differentiation and activity while simultaneously inhibiting osteoclast-mediated resorption. Furthermore, testosterone suppresses interleukin-6, a cytokine that activates osteoclasts and drives bone loss; thus, maintaining optimal testosterone levels is essential for preventing fractures and systemic bone degradation (25). While the ovaries naturally produce a spectrum of hormones including estrogen, progesterone, and androgens, the postmenopausal decline in estrogen is a well-established factor in bone loss. However, growing evidence suggests that age-related reductions in testosterone and potential changes in androgen receptor sensitivity also compromise bone density, as testosterone remains a vital influence on both skeletal growth and long-term maintenance (26). Calcium is essential for bone metabolism; osteoblast activity and bone formation are influenced by calcium imbalances. Increased calcium concentrations in osteoblasts may impede their differentiation through the activation of apoptosis in the endoplasmic reticulum and mitochondria (27). When intracellular calcium levels are elevated, the mitochondrial membrane function is disrupted, resulting in impaired bone formation (28). Our research suggests that the osteoporosis group exhibited higher blood calcium

concentrations than the control group. It implies that osteoclasts are activated by elevated calcium levels, which diminishes bone health and may reflect the likelihood of osteoporosis and fractures.

## 5. Conclusion

The levels of specific hormones and certain biochemical variables are altered by obesity. While some of these modifications promote bone health, others do not. Nevertheless, the most significant factor in the development of bone diseases in women is the onset of menopause and the aging process, which is accompanied by changes in the levels of specific biochemical variables and hormonal changes. These modifications induce osteoporosis by augmenting the activity of bone-resorbing cells and decreasing that of bone-forming cells.

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