



Original Paper

Osteoporosis and its association with hormonal changes in women approaching menopause

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ABSTRACT

Background: Osteoporosis is a major global public health problem, affecting millions of individuals and causing morbidity and death. However, it is more common in women as they age due to hormonal changes. Estradiol (E2) is the primary bone hormone in females. Normal estradiol levels inhibit the increased bone resorption. However, low estradiol levels lead to bone resorption and loss. progesterone (P4). The function of bone is to build up its density via progesterone receptors. Estradiol and progesterone work together in bone remodeling, influencing both bone resorption and bone formation. If the menstrual cycle is regular and ovulation occurs regularly, E2 and P4 levels are balanced, and bone density remains stable. However, normal menstrual cycles are often affected by ovulation problems (anovulation, short luteal phase). **Objective:** This study aims to investigate the clinical relationship between irisin, osteoporosis, and the hormones estrogen and progesterone. **Method:** This study examined 35 premenopausal women diagnosed with osteoporosis who were not taking any medications or supplements, and 35 healthy women of the same age. Blood was drawn from the control group, and their hormone levels (irisin, progesterone, and estrogen) were tested. Vitamin levels were also checked, and rheumatoid arthritis tests were performed. **Results:** observed a significant decrease in irisin, estrogen, and progesterone levels ($p < 0.001$), while bone mineral levels remained within normal ranges, and there were no signs of arthritis. **Conclusion:** As women approach menopause, the hormones progesterone, estrogen, and arginine begin to decline. These hormones are closely linked to bone formation, and therefore, these women are at risk of developing osteoporosis. However, tests for rheumatoid arthritis confirm that not every patient with osteoporosis also has rheumatoid arthritis.

KEYWORDS: Arthritis, Estradiol, Osteoporosis, Progesterone, Premenopause, Irisin.

1. INTRODUCTION

Osteoporosis is a persistent skeletal disorder marked by diminished bone density and structural alterations, elevating the risk of fractures. Bone density diminishes due to decreased bone mass and altered microarchitecture, increasing the likelihood of fragility fractures; 1 in 3 women and 1 in 5 men over the age of 50 will experience osteoporotic fractures at some stage in their life (Adejuyigbe et al., 2023). Osteoporosis presents considerable health complications, including disability, pain, and mortality, as well as socio-economic difficulties (Wang et al., 2023). The development of osteoporosis is affected by natural aging and extrinsic variables such as glucocorticoid use, hormonal deficits, reduced bone production, and microarchitectural abnormalities (Liu et al., 2023).

Numerous studies have evidenced the crucial function of bone as an organ that continuously exchanges and controls various tissues. Consequently, it is logical that bone, beyond its traditional functions in locomotion, regulates mineral equilibrium and safeguards internal organs. Bone performs numerous essential activities within the body. It is a dynamic tissue that provides support, stores calcium, forms bone marrow, and facilitates smooth movement (Deng et al., 2022). Osteoporosis is primarily classified into two categories: primary and secondary osteoporosis. Primary osteoporosis refers to bone issues that lack a medical etiology. These include involutional and idiopathic osteoporosis. The etiopathogenesis of idiopathic osteoporosis remains unidentified, especially affecting children and young individuals (Aibar-Almazán et al., 2022). Type II osteoporosis predominantly affects individuals over 75, impacting certain women post-menopause and men, attributable to endocrine malfunction or genetic predispositions. Involutional osteoporosis, also referred to as "senile osteoporosis. The pattern of bone loss in this condition predominantly affects trabecular and cortical bone (Sözen et al., 2016).

Fewer than 5% of osteoporosis cases are secondary, attributable to an underlying condition or pharmacological intervention. The condition arises from a disruption in bone metabolism, characterized by resorption surpassing production. Numerous aspects (Anagnostis et al., 2017).

Factors contributing to this imbalance include age-related alterations, hormonal shortages (notably post-menopausal estrogen insufficiency), genetic predispositions, dietary condition, lifestyle choices such as smoking, and insufficient physical activity. Other causes of illness onset and progression are also important e.g. drugs (e.g. glucocorticoids, proton pump inhibitors, antiepileptics) and diseases (e.g. hyperparathyroidism, thyroid disorders, chronic renal disease). (Inderjeeth and Inderjeeth, 2025). Bone resorption is connected with inflammatory illnesses such as rheumatoid arthritis and systemic lupus erythematosus (SLE) (Sakthiswary et al., 2022). Immunoendocrinological alterations are part of the aging process, with significant impact on morbidity and mortality. (Lee et al., 2022). The major hormonal and immune changes induce important changes in immune cell function including serum antibody levels and changes in the cytokine milieu. (Barb -Tuana et al., 2020). At the same time, factors such as hyperparathyroidism, low vitamin D levels, and decreased osteoblast activity increase the risk of osteoporosis (Li et al., 2023).

Moreover, the interaction of metabolic pathways, genetic and epigenetic influences, and chronic environmental exposures under stress conditions leads to the developing concept of "inflammaging," which is pivotal in the progression of age-related disorders (Aitella et al., 2025). Estradiol (E2), known as the 'women's hormone,' and progesterone (P4), its ovarian counterpart, are crucial for maintaining bone homeostasis. E2 inhibits bone resorption, while P4 promotes bone growth (Prior, 2018). The significance of P4 for bone health is contentious. One reason is that E2 inhibits bone resorption, the principal cause of BMD decrease (Khosla et al., 2011).

RA is a persistent autoimmune condition characterized by ongoing synovial inflammation, progressive joint destruction, and other extra-articular symptoms. Beyond its significant impact on the musculoskeletal system, RA is acknowledged as a multisystem condition associated with several systemic consequences, including cardiovascular morbidity, haematologic abnormalities, and notably, osteoporosis (Mousa et al., 2023). Chronic inflammatory disorders like rheumatoid arthritis induce an increased secretion of pro-inflammatory cytokines, disrupting the normal balance between bone production and resorption. This cytokine-mediated imbalance modifies bone composition and significantly contributes to the development of osteoporosis in persons with rheumatoid arthritis (Ibrahim et al.). Irisin, identified in 2012, is an innovative myokine encoded by the *FNDC5* gene that has attracted interest in current trends (Zhu H, 2023). Irisin has been associated with the regulation of a variety of endocrine and metabolic disorders, including obesity and insulin resistance. (Shen, 2024)

The correlation between serum irisin levels and bone health indicators in various populations has been demonstrated in a multitude of clinical studies. For instance, Colaianni reported that irisin levels were positively correlated with BMD in aged adult patients. (Colaianni G et al., 2021) Furthermore, numerous clinical studies have demonstrated that irisin levels decreased in postmenopausal women with osteoporosis, and a correlation exists between the risk of osteoporotic fractures and the lower irisin levels. (Badr Roomi A et al., 2021)

This study aims to delineate the irisin and E2–P4 association in healthy bone and examine P4's practical and clinical functions in osteoporosis.

2-MATERIAL AND METHOD

Blood samples were obtained from 70 healthy adult women to fulfill the research requirements. This study approved by Ethics Committee of Al-Nahrain University, Baghdad, Iraq (code:2013.2). The samples were categorized into two groups: one including 35 premenopause women with osteoporosis and a control group of 35 healthy women. The research was carried out from October 3, 2025, to December 1, 2025, at a private clinic and Baghdad Teaching Hospital in Baghdad. The women's ages ranged from 35 to 50 years. Women with chronic autoimmune diseases, diabetes, hepatic or renal disease, and other endocrine problems were excluded from the study. This research was performed on Iraqi patients. All participants had a thorough physical examination and an assessment of their medical history. All individuals underwent measurements of weight, height, and body mass index (BMI). The formula for calculating BMI is: $BMI = \text{weight in kilograms} / \text{height in meters}^2$. Participants submitted venous blood samples at various times during the day, which were thereafter preserved at -20°C until analysis. All specimens were obtained in Vacutainer tubes containing gel.

Serum calcium and phosphorus concentrations were assessed utilizing the ortho-cresol-phthalein method with the Randox Calcium Test Kit (my BioSource, CA8309). Vitamin D3 concentrations were assessed with the Abcam 25(OH) Vitamin D ELISA Kit (my BioSource, MBS580159). Irisin, estradiol and progesterone concentrations were quantified via Irisin ELISA Kit (my BioSource, MBS706887) the Neogene Estradiol ELISA Kit (my BioSource, MBS494191), progesterone (my BioSource, MBS162306) alongside the Arthritis Biomarker.

Statistical Examination

GraphPad Prism (version 8.0.2; GraphPad Software, San Diego, CA, USA) was used for statistical analysis. Mean $\pm$ standard deviation (SD) was used to express the data. An independent-samples t-test was used to compare the patient and control groups. Statistical significance was defined as a p-value of less than 0.05.

3-RESULT

Table 2 displays the results for two groups of women: those with osteoporosis who are of normal weight and healthy females. The serum concentrations of calcium, phosphorus, and vitamin D3 were markedly elevated in the cohort of women with osteoporosis (Ca 7.915 ± 0.336 mg/dl, P 5.623 ± 0.413 mg/dl, and V.D3 15.415 ± 2.934 IU/L) in comparison to the control group (10.655 ± 1.437 , 2.745 ± 0.366 mg/dl, and 31.515 ± 2.165 IU/L, respectively). Conversely, the women in both cohorts did not exhibit symptoms of arthritis, as indicated in Table 3. The P value for Anti.ccp, Rheumatoid Factor and the ESR analysis was >0.05 . Serum E2 and P4 concentrations were significantly elevated in osteoporosis patients compared to the control group (149.4 ± 2.643 pg/ml and 2.431 ± 0.476 ng/ml, respectively). E2 levels were (8.697 ± 0.493 pg/ml), and P4 levels were (0.492 ± 0.042 ng/ml), as shown in Table 4, where the p-value for both hormones was <0.001 . Irisin levels were lower in the patients (2.431 ± 0.476 U/ml) compared to the control group (0.492 ± 0.042 U/ml) as shown in figer1.

Table 1: The Age of Patient and Control Groups

Groups	Number	Age(Years)	p-value
premenopausal women	35	49.95 ± 4.173	>0.05
Control	35	49.55 ± 3.561	

*The difference is significant at $p < 0.05$ and highly significant at $p < 0.001$.

Table 2: Mean values $\pm$ SD Bone biomarkers of the criteria in the premenopausal women and the control group

Parameters	Patient 35	Control 35	p-value
Ca mg/dL	7.915 ± 0.336	10.655 ± 1.437	$<0.001^*$
Pi mg/dL	5.623 ± 0.413	2.745 ± 0.366	$<0.001^*$
V.D3 IU/L	15.415 ± 2.934	31.515 ± 2.165	$<0.001^*$

*The difference is significant at $p < 0.05$ and highly significant at $p < 0.001$.

Table 3: Mean values $\pm$ SD Biomarkers of arthritis in the premenopausal women group and the control group

Parameters	Patient 35	Control 35	p-value
Anti.ccp U/ml	3.213 ± 0.569	3.145 ± 0.483	>0.05
Rheumatoid Factor IU/ml	2.846 ± 0.515	2.781 ± 0.551	>0.05
ESR mm/hr	38.9 ± 4.722	36.55 ± 5.689	>0.05

*The difference is significant at $p < 0.05$ and highly significant at $p < 0.001$.

Table 4: Average levels $\pm$ standard deviation of hormones associated with osteoporosis based on criteria in the premenopausal women and control group

Parameters	Patient 35	Control 35	p-value
Irisin(ng/ml)	18.08 ± 6.828	37.56 ± 8.795	$<0.001^*$
E2(Estradiol) pg/ml	8.697 ± 0.493	149.4 ± 2.643	$<0.001^*$
Progesterone ng/ml	0.492 ± 0.042	2.431 ± 0.476	$<0.001^*$

*The difference is significant at $p < 0.05$ and highly significant at $p < 0.001$.

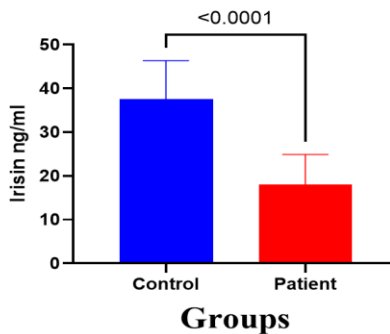


Figure 1: Serum level of Irisin in patient compared to control groups.

4-DISCUSSION

Clinical trials and scientific investigations have demonstrated a correlation between irisin, estrogen and progestin hormones and osteoporosis, particularly in women nearing or undergoing menopause. Bone consists of roughly 60% minerals, 30% organic material, and 10% cells (Stanczyk et al., 2026). Mature bone comprises two types of tissue: cortical bone and trabecular bone, accounting for 80% and 20% of the skeleton, respectively (Stanczyk et al., 2026). Cortical bone constitutes the dense outer layer of bone and the diaphysis of long bones. Conversely, trabecular bone forms the termini of long and flat bones, including interconnected trabeculae encased in bone marrow (Dempster et al., 2018). Most scientists regard estradiol as the exclusive bone-active gonadal steroid in women. E2 and P4 function collaboratively in all tissues within women's normal physiology (Baxter, 2009). Estrogens exert a biphasic influence on the formation of long bones (Noirit-Esclassan et al., 2021). Estradiol exerts its beneficial effects on bone mostly through two principal mechanisms: Enhancement of vitamin D-mediated intestinal Ca^{+2} absorption and inhibition of bone resorption via the osteoprotegerin nuclear transcription factor receptor kappa B and its receptor (RANK/RANKL) (Seifert-Klauss and Prior, 2010).

As women approach menopause, the drastic decline in blood estrogen affects practically every system in the body, affects practically every system in the body, including the genitourinary system, reproductive system, cardiovascular system, neurological system, skeletal system, integumentary system, immunological system, and digestive system (Yang et al., 2024). The basic scientific literature shows that estrogen receptors (ERs) exist in many organ systems and are associated with many beneficial effects in women and men, even in old age. Estrogen insufficiency can have a huge impact on the systems of organs, negatively influencing quality and quantity of life for women (Santen and Simpson, 2019). Therefore, women entering menopause are more prone to osteoporosis because the rate of bone resorption is higher than the rate of bone formation, creating an imbalance between bone resorption and bone formation. Estrogen is important in regulating bone remodeling and preservation of skeletal homeostasis. The physiological mechanisms in which estrogen acts on bone are still controversial but recent studies suggest that estrogen mainly regulates bone remodeling by modifying the expression of RANKL via estrogen receptor alpha ($\text{ER}\alpha$) signaling. RANKL is a key cytokine for osteoclast formation, activation and lifespan (Streicher et al., 2017, Li et al., 2000).

Progesterone is a key regulator of bone regeneration through stimulation of osteoblasts, activation of type I collagen synthesis and promotion of bone mineralization (Medvedeva et al., 2026). Progestogens constitute a diverse category of steroid hormones that can bind to and activate the P4 receptor, hence inducing biological effects analogous to those of natural progesterone (Foschi et al., 2025). With the onset of menopause, a decline in progesterone results in diminished osteoblast activity and a reduction in new bone formation (Prior, 2018). Clinical observations demonstrate that combination estrogen and progestin therapy results in a more significant enhancement of spinal bone mineral density than estrogen monotherapy (Prior et al., 2017). Verifying that progesterone insufficiency autonomously contributes to osteoporosis. We conducted tests to measure the levels of calcium, phosphate, and vitamin D3, all of which were found to be normal in the patients' blood serum, confirming that the osteoporosis was attributable to ageing and the onset of menopause, rather than the usage of specific pharmaceuticals. These results imply that irisin might be a predictive and prognostic biomarker of OP. Further Experimental data have verified the essential function of irisin in bone metabolism and remodeling (Luo Y et al., 2020). Based on the findings from both clinical and experimental research, medicines utilizing irisin may serve as promising avenues for osteoporosis treatment. Moreover, diminished estrogen levels in postmenopausal women elevate the prevalence of metabolic disorders, which are recognized risk factors for osteoporosis (Lobo and Anne, 2022). Furthermore, research has associated diminished irisin concentrations with sarcopenia in postmenopausal females, a recognized risk factor for fractures (Park HS et al., 2019). Recent investigations have revealed inconsistent outcomes related to the connection between irisin and bone mineral density (BMD) (Yan J et al., 2018).

Comparable discrepancies are observed in premenopausal women concerning the association between irisin and bone mineral density (Maïmoun L et al., 2022).

The current findings align with a previous study, which Prior, J. C. in 2018, examined a cohort of women and identified a significant reduction in progesterone and estrogen levels due to menopause and the onset of osteoporosis. He subsequently administered hormone therapy to elevate their hormone levels (estrogen and progesterone) because of their association with bone growth (Prior, 2018). Our findings correspond with those of Shah and Nandi (2023), who investigated hormonal alterations preceding and following menopause and their association with osteoporosis (Shah and Ariel, 2023). do not experience arthritis, suggesting an absence of definitive evidence connecting the two conditions. This was corroborated by Kim, Dongkeun (2022) (Kim et al., 2022). Looking at Table 3, we find that the patients are not suffering from rheumatoid arthritis. Not everyone with osteoporosis has rheumatoid arthritis. Our results agree with those of Dr. Kosuke Ebina, who found that more than half of the patients did not have rheumatoid arthritis (Ebina K et al., 2024).

5-CONCLUSION

Osteoporosis is a systemic skeletal disorder whose prevalence increases with the aging of the world's population. Balanced estrogen and progesterone levels help maintain bone mineral density and reduce risk factors. Progesterone is secreted in increasing amounts for two weeks during each menstrual cycle in women with regular cycles. Therefore, as women approach menopause and the production of these hormones declines, they become more susceptible to osteoporosis. Our current findings indicate that decreased irisin levels are strongly associated with osteoporosis and fractures in women approaching menopause, suggesting its potential use as a biomarker for early detection of the disease. Progesterone is a novel agent under development to achieve and maintain adequate bone mass and prevent bone loss before and during menopause; further research is needed, as it is being considered a preventive medication. There are some limitations that must be considered when starting work on this research, namely the small size of the blood sample taken from the participating persons, which limits the possibility of generalizing the results, in addition to the inability to measure all the hormones related to the disease.

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