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Revisión

Luteinizing hormone and follicle-stimulating hormone in bone physiology and pathophysiology: A narrative review

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Abstract

Context: Bones are highly dynamic organs that depend on constant and balanced remodeling to maintain their homeostasis. Bone tissue is sensitive to hormonal stimuli, which can influence bone remodeling processes and, in some cases, lead to imbalances that result in various bone-related diseases. Recent research has shown that bone cells are sensitive to follicle-stimulating hormone (FSH) and luteinizing hormone (LH), which appear to affect bone remodeling in health and disease.

Objectives: To explore the roles of luteinizing hormone and follicle-stimulating hormone in bone remodeling and the development of systemic and alveolar bone diseases in males and females.

Methodology: A literature search was conducted in the PubMed and Google Scholar databases. We used the following keywords and their combinations as search criteria: FSH, LH, follicle-stimulating hormone, luteinizing hormone, bone remodeling, alveolar bone, periodontitis, arthritis, osteoporosis, bone metastasis, men, and women.

Results: Emerging evidence suggests that follicle-stimulating hormone and luteinizing hormone play a significant role in bone metabolism and actively contribute to bone diseases such as osteoporosis, rheumatoid arthritis, bone metastasis, and periodontitis through inflammatory and pro-apoptotic mechanisms and by modulating the differentiation and activity of osteoblasts and osteoclasts.

Conclusion: The increase in follicle-stimulating hormone and luteinizing hormone are associated with the development and severity of different bone diseases. These findings provide a fresh perspective on the relationship between bone health and gonadotropins. Modulation of gonadotropin levels may represent a good therapeutic target for the treatment of various systemic pathologies of the skeleton and oral cavity.

Keywords: Luteinizing hormone, Follicle-stimulating hormone, Bone, Periodontitis, Osteoporosis, Rheumatoid arthritis, Bone metastasis.

Highlights

- Follicle-stimulating hormone (FSH) and luteinizing hormone (LH) have important functions in bone remodeling and homeostasis.
- Increased FSH levels have been associated with high osteoclast activity and bone disease development and severity.
- LH appears to play a role in the pathophysiology of bone diseases, but its role remains unclear.
- Studies that directly evaluate the role of gonadotropins in bone diseases are needed.
- Modulating gonadotropin levels is promising for the treatment of bone diseases.

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Las hormonas luteinizante y folículo estimulante en la fisiología y fisiopatología ósea: una revisión narrativa

Resumen

Contexto: los huesos son órganos altamente dinámicos que dependen de una remodelación constante y equilibrada para mantener su homeostasis. El tejido óseo es sensible a los estímulos hormonales, que influyen en el remodelado óseo, y los desequilibrios hormonales pueden conducir al desarrollo de enfermedades óseas. Investigaciones recientes han demostrado que las células óseas son sensibles a las hormonas folículoestimulante (FSH) y luteinizante (LH), que parecen afectar la remodelación ósea tanto en la salud como en la enfermedad.

Objetivo: explorar el papel de la hormona folículoestimulante y la luteinizante en la remodelación ósea y en el desarrollo de enfermedades óseas sistémicas y alveolares en hombres y mujeres.

Metodología: se realizó una búsqueda bibliográfica en las bases de datos PubMed y Google Académico. Se utilizaron las siguientes palabras clave y sus combinaciones como criterios de búsqueda: FSH, LH, hormona folículoestimulante, hormona luteinizante, remodelación ósea, hueso alveolar, periodontitis, artritis, osteoporosis, metástasis ósea, hombres y mujeres.

Resultados: la hormona folículoestimulante y la luteinizante desempeñan un papel importante en el metabolismo óseo y contribuyen activamente al desarrollo de enfermedades óseas como la osteoporosis, la artritis reumatoide, la metástasis ósea y la periodontitis, a través de mecanismos inflamatorios y proapoptóticos, así como mediante la modulación de la diferenciación y la actividad de osteoblastos y osteoclastos.

Conclusiones: los niveles elevados de la hormona folículoestimulante y la luteinizante se asocian con el desarrollo y la gravedad de diversas enfermedades óseas. Estos hallazgos aportan una perspectiva novedosa sobre la relación entre la salud ósea y las gonadotropinas. La modulación de los niveles de gonadotropinas puede representar un blanco terapéutico para diversas patologías óseas.

Palabras clave: hormona luteinizante, hormona folículoestimulante, hueso, periodontitis, osteoporosis, artritis reumatoide, metástasis ósea.

Destacados

- Las hormonas foliculoestimulante (FSH) y luteinizante (LH) desempeñan funciones importantes en la remodelación ósea y la homeostasis.
- El aumento de los niveles de FSH se ha asociado con una mayor actividad osteoclástica y con el desarrollo y la severidad de las enfermedades óseas.
- La LH parece desempeñar un papel en la fisiopatología de las enfermedades óseas, pero su función aún no está del todo clara.
- Se necesitan estudios que evalúen directamente el papel de las gonadotropinas en las enfermedades óseas.
- La modulación de los niveles de gonadotropinas es prometedora para el tratamiento de las enfermedades óseas.

Introducción

Bones are highly dynamic organs that perform multiple functions in the body, such as protecting vital organs, locomotion, mineral homeostasis, hematopoiesis, energy metabolism, and multiple endocrine functions (1). Bone tissue is classified as cortical and trabecular, and both are made up of organic and mineral tissue, both synthesized by osteoblasts (2). The organic portion is composed mainly of collagen proteins, mostly type 1, non-collagenous proteins such as osteonectin, osteocalcin, bone morphogenetic proteins, alkaline phosphatase, bone sialoprotein, growth factors, albumin, water, and lipids, while the mineral portion consists of calcium phosphate molecules, hydroxyapatite, and other less abundant minerals (3-4). All these elements provide bones with elasticity, flexibility, mechanical rigidity, and resistance (3-4).

Bone remodeling is a process that replaces mature or damaged bone tissue with new bone tissue, which is necessary to maintain bone and mineral homeostasis as well as bone strength and structure (5-6). Bone remodeling occurs through the combined action of bone cells (osteoblasts, osteocytes, lining cells, and osteoclasts) and immune cells such as macrophages and T lymphocytes, which work together to ensure that the five steps of bone remodeling occur cyclically: initiation, resorption, reversal, formation, and termination (5-6). Bone remodeling is mainly

regulated by the osteoprotegerin system (OPG, secreted by active osteoblasts), the receptor activator of nuclear factor κB ligand (RANK-L, secreted by osteocytes and immune cells), and its receptor RANK (expressed on the surface of immature osteoclasts) (7).

Bone cells constitutively express receptors for sex steroids, such as androgens and estrogens, as well as gonadotropic hormones such as follicle-stimulating hormone (FSH) and luteinizing hormone (LH), making these cells susceptible to changes in hormone levels (8). Sex hormones such as testosterone and estradiol have been shown to play an important role in bone formation and resorption (9-12). Although estrogens and androgens have been widely studied in relation to bone tissue health and pathophysiology, the gonadotropins FSH and LH, which in turn control the synthesis of androgens and estrogens (13), have been shown to play a significant role in bone metabolism, both directly or indirectly (14), and increased levels of these hormones can even lead to pathological skeletal diseases (15).

The aim of this narrative review is to examine the role of LH and FSH in bone remodeling and their involvement in bone pathologies such as rheumatoid arthritis, osteoporosis, bone metastases, and periodontitis, thereby providing a broader view of the impact of gonadotropic hormones on bone tissue.

Methodology

A literature search was conducted in the PubMed and Google Scholar databases up to December 2024. We used different combinations of the following keywords as search criteria: FSH, LH, follicle-stimulating hormone, luteinizing hormone, bone remodeling, alveolar bone, periodontal disease, orthodontic movement, arthritis, osteoporosis, bone metastasis, men, women, males, and females. Preference was given to articles published in the last five years, but previously published reports were considered based on their contribution to the present review. This work is a narrative literature review of literature and did not involve research on humans or animals. Therefore, ethics committee approval was not required.

Gonadotropic hormones and bone remodeling

Gonadotropic hormones have been shown to play an important role in bone metabolism, as evidenced by the skeletal changes that occur due to increased FSH and LH levels under different conditions. The general mechanisms by which gonadotropins influence bone remodeling are summarized below.

Luteinizing hormone

Female knockout mice lacking the LH receptor have been reported to exhibit a loss of mineral density and a reduced number of trabeculae in the femur and tibia, likely due to altered bone cell activity (16). Furthermore, in premenopausal, perimenopausal, and postmenopausal women, elevated LH levels were positively correlated with serum concentrations of OPG and transforming growth factor (TGF)-β2 and negatively correlated with TGF-β1, with these associations being most pronounced during perimenopause (17). TGF-β1 promotes osteoblast differentiation and activation, thereby enhancing bone formation, while OPG inhibits osteoclastic activity by blocking RANK-L (18). In contrast, overexpression of TGF-β2 is associated with bone loss (19).

In centenarian women, LH levels were positively correlated with osteocalcin, carboxyl-terminal propeptide (CTx), and parathyroid hormone (PTH) levels and negatively correlated with vitamin D levels and bone resorption markers (20).

This evidence suggests a potential anabolic role of LH in bone tissue (figure 1). However, current evidence is limited and largely associative.

Follicle-stimulating hormone

FSH has been shown to have modulatory effects on bone remodeling. An increase in bone mass has been reported in transgenic mice with FSH or its receptor deficiency, even in female mice with an estrogen deficiency (21). Additionally, in healthy or gonadal estrogen-deficient mice, the use of specific antibodies targeting FSH has been shown to increase bone mass, cortical bone thickness, and the number and thickness of trabeculae (14), suggesting that FSH may play an important role in bone loss.

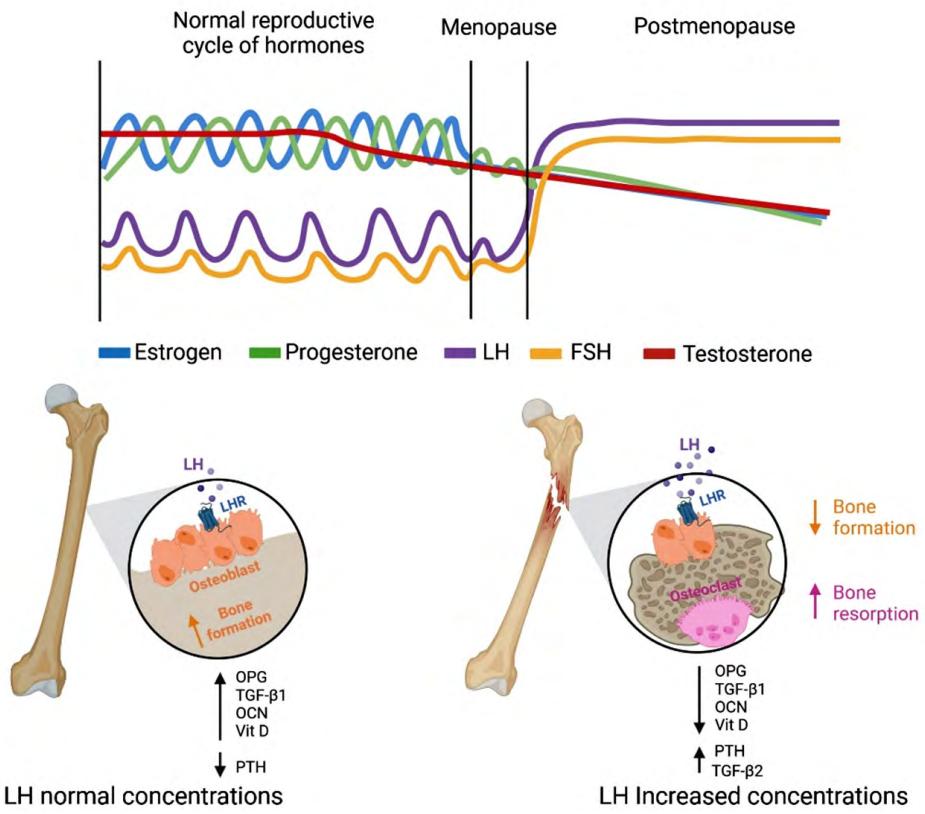


Figure 1. Role of LH in bone remodeling

Note. At normal LH concentrations, LH binds to its receptor (LHR) on osteoblast cells, increasing the levels of osteoprotegerin (OPG), transforming growth factor-beta 1 (TGF-β1), osteocalcin (OCN), and vitamin D (Vit D), while decreasing parathyroid hormone (PTH) levels. This promotes bone formation and homeostatic bone remodeling. An increase in LH, such as that observed during postmenopause, leads to a decrease in OPG, TGF-β1, OCN, and Vit D, along with an increase in PTH and TGF-β2, resulting in higher bone resorption and lower bone formation, which in turn causes bone fragility.

Source: Own elaboration.

The negative effects of FSH on bone mass may be mediated by an increase in osteoclastic activity. Expression of the FSH receptor has been observed in osteoclasts and osteoclast precursors (21), and FSH also stimulates the secretion of tumor necrosis factor (TNF)-α in macrophages and granulocytes in the bone marrow, which stimulates bone resorption (22). The inducing effect of FSH on osteoclastogenesis and osteoclastic activity was further confirmed by blocking FSH with specific antibodies, which inhibited osteoclastic function and induced osteoblastic activity in vivo (14).

Studies in humans have shown an association between increased FSH and higher levels of bone remodeling markers, such as P1NP in urine and serum osteocalcin, as well as an association with reduced bone mineral density (BMD) in the spine and hip in peri- and postmenopausal women (23-24). In women with secondary amenorrhea, lower BMD was observed in women with hypergonadotropic amenorrhea and FSH concentrations greater than 40 IU/L compared with those with hypogonadotropic amenorrhea and FSH levels less than 40 IU/L (25).

In eugonadal men, FSH does not appear to affect the rate of bone turnover, and the effects of sex steroids on bone resorption appear to be independent of FSH action (26). This supports the

notion that FSH does not appear to be an important regulator of skeletal metabolism, at least in men. Furthermore, no association was observed between FSH levels and BMD in older men and women (27).

These findings suggest that FSH has important effects on bone resorption. Thus, decreasing FSH levels in women may be an important therapeutic target for the treatment of bone diseases in peri- and postmenopausal women.

Influence of gonadotropic hormones on bone pathologies

Rheumatoid arthritis

Rheumatoid arthritis (RA) is an autoimmune disease that leads to chronic systemic and joint inflammation, causing irreversible joint and bone destruction and degeneration. It is influenced by different genetic, environmental, and immunological factors that, to date, have not been fully elucidated (28). RA can also be affected by fluctuations in the levels of LH and FSH (figure 2).

Luteinizing hormone. It has been suggested that elevated LH may predispose individuals to greater RA severity, since an LH increase was found in premenopausal women with severe RA compared to those in remission (15). In men and postmenopausal women with RA, changes in LH levels between two different days were positively correlated with the percentage of change in the levels of proinflammatory cytokines and chemokines, such as TNF-α, interleukin (IL)-1β, IL-12, monocyte chemoattractant protein (MCP)-1, macrophage inflammatory protein (MIP)-1α and β, and the CCL11 chemokine. Taken together, these data indicate that LH fluctuations may play an important role in the severity of systemic inflammation, thereby exacerbating RA (29).

In a controlled study testing the efficacy of the oral gonadotropin-releasing hormone antagonist ASP1707 in postmenopausal patients with RA, no clinical improvement was observed after 12 weeks of treatment, despite a reduction in LH levels of over 90% (30). Similarly, in premenopausal women with RA treated with methotrexate (a cell proliferation inhibitor that can lead to premature ovarian failure), no correlation was observed between LH concentrations and clinical parameters of RA activity. However, women treated with methotrexate maintained LH levels within the normal range (31). In premenopausal women with RA, a higher predisposition to premature menopause was observed among those with elevated LH levels, though LH was not associated with disease activity parameters (32).

Overall, evidence linking LH to RA severity is inconsistent and remains associative, suggesting that LH may reflect underlying gonadal dysfunction rather than directly driving disease pathogenesis.

Follicle-stimulating hormone. There is evidence supporting the role of FSH in RA. Human and mouse chondrocytes express the FSH receptor, which, when stimulated with an analogue of this hormone, increases cAMP (33), this suggests that articular cartilage may respond to FSH stimuli. Indeed, in the ATDC5 cell line (chondrocyte-like cells), FSH stimulation reduces the production of aggrecan and type II collagen in a concentration-dependent manner, while silencing the FSH receptor in these cells reverses these effects (34). Moreover, in a mouse model of osteoarthritis induced by medial meniscus destabilization, silencing the FSH receptor reduced joint damage (35).

In another report of women with RA, it was found that elevated FSH levels were associated with an increase in erythrocyte sedimentation rates, C-reactive protein (PCR) levels, and diagnostic markers such as DAS28-CRP and DAS28-ESR. Therefore, the authors proposed that elevated FSH levels are a risk factor for RA. (36). Similarly, in premenopausal women, higher FSH levels were correlated with greater RA severity (15).

In a study involving men and women with RA, FSH levels were positively correlated with serum concentrations of TNF-α, IL-1β, IL-2, the IL-2 receptor, IL-8, MCP-1, MIP-1α, MIP-1β, and eotaxin (29). Additionally, in a collagenase-induced osteoarthritis mouse model, FSH administration increased cartilage degradation, serum osteocalcin levels, the percentage of CD14+/RANK+ monocytes and CD19+/RANK+ B cells, and osteoclast formation induced by dual stimulation with macrophage colony-stimulating factor (M-CSF) and RANKL (37).

Overall, current evidence supports that FSH plays a direct role in RA development, potentially enhancing disease activity and severity by inhibiting

chondrogenic activity, promoting joint inflammation, and stimulating osteoclastic activity.

Osteoporosis

Osteoporosis is the most prevalent metabolic bone disease, affecting half of women and one-third of men, primarily in the sixth and seventh decades of life. It is characterized by uncoupled bone resorption and formation phases, resulting in low bone mass, changes in microarchitecture and biomechanical properties, and an increased risk of fractures (38). Postmenopausal women are at a higher risk of developing osteoporosis, underscoring the importance of sex hormones in its pathophysiology (38).

Luteinizing hormone. In recent decades, the role of gonadotropic hormones in skeletal metabolism has been studied. Expression of the LH receptor has been demonstrated in cell cultures of human and murine osteoblasts (39). Accordingly, LH receptor depletion in mice causes a decrease in BMD in the femur and tibia at five months of age in male mice, while in females, no changes in BMD were observed; however, a decrease in bone volume and in the number and thickness of the trabeculae of the distal and proximal epiphyses was observed, indicating that LH can modulate bone formation (39).

Conversely, in clinical studies, LH concentrations have been associated with a decrease in BMD and an increase in the risk of fractures. In a group of 699 Chinese women aged 20-82 years, higher LH levels were associated with lower BMD in the spine, hip, radius, and ulna; furthermore, women who had LH levels greater than 11.26 IU/L had a higher incidence of osteoporosis compared with those lower LH levels (40). In another study of 260 Mongolian women, higher LH concentrations were found in postmenopausal women compared with menopausal and perimenopausal women, and increased LH levels were weakly associated with decreased BMD in the forearm and tibia, whereas low estradiol levels were more strongly associated with decreased BMD (41).

In a longitudinal study of 1.705 aged Australian men, a significant increase in LH levels was observed after 5 years of follow-up, and this increase in LH was associated with lower hip BMD (42). Additionally, in men with prostate cancer, administration of goserelin, an LH-releasing hormone analogue, was associated with an increased risk of fracture due to decreased BMD and increased bone remodeling markers such as P1NP in urine and ALP in serum compared with untreated men (43).

Associative clinical findings suggest that increased LH due to menopause or aging may be a biomarker for low BMD and an increased risk of fractures (figure 2). However, preclinical studies demonstrate that LH receptors may participate in the maintenance of bone mass. Therefore, it is possible that bone alterations observed in humans are primarily due to decreased estrogen or androgen levels, which subsequently lead to increased circulating LH levels. In this context, the association between elevated LH levels and low BMD in humans may reflect a consequence of hypogonadism rather than a direct causal effect of LH. Nevertheless, bone cells are sensitive to LH, and further investigation into the direct or indirect actions and underlying mechanisms of LH in bone is necessary.

Follicle-stimulating hormone. Increased FSH has been shown to be an important factor in the development of osteoporosis. For example, serum FSH levels have been shown to correlate with bone turnover and bone mineral density in perimenopause (44), and polymorphisms in the FSH receptor have been associated with decreased bone mineral density in postmenopausal women (45), as well as with FSH blockade with antibodies (14, 46), which have been used as vaccines to prevent bone loss in hypogonadal mice. On the other hand, it has been observed that exogenous administration of FSH in rodents exacerbates ovariectomy-induced bone loss, while the use of an FSH antagonist mitigated this bone loss (47).

The proposed mechanism by which FSH has these negative effects on bone tissue is through stimulating the differentiation and activation of osteoclasts. Indeed, the use of the first humanized anti-FSH antibody inhibited osteoclast formation in mouse bone marrow cells stimulated with RANKL, M-CSF, and FSH (48). In contrast, FSH decreases osteoblast differentiation, and the use of FSH-blocking antibodies has been shown to increase the amount of osteoblast precursors, contributing to increased bone formation (49). This indicates

that increased FSH may promote an osteoporotic phenotype by inducing osteoclastogenesis and suppressing bone formation (figure 2).

Bone metastasis

Bone metastasis, the third most common site of metastatic cancer, occurs when primary tumors spread to highly vascularized bone tissue (50). Among the cancers that frequently metastasize to bone are breast, lung, and prostate cancers, as well as renal and thyroid cancers (50). The metastatic process involves tumor cells expressing CXCR4 and RANK-L, which interact with bone marrow stromal cells, thereby promoting homing. Depending on the type of cancer, bone metastases are classified as osteoblastic (e.g., prostate cancer), osteolytic (e.g., breast, lung, and kidney cancer), or mixed (e.g., breast cancer) (50).

Luteinizing hormone. Studies have largely focused on the effects of luteinizing hormone-releasing hormone (LHRH) agonists on bone metastasis derived from prostate or breast cancers. LHRH therapy desensitizes cells to LH (figure 2). For instance, in a retrospective study of Korean male patients diagnosed with prostate cancer and bone metastasis who were receiving antiandrogen therapy and an LHRH agonist, those who were switched to LHRH-based monotherapy or castration after stabilization showed increased progression-free survival compared with patients who continued the initial treatment. These findings suggest that therapy based on suppression of the hypothalamic-gonadal axis through LHRH agonists may reduce disease progression and malignancy of metastatic cancer cells, similar to castration (51).

Similar results have been found in women with metastatic breast cancer. In a phase II study of women with ER-positive premenopausal metastatic breast cancer, the efficacy and safety of combination therapy with an LHRH analogue and an aromatase inhibitor were evaluated. A response rate of 18.9%, a clinical benefit rate of 62%, and an increase in progression-free survival of 7.3 months were observed (52). Likewise, a meta-analysis that included four clinical trials with a total of 506 premenopausal women with advanced breast cancer undergoing treatment with an LHRH agonist alone or combined treatment with an LHRH agonist plus tamoxifen showed that treatment with LHRH alone increased survival, progression-free survival, and a response to treatment of 29.7%; however, combined therapy with tamoxifen yielded better results (53). Additionally, in nude mice with triple-negative breast cancer xenografts (without estrogen receptor expression), gonadotropin-releasing hormone agonists were found to reduce tumor volume and bone metastasis (54).

One of the mechanisms by which LHRH agonists, or gonadotropin-releasing hormones, reduce the progression of metastatic breast and prostate cancers is through inducing a negative regulation of the LHRH receptors and their signaling pathways, resulting in a desensitization of gonadotropins and a marked reduction in the secretion of bioactive LH and FSH. This leads to a chemical castration derived from the complete inhibition of testicular or ovarian function and a significant decrease in sex steroid levels (55). Another mechanism may involve desensitization of breast or prostate cancer tumor cells expressing LHRH receptors, which reduces tumor growth (55). It should be noted that, during the first months of treatment with these agonists, an increase in the concentrations of LH, FSH, testosterone, and estrogen levels is induced, which are then drastically reduced; this increase may explain the side effects of these agonists (55).

Follicle-stimulating hormone. FSH has been shown to play an important role in bone metastasis (figure 2). One of the mechanisms by which FSH has these effects is through inducing an increase in osteoclastic activity that appears to stimulate the growth and progression of this condition (56). Increased osteoclastic activity is mediated by the expression of FSH receptors (FSHR) on osteoclast precursor cells, which, upon binding to its ligand, stimulates RANK expression. Additionally, bone marrow immune cells such as T lymphocytes, macrophages, and granulocytes also express FSHR, leading to the secretion of RANK-L, TNF-α, and IL-1β, which produce increased bone resorption (22, 57).

The increase in RANK-L mediated by FSH, together with TGF-β, which is constitutively expressed in bone tissue, stimulates the secretion of IL-6 and matrix metalloproteinase 9 (MMP-9) in metastatic cells, thereby facilitating the migration

and invasion of tumor cells into the bone. In response to resorption, osteoid matrix factors such as calcium, endothelial growth factor, fibroblast growth factor, and more TGFβ are released, causing the formation of abnormal new bone of poor quality and with a disorganized architecture, a clinical characteristic of prostate bone metastasis (56, 58).

In fact, some studies have reported that blocking gonadotropin-releasing hormone reduces prostate cancer progression and bone metastasis, as evidenced by a decrease in serum ALP, considered a marker of bone metastasis, and the effects of the blocker are greater compared to agonists such as leuprolide (59).

Furthermore, in different metastatic cancers of prostate or breast origin, including bone metastases, an increase in the expression of the FSH receptor in the tumor endothelium has been found (60). This finding supports the possibility that FSH may play an important role in tumor vascularization and metastasis through its binding to its receptor on the endothelium.

The relationship between gonadotropins and the development of bone and other tissue metastases has been associated by observing the expression of the receptors for these hormones in biopsies of osteosarcoma (61), indicating that modulation of gonadotropins or chemotherapy targeting these hormones may be a good therapeutic target for the control of bone metastasis.

Periodontitis

Periodontitis is a chronic inflammatory disease resulting from dysbiosis of the oral microbiome and the inflammatory response in individuals. This leads to the progressive destruction of periodontal support tissues, including gingival tissue, root cementum, periodontal ligament, and alveolar bone. If left untreated, it can result in the loss of teeth (62). Periodontitis is one of the most prevalent conditions in humans, with an estimated prevalence of 62% and 23.6% for aggressive periodontitis among dentate adults between 2011 and 2020 (62). While the mechanisms involved in the development and severity of periodontitis are linked to dysbiosis and inflammatory responses, gonadotropic hormones may play a role in enhancing these mechanisms (figure 2).

Luteinizing hormone. The role of LH in oral diseases such as periodontitis has been poorly explored. However, in women with polycystic ovary syndrome (PCOS), where LH levels are elevated, a positive correlation has been reported between LH levels and the concentration of matrix metalloproteinase 8 (MMP8), a collagenase enzyme implicated as a biomarker of the onset and progression of periodontitis. Furthermore, MMP8 concentrations in saliva have been positively correlated with alterations in periodontal parameters, such as periodontal pocket depth (PD), bleeding on probing (BOP), and the plaque score (FMPS) (63). This suggests that increased LH may contribute to periodontal tissue destruction. However, these observations remain associative.

In ovariectomized (OVx) rats with induced periapical lesions, continuous administration of leuprorelin, which suppresses LH and FSH, resulted in decreased alveolar bone loss and a lower number of osteoclasts. However, the protective effects of leuprorelin were primarily attributed to FSH suppression (64). Additionally, other studies have shown that LH stimulation does not affect the differentiation of human or mouse osteoclasts in vitro (65) and does not modify bone loss, the number of periapical osteoclasts, or the number of periapical cells positive for TNF-α and IL-1β in OVx mice with induced periapical injury (64). These findings support that LH may not be directly relevant to periodontal destruction. However, due to the limited number of studies conducted and the indirect evaluation of LH effects, its precise role remains inconclusive.

Follicle-stimulating hormone. The effects of follicle-stimulating hormone (FSH) on the development and severity of periodontitis have been more extensively studied than those of LH. Preclinical studies have shown that exogenous administration of FSH to ovariectomized rats with experimental periodontitis increased the distance from the cementoenamel junction to the alveolar crest and the area of bone loss, both of which correlated with an increase in FSH receptor-positive cells (66). In another study using OVx rats, administration of FSH significantly increased bone loss around the periapical lesion, the number of osteoclasts, and the expression of RANK-L, TNF-α, and IL-1β (67).

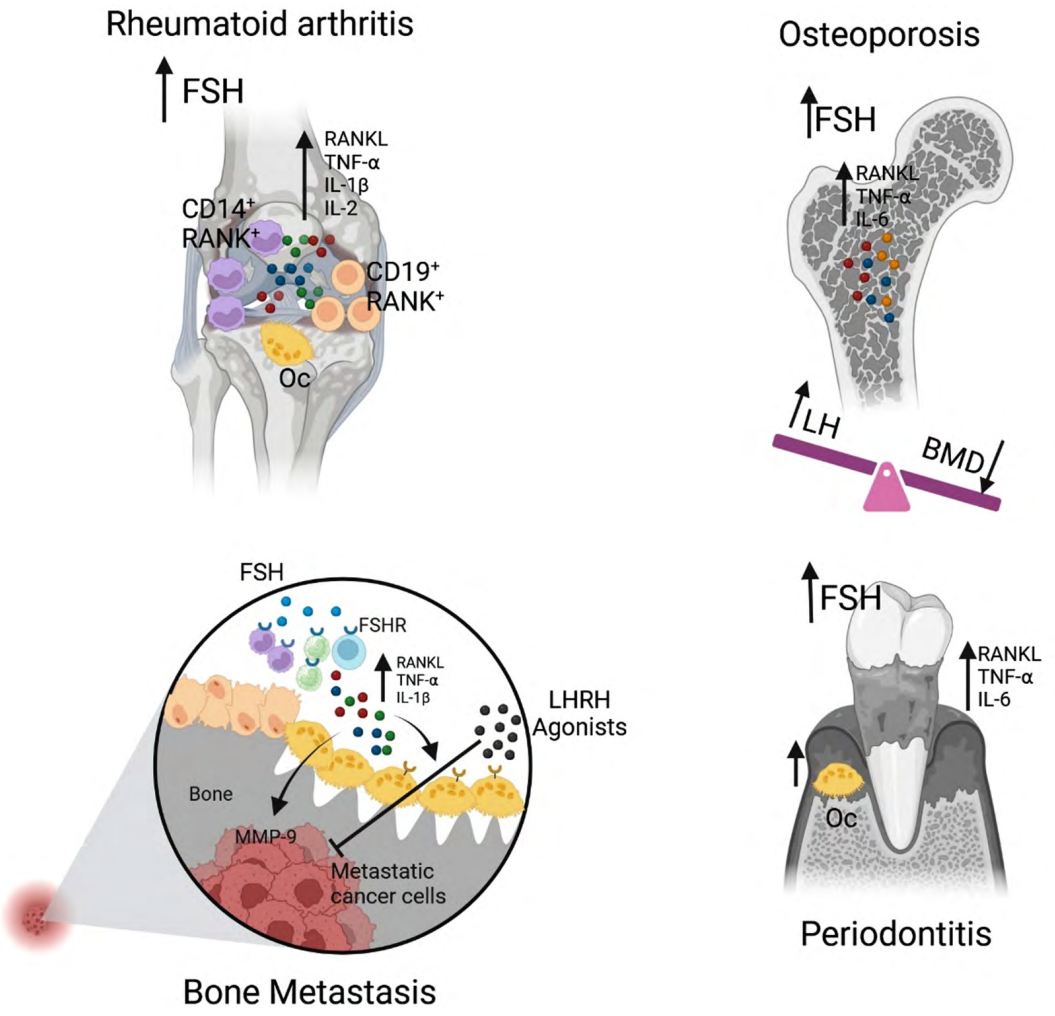


Figure 2. Gonadotropic hormones and their impact on bone diseases

Note. FSH in rheumatoid arthritis increases monocytes CD14+ RANK+ and B lymphocytes CD19+ RANK+, which produce inflammatory cytokines TNF-α, IL-1β, and IL-2, as well as RANKL to activate osteoclasts. In osteoporosis, the increase in LH is a biomarker of decreased bone mineral density (BMD), and the increase in FSH is positively correlated with inflammatory cytokines TNF-α, IL-1β, and IL-6, as well as RANKL, to activate osteoclasts. Luteinizing hormone-releasing hormone (LHRH) agonists inhibit bone metastasis from breast and prostate cancer. Immune cells express the FSH receptor (FSHR), which produces TNF-α, IL-1β, and RANKL to induce bone loss and induces the expression of matrix metalloproteinase 9 (MMP-9), facilitating the invasion of metastatic cells into bone. In periodontitis, alveolar bone loss is associated with increased FSH, which induces the expression of inflammatory cytokines TNF-α, IL-1β, and IL-6, as well as RANKL, to activate osteoclasts.

Source: Own elaboration.

Furthermore, administration of triptorelin, an FSH inhibitor, in ovariectomized rats with induced periodontitis increased bone volume, reduced the distance from the amelocemental junction to the alveolar crest, and decreased the expression of COX-2 in the periodontal ligament. Additionally, in human periodontal ligament cells, stimulation with FSH increased the expression of COX-2 and prostaglandin E2 (68).

Administration of the FSH inhibitor leuprorelin in rats decreased systemic inflammation, alveolar bone loss, the number of TRAP+ cells (osteoclast-

like cells), the volume of the periapical lesion, and the expression of toll-like receptor-4 (TLR-4) in the periodontal ligament (69). In contrast, FSH stimulation, either alone or in combination with lipopolysaccharide from *Porphyromonas gingivalis*, in healthy periodontal ligament cultures from women increased the protein and mRNA expression of TNF-α, IL-1β, and IL-6 (69).

In women undergoing FSH-based infertility treatment, three cycles of hormone therapy were associated with increased periodontal inflammation characterized by a higher gingival index, increased bleeding on probing, and a higher volume of gingival crevicular fluid (70). This confirms observations from experimental models that increased FSH promotes periodontal inflammation.

It is worth noting that there are few studies in humans, and the effects of FSH in men or in experimental studies involving male animals are very poorly understood. However, the available data suggest that, at least in women, FSH may contribute to the severity of periodontitis and alveolar bone loss by inducing increased osteoclastogenesis through elevated RANK-L and proinflammatory cytokines, as well as increasing the sensitivity of osteoclasts to FSH, thereby enhancing skeletal bone loss (14).

Conclusions

Gonadotropic hormones may play an important role in bone tissue in health and disease and could influence the bone microenvironment by inducing the production of cytokines and chemokines that activate the immune system, as well as the release of growth factors that together affect bone remodeling, leading to different systemic skeletal and alveolar bone pathologies. Gonadotropins may represent a therapeutic target for skeletal and oral cavity pathologies. However, it is important to note that most clinical evidence remains associative, highlighting the need for mechanistic and interventional studies to define the direct role of gonadotropins in bone pathophysiology.

Authors' contributions

Cifuentes-Mendiola SE: conceptualization, funding acquisition, investigation, methodology, project administration, supervision, visualization, writing – original draft, writing – review and editing. Martín del Campo-Lozano I: investigation, writing – original draft, writing – review and editing. García-Hernández AL: investigation, visualization, writing – review and editing.

Ethical implications

This work is a literature review and did not involve research involving humans or animals. Therefore, ethics committee approval was not required.

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Conflict of interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Artificial intelligence (AI) disclosure statement

The authors declare that they did not use AI in the preparation or writing of this article.

Data availability statement

The authors declare that no datasets are publicly available in open-access repositories. For any inquiries or requests related to this article, please contact the corresponding author.

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