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REVIEW

Exploring the Interaction Between Sjögren's Syndrome and Osteoporosis: Pathophysiological Mechanisms and Management Strategies

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Abstract: Sjögren's syndrome (SS) is a systemic autoimmune disorder predominantly affecting middle-aged and elderly women, characterized by lymphocytic infiltration of exocrine glands—particularly the salivary and lacrimal glands—resulting in xerophthalmia and xerostomia. Osteoporosis (OP), sharing similar age of onset and gender predilection, is a skeletal disorder defined by reduced bone mineral density and heightened fracture risk. The comorbidity of SS and OP represents a prevalent clinical phenomenon, with studies reporting an incidence rate of 33.1% to 51.6% among SS patients, significantly higher than that observed in healthy elderly populations. Vitamin D metabolism, widespread abnormal immune responses, hormonal imbalances, metabolic acidosis, and the RANKL/RANK/OPG axis exert significant contributory roles in the pathogenesis of both conditions. Treatment regimens for SS and OP may present certain overlaps yet potential contradictions. In this narrative review, we summarize the bidirectional relationship between these two diseases, thoroughly discuss the existing challenges in their management, and emphasize that recommending a comprehensive management strategy for SS patients with concurrent OP is crucial for enhancing patients' quality of life.

Keywords: Sjögren's syndrome, osteoporosis, immune system, pathophysiological mechanisms

Introduction

Sjögren's Syndrome (SS) is a complex systemic autoimmune disorder that most often affects middle-aged and elderly women.[1,2] The clinical manifestations of SS range from localized symptoms of xerophthalmia and xerostomia to systemic involvement of multiple organ systems, including the respiratory, musculoskeletal, hematological, renal, and neurological systems.[3,4] Furthermore, patients experience significant subjective burden, which may lead to psychiatric conditions such as anxiety, depression, and insomnia, severely impacting quality of life.[5] The complex clinical presentation results in high disease heterogeneity, posing substantial challenges for disease management.[3]

Osteoporosis (OP) is characterized by reduced bone mineral density (BMD) and structural deterioration, leading to fragile bones susceptible to fractures.[6–8] Similar to SS, OP shows a predilection for middle-aged and postmenopausal women.[9–11] The incidence of OP is significantly higher in patients with SS, with multiple studies confirming that individuals with SS are particularly susceptible to developing OP. A study of 128 Chinese patients with primary SS found that 32.8% had osteopenia and 51.6% met the diagnostic criteria for OP.[12] In another study involving 118 SS patients, the prevalence of OP was 33.1%.[13] Contributing factors include genetic determinants, hormonal influences, inadequate dietary intake of calcium and vitamin D (VD), physical inactivity, and prolonged use of certain medications, all of which are closely associated with the comorbidity of these two conditions.[14]

Moreover, the comorbidity of SS and OP undoubtedly increases disease burden, enhances fracture risk, and creates medication contradictions that further complicate disease management.[15] This review elucidates the key comorbidity mechanisms between SS and OP, examines current pharmacotherapeutic approaches, and provides a basis for clinical

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medication selection and new drug development. It also calls for more targeted future research to establish better disease prevention, risk stratification, and management strategies for comorbid patients.

SS and OP Share Similar Pathophysiological Mechanisms

VD and VD Metabolites

VD, best known for its role in skeletal health, has emerged as a key regulator of immune.[16] The metabolic process of VD in the endocrine system is complex and extensive, involving numerous enzymes, metabolites, the vitamin D receptor (VDR), VD binding protein (DBP), and other regulatory hormones.[17] Upon absorption, VD binds with DBP and is transported to the liver, where it undergoes conversion by 25-hydroxylase to form 25-hydroxyvitamin D (25(OH)D). This compound then binds to DBP and is transported to various tissues: primarily the kidneys, where it is filtered through the glomerulus; subsequently, it is captured by transmembrane proteins and absorbed into tubular epithelial cells, during which hydroxylation occurs to produce 1,25-dihydroxyvitamin D (1,25(OH)2D), the active form of VD. The final hydroxylation step in the kidney, acting on both 25(OH)D and 1,25(OH)2D, results in the formation of 24,25-dihydroxyvitamin D (24,25(OH)2D), an inactive metabolite that is readily eliminated from the body[18–20] (Figure 1).

Fundamentally, VD facilitates increased intestinal absorption of calcium and phosphorus, playing a vital role in maintaining normal serum calcium and phosphate levels, which is essential for satisfactory bone mineralization.[21,22] Meanwhile, multiple tissues, including bone and immune cells, express VDR that respond to 1,25(OH)2D, which is crucial for normal bone metabolism and immune system function.[23]

Bone remodeling is a dynamic equilibrium process jointly constituted by osteoclast-mediated bone resorption and osteoblast-mediated bone formation.[24] Osteoblasts—derived from mesenchymal stem cells—accomplish new bone formation by synthesizing matrix proteins (including type I collagen) and regulating hydroxyapatite deposition.[25] In contrast, as specialized multinucleated giant cells, osteoclasts degrade mineralized bone matrix through the secretion of acidic substances and proteolytic enzymes.[26] VD plays an essential role in bone formation and remodeling processes by regulating the functions of osteoblasts and osteoclasts.[27] Studies utilizing VDR knockout mice have demonstrated that osteoblasts from these animals exhibit enhanced expression of alkaline phosphatase, bone sialoprotein, and osteocalcin compared to wild-type counterparts, accompanied by accelerated mineralization capacity both in vitro and in vivo.[28] Furthermore, additional studies highlight the precise phase-specific regulatory mechanisms of VD in osteogenesis, which exhibit distinct temporal-dependent characteristics. Specifically, early addition of 1,25(OH)2D to osteoblast cultures

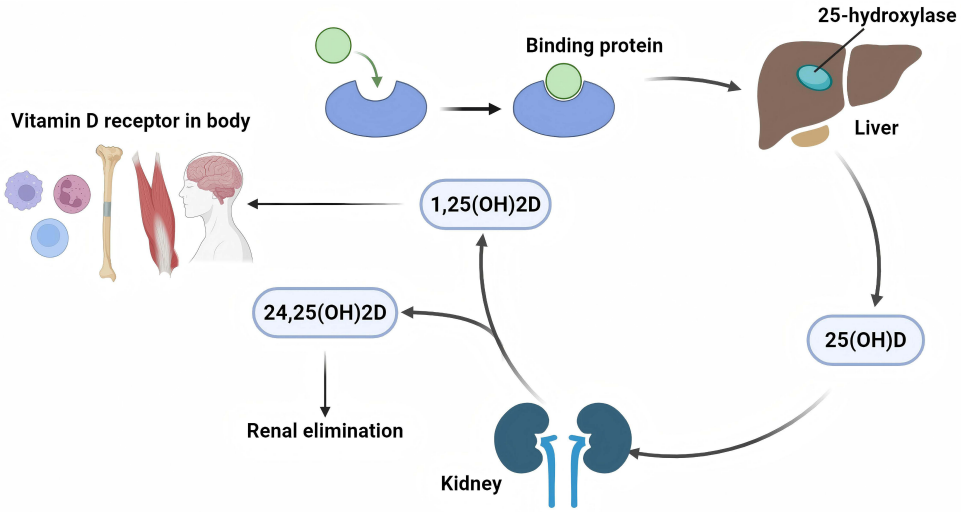

Figure 1 The overview of VD Metabolites. VD binds to vitamin D binding protein and is transported to the liver, where it is converted into 25(OH)D. After binding to DBP, 25(OH)D is absorbed into the renal tubular epithelial cells, where it undergoes hydroxylation to form 1,25(OH)2D. 1,25(OH)2D can bind to VD receptors in the body and exert various physiological effects.

suppresses the expression of collagen type 1 and alkaline phosphatase, whereas its administration during later differentiation stages stimulates their expression, thereby exerting biphasic regulatory effects on osteoblast function.[29]

Furthermore, under VD regulation, osteoblasts also participate in bone resorption processes. Numerous studies have demonstrated that under induction by 1,25(OH)2D, osteoblasts produce membrane-associated RANKL, which activates RANK on osteoclasts and their precursors to stimulate both differentiation and activation of osteoclast precursors.[30] In contrast, osteoblasts from VDR-knockout mice fail to support 1,25(OH)2D-induced osteoclastogenesis, whereas when co-cultured with wild-type osteoblasts in the presence of 1,25(OH)2D, osteoclast precursors regain the ability to differentiate into osteoclasts.[31]

Although the exact pathogenesis of SS remains unclear, it has been widely confirmed to be associated with various immune cells that express VDR and are regulated by 1,25(OH)2D. Reduced levels of 1,25(OH)2D have been observed in the peripheral blood of SS patients, showing a certain correlation with clinical and immuno inflammatory status.[32,33] Additionally, in murine models, 1,25(OH)2D or VDR agonists have been shown to reduce lymphocytic infiltration in salivary glands[34] (Figure 2).

For neutrophils, 1,25(OH)2D decreases neutrophil extracellular traps (NETs) formation and exhibits an antagonistic effect against the type I interferon signaling pathway in neutrophils of SS patients.[35]

Regarding dendritic cells (DCs), 1,25(OH)2D induces a shift toward a tolerogenic phenotype capable of producing anti-inflammatory factors, promoting regulatory T (Treg) cell differentiation, reducing antigen presentation, and thereby decreasing T cell activation.[36,37]

In SS patients, CD8+ T cells, Treg cells, and plasma cells accumulate around acini within exocrine glands, whereas their proportions are reduced in peripheral blood. The degree of this infiltration positively correlates with disease activity.[38–40] Through modulating cytokine secretion by DCs, 1,25(OH)2D can shift the T helper (Th) cell balance from a Th1/Th17-dominant state toward a Th2 phenotype.[41,42] Conversely, observations indicate that decreased peripheral Th2 cell frequencies and an elevated Th1/Th2 ratio may constitute the immunological mechanism underlying interstitial lung disease development in SS patients, reflecting higher disease activity.[43]

Notably, 1,25(OH)2D induces the generation of Tregs by binding to the FoxP3 promoter region.[44] Animal models have demonstrated that VD analogs increase the number of FoxP3$^+$ Tregs in salivary glands and alleviate glandular inflammation.[34] Moreover, 1,25(OH)2D induces apoptosis of activated B lymphocytes and modulates the NF-κB pathway through regulation of CD40 expression, thereby suppressing the generation of plasma cells and class-switched memory B cells.[45,46]

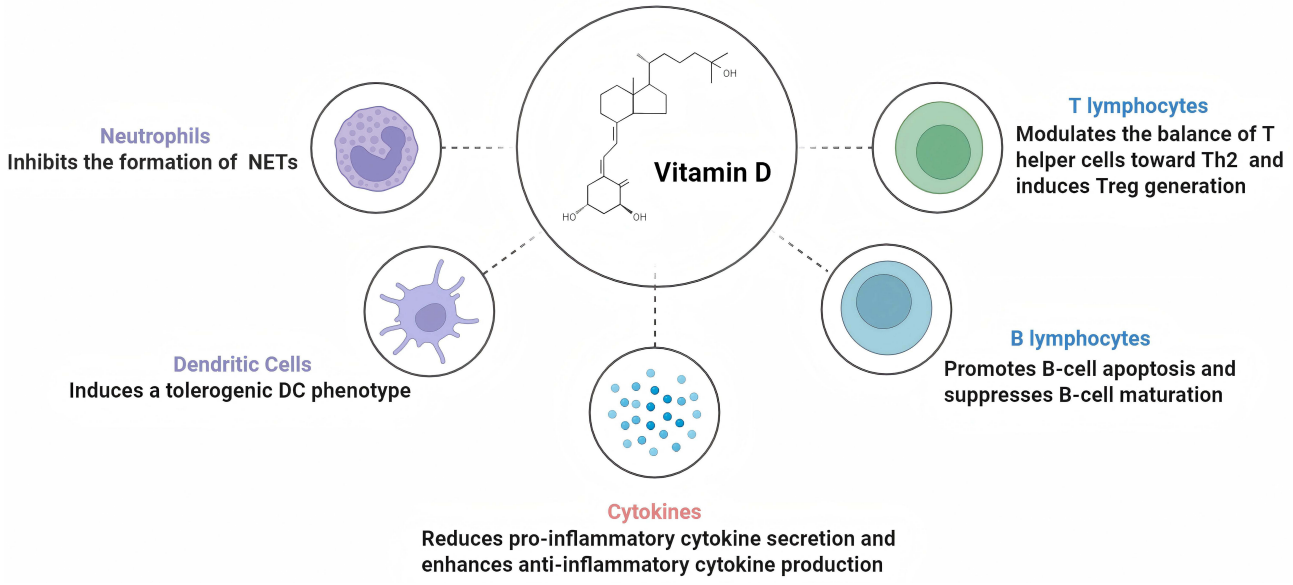

Figure 2 Overview of the effects of vitamin D on cytokines and immune cells, including neutrophils, dendritic cells, B lymphocytes, and T lymphocytes.

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Regarding cytokine modulation, 1,25(OH)2D significantly reduces secretion of the pro-inflammatory cytokines IL-6 and IL-12 while enhancing production of the anti-inflammatory cytokine IL-10.[47]

Sex Hormones

Sex hormones are a class of hormones that regulate sexual characters, sexual development, and reproductive functions in organisms. Sex hormones mainly include estrogens, progesterones, and androgen.[48] In addition to some fundamental functions related to sexual differentiation and the development and maintenance of sexual traits, sex hormones also participate significantly in the regulation of various physiological processes including but not limited to immune function, bone health, and cardiovascular system.[23,49,50] It is intuitive, therefore, that sex hormones may influence both conditions since both SS and OP mainly affect middle-aged and elderly women.

Estrogen

Estrogen influences both osteoblasts and osteoclasts and is important for multiple processes maintaining bone metabolic homeostasis (Figure 3). It induces osteoblasts to upregulate the expression of genes such as TIEG, IGF-I, and TGF-β, confirmed to directly promote osteoblast growth.[51–57] Estrogen stimulates Fas ligand expression in osteoclasts, which in turn exerts pro-apoptotic effects on osteoclast activity. Furthermore, estrogen decreases RANKL expression and increases OPG expression, thereby inhibiting osteoclast differentiation.[58–60] Additionally, estrogen participates in complex bone metabolic balance by promoting the expression of 1,25(OH)2D receptors, modulating osteoblast responses to parathyroid hormone (PTH), and promoting IGFBP-4 expression while reducing its proteolytic degradation.[61] PTH stimulates bone resorption, renal tubular calcium reabsorption, and the production of 1,25(OH)2D.[62] IGFBP-4 binds to IGF, thereby reducing its availability to IGF receptors and partially inhibiting IGF's biological effects on osteoblasts, including cell proliferation, differentiation, and bone formation and remodeling.[63]

Clinically, multiple studies have found decreased estrogen levels and an abnormal estrogen-progesterone ratio in patients with SS.[64–66] Elevated levels of Bcl-2, Fas, and FasL in the salivary gland tissues of SS patients correlate with

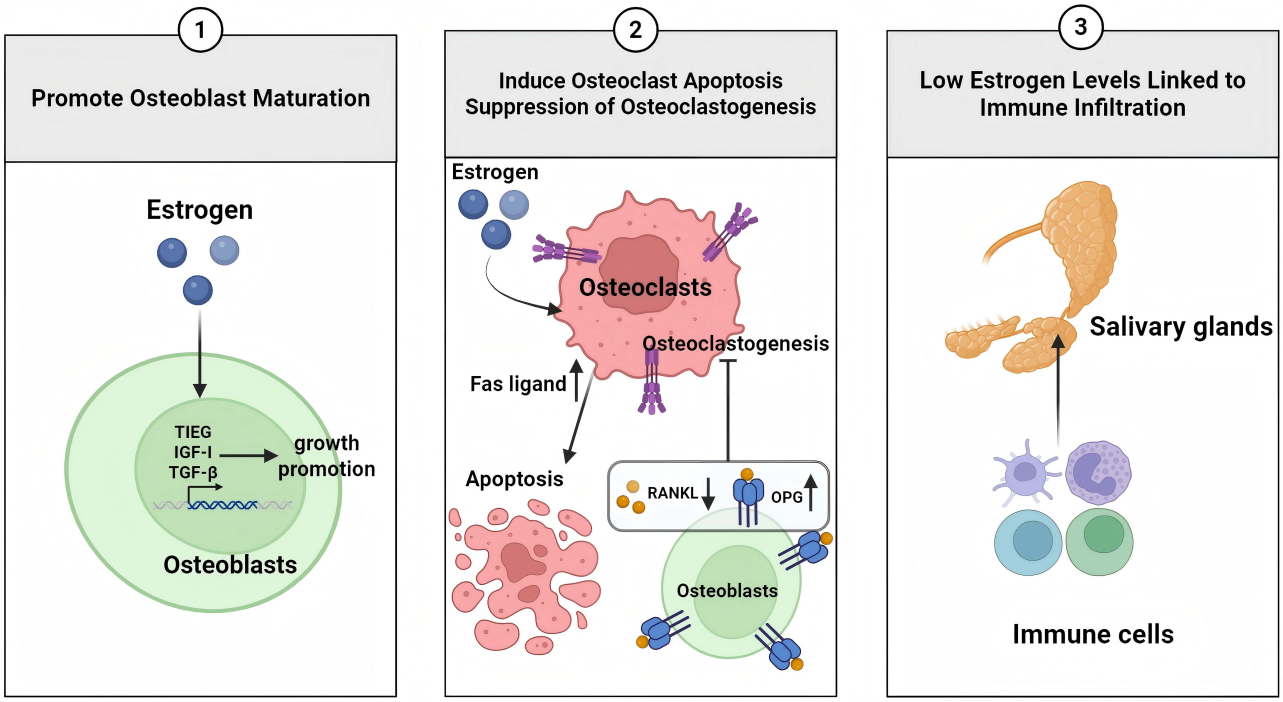

Figure 3 The Role of Estrogen in Bone Metabolism and Sjögren's Syndrome. This figure depicts three vertically arranged sections illustrating the multifaceted effects of estrogen: 1. Estrogen exerts growth-promoting effects on osteoblasts by upregulating the expression of TIEG, IGF-I, and TGF-β. 2. Estrogen induces osteoclast apoptosis through increased FAS ligand expression. Concurrently, it reduces RANKL secretion and enhances osteoblastic OPG production, which competitively binds RANKL to further inhibit osteoclast maturation. 3. Decreased estrogen levels are associated with enhanced immune cell infiltration in the exocrine glands of SS patients.

inflammatory severity and are significantly higher than in healthy controls.[67] Animal studies demonstrate that ovariectomy induces selective apoptosis of submandibular salivary gland acinar cells in mice, which subsequently develop focal lymphadenitis and SS-like disease with positive autoantibodies.[68] In ovariectomized rabbit and mouse models, estrogen supplementation prevents lacrimal cell death and lymphocytic infiltration.[69,70] These findings suggest acinar cell atrophy and apoptosis in SS may relate to estrogen deficiency, though specific mechanisms require further investigation.

Progesterone

Progesterone, also known as P4, is a 21-carbon steroid hormone. Progesterone provides multiple protections for the developing fetus and plays a key role in neuroglial cells, synapses, dendritic activity, neural development, and tissue repair. Additionally, progesterone also acts on a wide range of tissues, including the bones, heart, and brain.[71–73] Studies have found that the bone formation marker BAP increases during the luteal phase of the ovulatory cycle when progesterone levels are high, but does not increase during an anovulatory cycle. The bone resorption marker pyridinoline decreases during the luteal phase of the ovulatory cycle when progesterone levels are high, with a smaller decrease during an anovulatory cycle.[74] This suggests that elevated progesterone could be linked to an increase in bone formation while resulting in a slight reduction of bone resorption. Another research has indicated that elevated levels of progesterone can effectively suppress osteoblasts differentiation by as much as 80%.[75] Considering these factors, an appropriate amount of progesterone could be beneficial in managing OP.[76,77]

There is a scarcity of research exploring the influence of progesterone on SS, indicating a need for additional studies in this area.

Androgen

Testosterone is the primary androgen circulating in men, binding to both albumin and sex hormone-binding globulin in the bloodstream. In peripheral tissues, testosterone is converted into 5α-dihydrotestosterone by the enzyme 5α-reductase. Both testosterone and 5α-dihydrotestosterone are capable of activating the androgen receptor (AR).[78] Additionally, testosterone can be converted into estradiol (E2) by the enzyme aromatase, which is also expressed locally in bone tissue. The AR is expressed in both osteoblasts and osteocytes.[79] Studies have shown that osteoblasts from cortical bone have a stronger AR binding capacity compared to those from trabecular bone, although there is no gender difference in AR expression.[80,81] This suggests that both testosterone and E2 may play important roles in maintaining skeletal health in both sexes. Testosterone directly inhibits osteoclast differentiation and bone resorption, while the inhibitory effect of E2 on osteoclasts is mainly mediated indirectly through osteoblasts.[82] The effects of androgens on bone cells are regulated by three main factors: TGF-β, IGFs, and IL-6. Androgens may promote bone formation by activating TGF-β and IGFs or reduce osteoclastogenesis by inhibiting IL-6.[83–85] Additionally, androgens may directly affect osteoclasts or indirectly influence osteoclast formation by affecting bone marrow stromal cells, thereby regulating osteoclastogenesis induced by RANKL.[86]

There is currently no clear conclusion regarding the relationship between androgens and SS. Some studies have found that patients with SS have lower serum levels of dehydroepiandrosterone, 5α-dihydrotestosterone, and dehydroepiandrosterone sulfate. As age increases and the aging process begins, androgen levels naturally decline. By the age of 40, women's testosterone levels gradually decrease to half of what they were at 20 years old. Given the age of onset in SS patients, the decline in androgen levels may be closely related to the onset of SS.[66,87,88] Androgens can regulate the function of the lacrimal glands and meibomian glands, modulate lipid production in these tissues, and promote the formation of the lipid layer of the tear film. Androgen deficiency may lead to meibomian gland dysfunction and evaporative dry eye.[89,90] Some studies have also found defects in androgen deficiency and the processing of dehydroepiandrosterone secretion in the salivary glands of SS patients.[91] Therefore, the dry mouth and dry eyes in SS patients may be related to androgens, but further research is needed to verify this.

In summary, sex hormones, especially estrogens and androgens, play an essential role in regulating bone health, glandular function, and various physiological processes. Estrogen influences bone metabolism by regulating osteoblasts and osteoclasts, while also affecting the health of glands such as the lacrimal and salivary glands. Androgens, meanwhile, help maintain BMD and strength by balancing bone resorption and formation. They also play a critical role in the

function of the lacrimal and meibomian glands, which affect tear production and eye health. As a result, any abnormalities in sex hormone levels, particularly a deficiency or imbalance of estrogens and androgens, could significantly contribute to the co-occurrence of SS and OP. These hormonal changes not only directly impact bone and glandular function but may also indirectly trigger the development and progression of these conditions through immune system mechanisms. Gaining a deeper understanding of how sex hormones affect the comorbidity of SS and OP may offer new avenues for the treatment and management of these diseases.

RANKL/RANK/OPG Axis

The RANKL-RANK-OPG axis plays a pivotal role in mediating communication between osteoblasts and osteoclasts.[92,93] Upon RANK activation, signaling adaptor proteins such as TRAF6 are recruited and activated, triggering a kinase cascade that leads to nuclear translocation and activation of transcription factors including NFATc1, c-Fos, and NF-κB—key regulators of osteoclast-specific gene expression. Co-stimulatory signals mediated by ITAM-containing proteins (DAP12 and FcRγ), which bind to receptors such as OSCAR, PIR-A, or TREM-2, activate the Syk-PLCγ pathway and induce calcium influx. This calcium influx subsequently activates calcium-dependent phosphatase signaling, enhancing NFATc1 and CREB activity to promote osteoclast-specific gene expression. This process initiates osteoclast differentiation, ultimately leading to the formation of mature multinucleated osteoclasts through cell fusion and incomplete cytokinesis.[94–97]

Osteoprotegerin (OPG), primarily expressed by osteoblasts, is regulated by estrogen, IL-4, TGF-β, and PGE2.[98] By competitively binding to RANK with RANKL, OPG inhibits osteoclast formation and suppresses bone resorption activity[96] (Figure 4).

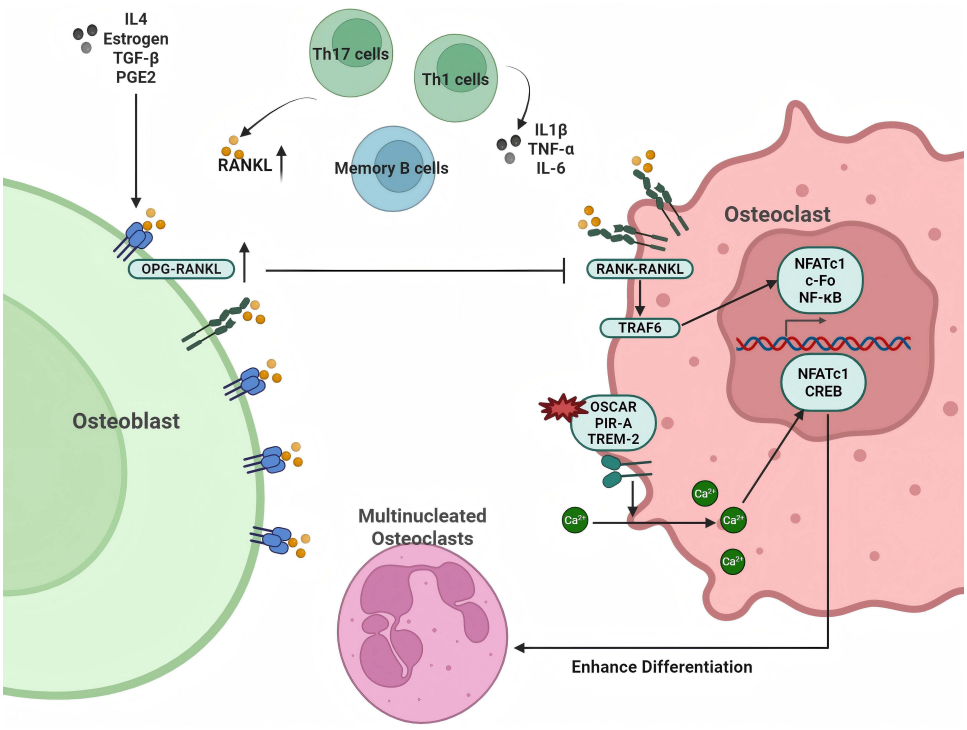

Figure 4 The communication between osteoblasts and osteoclasts through RANKL/RANK/OPG axis. Upon RANK activation, adaptor proteins such as TRAF6 are recruited and activated, leading to the activation of kinases and subsequent nuclear translocation and activation of transcription factors including NFATc1, c-Fos, and NF-κB, which are essential for regulating osteoclast-specific gene expression. Co-stimulatory signals mediated by ITAM-containing proteins DAP12 and FcRγ, through binding to receptors such as OSCAR, PIR-A, or TREM-2, further trigger the Syk-PLCγ pathway and calcium influx. The resulting calcium influx activates calcium-dependent phosphatase signaling, enhancing NFATc1 and CREB activity to promote osteoclast-specific gene expression and initiate osteoclast differentiation. Subsequently, cells undergo fusion and incomplete division to form mature multinucleated osteoclasts. OPG competes with RANKL for binding to RANK, thereby inhibiting osteoclastogenesis and reducing bone resorption.

In SS, activated Th1 and Th17 cells lead to elevated levels of IL-1β, TNF-α, and IL-6, which promote RANKL expression.[99–103] Furthermore, activated Th17 cells and memory B cells further produce RANKL. These cytokines collectively suppress OPG expression, ultimately disrupting bone homeostasis.[104,105] However, direct evidence confirming this mechanism in SS remains limited.

Relevant studies have been conducted in systemic lupus erythematosus (SLE) and rheumatoid arthritis (RA). Among SLE patients, the frequency of the OPG 245 G allele is significantly higher in those with low BMD than in those with normal BMD (31.4% vs 18.1%, $p = 0.04$),[106] indicating that OPG 245 G may be a genetic factor underlying OP in autoimmune diseases. In another study that collected blood and synovial fluid from 167 RA patients and 25 healthy volunteers, elevated levels of inflammatory cytokines were observed in RA. Exposure to IL-21 or IL-23 down-regulated the production of cytokines, TNF-α, IFN-γ, IL-17, and RANKL in these cells. This further suggests that increased TNF-α and IL-6 levels may underlie the elevated RANKL observed in SS, and that the IL-21/IL-23 axis plays a pivotal role in modulating both inflammation and RANKL expression.[107]

Renal Tubular Acidosis (RTA)

RTA refers to a collection of transport abnormalities marked by a diminished reabsorption of bicarbonate (HCO3−) in the proximal tubule, decreased secretion of distal hydrogen ions (H+), or a combination of both. This leads to impaired net acid excretion and ongoing hyperchloremic metabolic acidosis, all while the glomerular filtration rate stays within the normal range.[108] From a pathophysiological perspective, RTA is mainly categorized into three distinct types. Type 2, or proximal RTA, results from the impaired reabsorption of filtered bicarbonate in the proximal tubule. In contrast, type 1 (distal) RTA (dRTA) is caused by a deficiency in distal H+ secretion, while type 4 RTA is characterized by decreased secretion of both H+ and K+ in the collecting ducts, often due to lower aldosterone secretion or response. Most cases observed in children are primary and stem from inherited factors. Types 1 and 4 RTA might also arise secondary to other underlying issues, especially when symptoms emerge at a later stage. Type III or combined RTA is a type of renal tubular dysfunction that exhibits features of both proximal RTA and dRTA.[109]

The prevalence of dRTA in patients with SS varies significantly across different studies, ranging from 6.8% to 70%.[110–113] SS may be caused by tubulointerstitial infiltration of T cells, B cells, and plasma cells, or, less commonly, by autoantibodies. The majority of patients exhibit clinical symptoms as a direct consequence of lymphocyte infiltration in the interstitium, which promotes interstitial fibrosis, leading to chronic kidney disease. dRTA is the most common electrolyte disturbance in SS, involving the connecting tubules and collecting ducts.[114] dRTA is associated with growth retardation, skeletal pain, abnormal bone metabolism, and pathological fractures, which mainly originates from the physicochemical dissolution of minerals caused by acidosis, leading to changes in bone cell function. Studies have found significant suppression of both bone formation and bone resorption in dRTA patients, along with a mild increase in osteoid volume.[115] Additionally, most dRTA patients have a significant reduction in BMD in the spine and hips.[116]

The Medications Used to Treat SS May Lead to OP

GCs

GCs are widely used to suppress inflammation and immune system responses due to their potent anti-inflammatory, immunosuppressive, and metabolic regulatory functions. They exert therapeutic effects by binding to GCs receptors in the body, thereby regulating a series of biological processes. GCs can significantly inhibit the overactivity of the immune system, which is why they are extensively used in diseases caused by immune system dysfunction, such as SS.[117]

Glucocorticoid-induced osteoporosis (GIO) is the most common secondary cause of OP and the most common iatrogenic cause. Bone loss caused by GIO can be roughly divided into two stages. The initial stage, within the first year of treatment, sees a rapid loss of BMD at a rate of about 6–12%. In the long-term stage, the rate of BMD loss slows down, with an annual loss of about 3% thereafter.[118,119] In a study, the risk of vertebral fractures in individuals taking oral GCs was nearly three times higher than that of the general population, while the risk of hip fractures doubled.[120] Additionally, the incidence of fractures was influenced by the duration of use (cumulative dose) and the current dose.[121]

The pathophysiology of GIO primarily involves a long-term reduction in bone formation, with an increase in bone resorption during the early phase (the first year after starting treatment). GCs inhibit the formation of osteoblasts, induce apoptosis in both osteoblasts and osteocytes, and prolong the lifespan of osteoclasts.[119]

GCs exert multiple direct effects on osteoblast signaling pathways. They enhance the expression of PPARγ2, KLF15, C/EBPα, and aP2, which leads to the preferential differentiation of multipotent progenitor cells into adipocytes rather than osteoblasts, thus reducing the number of osteoblasts.[122] In the WNT–β-catenin signaling pathway, GCs increase the expression of sclerostin and other inhibitory factors, while suppressing the expression of WNT16 in a dose- and time-dependent manner. This results in a decrease in osteoblastogenesis and bone loss.[123] At low or physiological doses, GCs appear to induce autophagy and support the activity and function of osteoblasts. However, at doses higher than physiological levels, this process is inhibited, leading to a loss of osteoblast-related gene expression and increased apoptosis.[124] Additionally, GCs affect the RANK–RANKL–OPG axis by increasing RANKL production and decreasing the transcription of OPG mRNA in osteoblasts and osteocytes. GCs influence osteoblasts to elevate the ratio of RANKL to OPG, which enhances bone resorption and promotes the differentiation and maturation of osteoclasts.[125] However, the long-term impact of GCs on osteoclast function is still not fully understood.

GCs affect bone metabolism through various indirect pathways. They suppress the transcription of the IGF1 gene, thereby reducing bone formation, whereas IGF1 typically promotes bone formation by stimulating type I collagen synthesis, inhibiting collagen degradation, and preventing osteoblast apoptosis.[126] Additionally, GCs disrupt calcium homeostasis by decreasing calcium absorption in the intestine and inhibiting calcium reabsorption in the renal tubules, which can lead to hypocalcemia and secondary hyperparathyroidism.[127] GCs may also enhance the sensitivity of bone cells to PTH by increasing the number and affinity of PTH receptors. They inhibit growth hormone secretion, reducing its anabolic effects on bone, and suppress gonadotropin secretion, leading to decreased estrogen and testosterone levels, which further promotes bone resorption.[125] These combined effects contribute to bone loss caused by GCs.

In summary, although GCs are effective in treating inflammatory and immune-related conditions, prolonged use can result in considerable bone loss and a higher risk of fractures. This is due to the intricate combination of direct and indirect effects on bone metabolism. The main factors contributing to GIO include the inhibition of osteoblast function, increased bone resorption, and disturbances in calcium balance. A thorough understanding of these mechanisms is essential for creating strategies to reduce bone loss and safeguard bone health in individuals undergoing GCs treatment.

Disease-Modifying Antirheumatic Drugs (DMARDs)

Methotrexate (MTX)

MTX is one of an often-prescribed DMARDs that is extensively used for the management of a variety of conditions such as cancers and disorders of the immune system. It operates by targeting dihydrofolate reductase, which leads to a decrease in folate production. Folate plays an essential role in the process of DNA and RNA synthesis in cells, and the reduction of its production significantly hinders the rate of cell division.[128]

Currently, the impact of MTX on BMD among patients with SS is still not well-established, as there exists a scarcity of research and ongoing discussions surrounding the issue. The administration of MTX may result in a reduction of osteoblasts, osteocytes, and chondrocytes within the growth plate, concurrently elevating the quantity and activity of osteoclasts.[129] Between 2011 and 2019, there were reports of five instances in which individuals exhibited reduced BMD or sustained fractures following the administration of MTX. Nonetheless, the sites of the fractures were uncommon for those typically seen with OP, and all individuals showed signs of recovery within a few months following the cessation of MTX.[130] Moreover, research indicates that there was an increase in BMD among patients with RA following treatment with MTX. Notably, findings in this area appear to be inconsistent, possibly due to the diverse mechanisms underlying autoimmune disorders and the differing intensities of disease activity.[131–133] The enhancement of BMD observed in individuals with RA might be attributed to the attenuation of the inflammatory response through the use of MTX.

Cyclophosphamide (CTX)

CTX is categorized as an alkylating compound. Its mechanism involves the introduction of alkyl groups into the DNA structure, which leads to breaks or cross-links within the DNA strands; this interference disrupts the processes of DNA

replication and repair, ultimately resulting in cellular apoptosis.[134] Due to the rapid division rate of cancerous cells, the agent is notably effective in suppressing their growth.[135] Simultaneously, CTX exerts a degree of suppression on immune system cells, which is why it is frequently utilized in managing diseases related to the immune system.[136,137] The occurrence of OP due to CTX is significantly connected to the decline in mesenchymal stem cells within the bone marrow and the inhibition of bone development. Alterations in the microenvironment resulting from CTX might enhance the persistence of osteoclasts, thus accelerating the processes of bone metastasis and bone degradation. Simultaneously, CTX has the capacity to impede the formation of osteoclasts through the inhibition of the RANKL signaling pathway, which contributes to the deceleration of bone resorption. The influence of CTX on bone metabolism encompasses both the suppression of osteoblast formation and the reduction of osteoclast development. These influences can result from the decrease in osteoclast function, the downregulation of bone degradation indicators, and the modulation of osteoblast formation processes, thereby contributing to the maintenance of bone integrity.[138] Research indicated that CTX may lead to OP in male C57BL/6 mice, likely due to its impact on hindering the formation of osteoblasts by diminishing both the quantity and differentiation of bone mesenchymal stem cells (MSCs), as well as reducing the activity and generation of osteoblasts.[139]

Calcineurin Inhibitors (CNI)

CNI are a class of drugs that regulate immune responses by inhibiting the activity of calcineurin. Calcineurin is a calcium-dependent enzyme that typically plays a role when T cells are stimulated. Calcineurin dephosphorylates the transcription factor NFAT (Nuclear Factor of Activated T-cells), allowing it to enter the nucleus and activate immune responses. Therefore, inhibiting the activity of calcineurin can prevent T cell activation and reduce immune responses.[140] The main calcineurin inhibitors used in clinical practice are Cyclosporine (CsA) and Tacrolimus (FK506). CsA binds to cyclophilin A, inhibiting the function of calcineurin. FK506, similar to CsA, has a more specific mechanism. It binds to the FKBP12 protein, and the resulting complex inhibits the activity of calcineurin.[141]

Studies have found that both CsA and FK506 significantly reduce the bone strength of the femoral shaft and the BMD of the tibia and femur in rats. Histological analysis of bone tissue shows that administration of both drugs leads to a decrease in bone volume, trabecular number and thickness, as well as an increase in trabecular separation. CsA increases both bone formation and bone resorption, leading to high-turnover bone loss, while FK506 increases bone resorption without affecting bone formation, resulting in bone loss.[142] Another study found that both CsA and FK506 reduced BMD in liver transplant patients, with FK506 treatment having more favorable long-term effects on bone metabolism compared to CsA treatment.[142]

Azathioprine (AZA)

AZA is converted into 6-mercaptopurine (6-MP) in the body. 6-MP inhibits the synthesis of purines, which in turn affects the synthesis of DNA and RNA, suppressing the proliferation of T cells and B cells, and slowing down the immune response.[143] A study found that MicroCT imaging of mice showed a significant adverse effect of azathioprine treatment on trabecular bone microstructure, with a significant reduction in bone volume/tissue volume and trabecular number.[144] Another study found that monotherapy with azathioprine did not alter the levels of ionized calcium, 1,25(OH)2D, or PTH, but a decrease in osteocalcin was observed, indicating impaired osteoblast activity.[145]

Management of Patients with SS-OP Comorbidity

There exists a significant therapeutic paradox between immunosuppressive therapy for SS and OP management, which manifests in three key aspects: Firstly, while immunosuppressants like glucocorticoids can effectively control inflammatory activity in SS, they simultaneously accelerate bone loss by inhibiting osteoblast function and promoting osteoclast activation. Furthermore, DMARDs such as MTX and CNI exhibit differential effects on bone metabolism, with some agents potentially exacerbating bone deterioration. Secondly, OP treatments including bisphosphonates and anti-RANKL monoclonal antibodies, while inhibiting bone resorption, may interfere with immune cell function and potentially compromise immunoregulation. Lastly, a clinical dilemma exists in treatment timing - the acute phase of SS necessitates intensive immunosuppression, yet this period often coincides with when drug-induced skeletal adverse

effects are most difficult to counteract, while early initiation of bone-protective therapy may be challenging due to high disease activity.

Currently, there is a significant lack of clinical management guidelines for autoimmune diseases complicated with OP. This knowledge gap is particularly prominent in research on individual specific autoimmune diseases complicated with OP. To date, only OP associated with RA has been partially studied. Other autoimmune disease areas still lack targeted consensus on bone health management. This current situation urgently needs to be addressed through multicenter clinical trials and systematic reviews. Furthermore, the current treatment for SS remains largely empirical, with a notable absence of standardized clinical guidelines. Based on these current circumstances, we propose a distinctive management strategy for SS-OP comorbidity (Figure 5).

In SS, multiple factors including inflammatory activation, VD deficiency, hypoestrogenism, and acid-base metabolic abnormalities may exacerbate bone destruction. First and foremost, it is crucial to monitor BMD and assess bone metabolism regularly. This includes periodic measurements of serum calcium, phosphorus, 25(OH)D, and PTH to evaluate metabolic risk. And higher doses of calcium and VD supplementation than peers may be necessary, but there are few direct studies in the field of SS. For RA patients, women aged 51 and above and men aged 71 and above require an increased intake of 1200mg per day. For individuals aged 50 and older, a daily VD supplementation of 800–1000 IU is routinely recommended, and is beneficial for reducing RA disease activity.[146,147]

Additionally, monitoring bone turnover markers such as β-C-terminal telopeptide and procollagen type I N-terminal propeptide provides valuable insights into ongoing bone remodeling processes.[148,149] Given that immune system activation in SS may enhance bone resorption, comprehensive bone metabolism tests are vital for these patients as they facilitate the detection of early bone loss and enable timely intervention. Furthermore, for patients receiving long-term corticosteroid treatment or those with additional risk factors (such as advanced age, low body weight, previous fracture history, smoking, excessive alcohol consumption, or physical inactivity),[8] regular dual-energy X-ray absorptiometry examination can monitor OP progression, and adjusting treatment regimens accordingly.[150] More supplementation with calcium and VD is recommended to maintain adequate serum 25(OH)D levels in this population to slow down bone damage.

Comprehensive assessment of BMD and bone metabolism not only facilitates early and timely intervention but also helps gain a better understanding of the skeletal health status of patients with SS and OP, allowing for effective therapeutic selection. Selection of specific agents should be tailored to patient characteristics: bisphosphonates may be considered for patients with mild renal impairment, with caution regarding esophageal dysmotility; denosumab represents a viable option for those with significant renal dysfunction,[151,152] while monitoring for infection risk; and teriparatide can be utilized in patients with high fracture risk, with attention to treatment duration limitations. In all

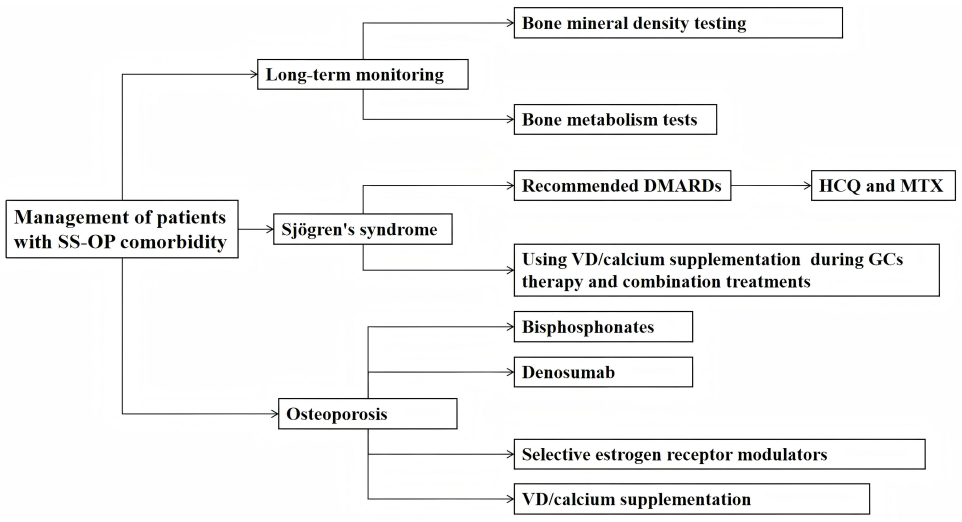

Figure 5 Overview of the management strategies for the comorbidity of Sjögren's Syndrome and Osteoporosis.

cases, careful consideration of potential SS-related comorbidities such as renal damage, esophageal motility disorders, and infection risk is essential for rational therapeutic selection and optimal patient outcomes.

In patients with comorbid SS and OP, the apply of DMARDs needs to be considered with caution, as some DMARDs may exacerbate OP or increase the risk of fractures. Recommended DMARDs include hydroxychloroquine (HCQ), and MTX. HCQ has been widely used in the treatment of SS to alleviate symptoms and control disease progression. Multiple studies have found that the impact of HCQ on bone metabolism may be relatively minor, and its anti-inflammatory effects may provide some protection for bone health.[153] MTX is a commonly used medication for treating immune system-related diseases, especially in conditions such as RA, psoriasis, and SLE, where it has shown significant efficacy. It works by suppressing the overactivity of the immune system to alleviate symptoms and control disease progression. In the treatment of SS, MTX also has certain applications, particularly in managing patients with notable arthritis, inflammation, or other systemic manifestations.[154,155] Although it has been mentioned earlier that MTX may have some effect on bone metabolism, the research is not conclusive, and the impact of MTX is relatively minor. In addition, some DMARDs are not recommended for SS patients with OP, such as CsA, AZA, FK506, etc., as these medications can have an adverse effect on bone metabolism, as mentioned earlier.

Challenges and Perspectives

The current understanding of the SS-OP association remains limited due to several fundamental challenges: (1) The pathogenesis of SS, a complex systemic autoimmune disorder, remains incompletely understood; (2) Significant clinical heterogeneity among SS patients creates population standardization difficulties; (3) Osteoporosis's strong dependence on age and gender introduces unavoidable confounding effects in current studies.

Building upon current evidence, future research should prioritize two key translational directions for SS-OP comorbidity: first, the development of specific biomarkers focusing on shared inflammatory mediators that concurrently associate with glandular dysfunction and accelerated bone loss, along with predictive markers for rapid BMD decline; second, the design of targeted clinical trials investigating therapeutic strategies against common inflammatory pathways, with dual emphasis on both immunomodulation and osteoprotection to comprehensively address disease progression. Current bone health management guidelines for autoimmune diseases primarily focus on GIO,[156] while lacking comprehensive evaluation of other medications and individualized analysis across different autoimmune conditions. Future research should address these gaps to optimize patient management.

Summary and Conclusion

OP poses a significant health challenge for individuals with SS, significantly increasing the risk of fractures, pain, and mobility limitations. These symptoms not only negatively impact physical health but also greatly interfere with daily life and overall quality of life. The two conditions are interrelated, with their interaction forming a vicious cycle, where each exacerbates the other's pathological state. For instance, individuals with SS often experience chronic inflammation and immune system abnormalities, leading to an imbalance in bone metabolism, which makes the bones more susceptible to damage and, in turn, triggers OP. Therefore, increased clinical focus on bone health in SS patients is warranted.

This review elucidates the interaction mechanisms between SS and OP. VD deficiency may worsen bone health problems and affect the progression of SS through immune system involvement. Hormones such as estrogen and androgens are vital for both bone and glandular health, and any imbalance in these hormones may serve as a link between SS and OP. Additionally, The RANKL/RANK/OPG signaling axis constitutes a pivotal interface coordinating bone metabolism and immune function. dRTA, the most prevalent electrolyte disorder in SS patients, may serve as a key pathogenic contributor to OP development. Furthermore, medications commonly used to treat SS may promote the development and progression of OP by inhibiting bone formation and accelerating bone resorption.

For patients with SS-OP comorbidity, we propose a rational management approach that includes: regular BMD monitoring and bone metabolism evaluation, prioritizing the use of DMARDs with minimal impact on bone metabolism, and combining bone-modulating agents with calcium/VD supplementation to synergistically control both autoimmune activity and bone loss progression.

These findings provide critical evidence for establishing integrated management protocols for bone health in SS patients, and offer fundamental insights for developing multidisciplinary approaches to autoimmune diseases with comorbid bone disorders.

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Author Contributions

All authors made a significant contribution to the work reported, whether that is in the conception, study design, execution, acquisition of data, analysis and interpretation, or in all these areas; took part in drafting, revising or critically reviewing the article; gave final approval of the version to be published; have agreed on the journal to which the article has been submitted; and agree to be accountable for all aspects of the work.

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Disclosure

ZH.S., JX.C. and L.X. declare that they have no conflicts of interest in this work.

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