Osteoporosis and Sarcopenia 8 (2022) 58–67

Contents lists available at ScienceDirect

Osteoporosis and Sarcopenia

journal homepage: http://www.elsevier.com/locate/afos

Review article

The impact of sex steroids on osteonecrosis of the jaw

Ranhee Kim [a, b], Sung Woo Kim [a], Hoon Kim [a, c, d], Seung-Yup Ku [a, c, d, *]

[a] Department of Obstetrics and Gynecology, Seoul National University Hospital, Seoul, South Korea
[b] Department of Obstetrics and Gynecology, Dongguk University Ilsan Medical Center, Goyang, South Korea
[c] Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Seoul, South Korea
[d] Institute of Reproductive Medicine and Population, Medical Research Center, Seoul National University, Seoul, 03080, South Korea

ARTICLE INFO

Article history:
Received 14 February 2022
Received in revised form
24 April 2022
Accepted 18 May 2022
Available online 17 June 2022

ABSTRACT

Sex steroid hormones play a major role in bone homeostasis. Therefore, the use of sex hormones or drugs may increase the risk of osteonecrosis of the jaw (ONJ), a complication caused by damaged bone homeostasis. However, few are known the impact of medications changing sex hormone levels on ONJ.

The pathophysiology of ONJ is not clearly understood and many hypotheses exist: cessation of bone remodeling caused by its anti-resorptive effect on osteoclasts; compromised microcirculation due to medication affecting angiogenesis, including bisphosphonate; and impairment of defense mechanism toward local infection.

The use of high-dose intravenous bisphosphonate in cancer patients is associated with a high prevalence of ONJ. Exogenous estrogen or androgen replacement was reported to be associated with ONJ. Polycystic ovarian syndrome (PCOS) patients demonstrate an androgen excess status, and androgen overproduction serves as a protective factor in the bone mineral density of young women. To date, there are no reports of ONJ occurrence due to androgen overproduction. In contrast, few reports on the occurrence of ONJ due to estrogen deficiency induced by drugs, such as selective estrogen receptor modulator (SERM), aromatase inhibitors, and gonadotropin-releasing hormone (GnRH) agonists, are available.

Thus, the role of sex steroids in the development of ONJ is not known. Further studies are required to demonstrate the exact role of sex steroids in bone homeostasis and ONJ progression. In this review, we will discuss the relationship between medication associated with sex steroids and ONJ.

1. Introduction

The skeleton is a metabolically active organ that undergoes a continuous process of bone remodeling, which occurs by two processes: bone resorption by osteoclasts and bone formation by osteoblasts. Therefore, bone homeostasis is established by the balance between osteoclasts and osteoblasts. Sex steroid hormones such as estrogen and androgen are known to play a major role in bone homeostasis [1]. After Fuller Albright [2] reported that estrogen deficiency in postmenopausal women leads to bone loss, estrogen was recognized as a key regulator of bone metabolism in women. In addition, androgen was assumed to be a key regulator of bone homeostasis in men; however, a large number of studies have shown that estrogen is a major regulator of bone metabolism not only in women but also in men.

The human skeleton consists of 2 bone types: the dense cortical bone found in the peripheral skeleton and the trabecular bone with a honeycomb-like structure found in the axial skeleton, such as the pelvis and spinal column. Remodeling is more active in trabecular bone than in cortical bone. Therefore, the impact of sex steroid hormones on trabecular bone is greater than that in cortical bone.

Although the mechanisms by which estrogen affects bone homeostasis have been heavily investigated, it is still unclear whether estrogen inhibits osteoclastic activity or promotes osteoblastic activity, or both. However, studies have shown that estrogen reduces osteoclastic activity by inhibiting receptor activator of the NF-kB ligand (RANKL) production, which plays an important role in the proliferation and survival of osteoclasts, and inhibits the secretion of cytokines that promote bone resorption.

* Corresponding author. Department of Obstetrics and Gynecology, Seoul National University College of Medicine, Daehak-ro 101, Chongno-gu, Seoul, 03080, South Korea.
E-mail address: jyhsyk@snu.ac.kr (S.-Y. Ku).
Peer review under responsibility of The Korean Society of Osteoporosis.

https://doi.org/10.1016/j.afos.2022.05.003

Surgical or natural menopause reduces the protective effects of sex steroid hormones on the bone, and a rapid bone loss ensues that necessitates medications to treat or prevent osteoporosis. Treatments for osteoporosis include the use of bone resorption inhibitors and bone anabolic agents. Estrogen replacement therapy and bisphosphonates are widely used among bone resorption inhibitors. In addition, estrogen replacement therapy is used to mitigate the inflammatory bone-microenvironment driven by estrogen deficiency. Bisphosphonate is a stable analog of pyrophosphate, which adheres to bone mineral calcium and inhibits osteoclast attachment and osteoclast apoptosis.

Osteonecrosis of the jaw (ONJ) is one of the side effects of long-term use of bisphosphonates.

ONJ associated with bisphosphonate use is defined as bone exposure in the maxillofacial region with the inability to heal within 8 weeks in a patient with a history of bisphosphonate use and no existing history of head and neck irradiation [3]. The first ONJ case report was described in 2003 [4]. ONJ incidence after oral and intravenous administration of bisphosphonate in osteoporosis patients is lower than that in cancer patients, however, it is necessary to be careful about patient selection and consider known risk factors, such as poor oral health, uncontrolled diabetes mellitus, smoking, extended bisphosphonate use (more than 4 years), prior or current glucocorticoid exposure [5]. The exact pathophysiology of ONJ is still unknown, therefore experts have different opinions towards how to prevent ONJ. Some insists that invasive procedures such as tooth extraction are considered to a major risk factor of developing ONJ since the incidence of ONJ in patients exposed to long term bisphosphonate therapy is greater when they underwent tooth extraction [6–8]. Therefore, they recommend postponing the invasive dental procedures after cessation of bisphosphonate therapy. However, recent papers have shown that not tooth extraction itself, but pre-existing inflammatory dental disease is a risk factor of ONJ, advocating early interventions such as tooth extraction for infected teeth [9–13]. Further, in addition to bisphosphonates, other medications can also cause ONJ. Denosumab and bevacizumab are well-known causes of medication-related ONJ. However, little is known about the impact of medications changing sex hormone levels on ONJ. This review will cover the relationship between medication associated with sex steroids and ONJ.

2. Methods

A narrative review using PubMed was conducted on ONJ and the medications that affect sex steroid levels. Search keywords were the following: sex steroid, bone, estrogen, testosterone, an aromatase inhibitor, selective estrogen receptor modulator, bone, osteonecrosis of the jaw, osteonecrosis of the bone, osteomyelitis, and mandible. Literature available from 1950 to 2021 was included. Articles written in English were reviewed. Searches were conducted by the 2 co-authors independently. Case reports, case series, reviews, and retrospective and prospective studies were included.

3. Results

3.1. Summary of medications related to the development of ONJ

Drugs previously reported in the literature related to the development of ONJ were categorized into 3 groups: anti-resorptive, anti-cancer medications, and immunosuppressants.

First, anti-resorptive medications included bisphosphonate, denosumab, selective estrogen receptor modulator (SERM), romosozumab (dual effect – increases bone formation and decreases bone resorption). Second, anti-cancer drugs consisted of angiogenesis inhibitors (bevacizumab, sunitinib, imatinib), and mTOR inhibitors (everolimus, temsirolimus). Third, immunosuppressants included methotrexate and corticosteroids.

Table 1
Summary of the incidence of ONJ in various drugs reported currently.

Medication	Reported ONJ incidence	Reference
Low dose oral BP	1.04–69 per 100,000 patient year	[5]
	114/126,293 (90.3 per 100,000 patient year)	[94]
	2.53 per 10,000 patient year (alendronate)	[95]
	22.2 per 100,000 patient year (alendronate)	[96]
Low dose IV BP	0-90 per 100,000 patient year	[5]
	7/8601 (81.4 per 100,000 patient year)	[94]
	20.4 per 100,000 patient year (ibandronate)	[96]
High dose IV BP	0-12,222 per 100,000 patient year	[5]
Low dose denosumab	0 per 100,000 patient year	[97,98]
	5.2 per 10,000 patient year	[99,100]
High dose denosumab	1800–5000 per 100,000 patient year	[101]
Bevacizumab	55 among 800,000 patients	[102]
Sunitinib	27 among 100,000 patients	[102]
Raloxifene	6 per 100,000 patient year	[70]

ONJ, osteonecrosis of the jaw; BP, bisphosphonate; IV, intravenous

3.1.1. Incidence

Reported ONJ incidence is summarized in Table 1. Following the first reported case on the long-term use of bisphosphonates in 2003, which was associated with ONJ development, many articles have addressed the incidence of ONJ with various other types of medications. The highest ONJ incidence is associated with the use of high-dose intravenous bisphosphonate in cancer patients. In 2010, after the approval by the food and drug administration (FDA) on the use of denosumab, increasing number of studies reported the occurrence of ONJ associated with its use. Despite a similar risk of ONJ occurrence, a significant difference between bisphosphonate and denosumab exists. Bisphosphonate-related ONJ occurs after long-term use (at least 3–4 years), whereas denosumab-related ONJ can occur after the first shot, independent of the duration of therapy [14].

Regarding other drugs, only case reports were available. A summary of published case reports on various drugs associated with ONJ is presented in Table 2. In case reports regarding the association of ONJ with drugs except for bisphosphonate and denosumab, many patients were exposed to bisphosphonate or denosumab currently or previously. Therefore, for clarity, we described these cases as 'number of reported cases excluding bisphosphonate and denosumab exposure/total number of reported cases in Table 2.

3.1.2. Pathophysiology

The jaws, including the maxilla (upper jaw) and the mandible (lower jaw), are the main sites of osteonecrosis owing to their susceptibility toward infections, while the long bones and cranium are not affected. A large number of bacteria are present in the oral cavity which is lined by a thin oral mucosa that can be easily injured. Moreover, since teeth penetrate the oral epithelial layer, it is easy to reach the inner bone through the affected teeth. In addition, the jaws are continuously stimulated by mastication, thus, its remodeling rate is faster than that of the other bones. In turn, this makes the jaws more susceptible to osteonecrosis [15,16].

The pathophysiology of medication-related ONJ remains unclear. This complex process is affected by several systemic and local factors, such as trauma, immunodeficiency, and oral hygiene. Initially, the suggested pathophysiology of ONJ was simple to understand and was mainly associated with the use of bisphosphonates that resulted in the cessation of bone remodeling caused by the action of anti-resorptive drugs on osteoclasts. Currently, since

Table 2
Summary of published case reports on various drugs associated with ONJ excluding bisphosphonate and denosumab exposure.

Medication	Category	Indication	Number of reported cases excluding BP and denosumab exposure/ number of total reported cases
Romosozumab	Anti-resorptive	Osteoporosis	1/2 [103]
Raloxifene	Selective estrogen receptor modulator	Osteoporosis	0/1 [67] 1/1 [68] 1/1 [69]
Imatinib	Angiogenesis inhibitor	Chronic myeloid leukemia	0/1 [104]
		Gastrointestinal stromal tumors	1/1 [105]
		Langerhans cell histiocytosis	1/1 [106]
Sorafenib	Angiogenesis inhibitor	Hepatocellular carcinoma	1/1 [107]
Regorafenib	Angiogenesis inhibitor	Colorectal cancer	1/1 [19]
Axitinib	Angiogenesis inhibitor	Renal cell carcinoma	1/1 [108]
Pazopanib	Angiogenesis inhibitor	Renal cell carcinoma	1/1 [109]
Cabozantinib	Angiogenesis inhibitor	Medullary thyroid cancer	1/1 [110]
Dasatinib	Angiogenesis inhibitor	Acute lymphatic leukemia	1/1 [111]
Everolimus	mTOR inhibitor	Renal cell carcinoma	0/1 [112] 1/1 [113]
		Breast cancer	1/1 [114]
Temsirolimus	mTOR inhibitor	Renal cell carcinoma	0/1 [115]
Methotrexate	Immunosuppressant	Rheumatoid arthritis	2/2 [116]

ONJ, osteonecrosis of the jaw; BP, bisphosphonate

not only anti-resorptive agents but also angiogenesis inhibitors are found to be associated with ONJ occurrence, another pathophysiology has been proposed. The second theory is based on the evidence that bisphosphonates also have antiangiogenic effects [17,18] and ONJ is caused by a compromised microcirculation due to these anti-angiogenesis drugs. Mucositis, stomatitis, and gingival inflammation further attenuate the decreased angiogenesis caused by medications and may worsen host defenses to infection [19]. Additionally, this explains why a patient on immunosuppressant therapy is at high risk of ONJ. Other possible mechanisms how medication-related ONJ occurs suggested so far are impaired healing of oral mucosa due to bisphosphonates [20], activation of gamma delta T cells due to bisphosphonate to produce proinflammatory cytokines resulting decreased appropriate immune response to infection [21], increase of adhesion of bacteria to bone hydroxyapatite coated with bisphosphonate [22], decreased macrophage growth and function due to antiresorptive drugs [23] and the decreased key defensive role of osteoclast to bone infection due to antiresorptive medication [24]. Since none of them fully explain the exact mechanism of ONJ, it is reasonable to conclude the process is multifactorial.

3.2. Mechanism underlying the effects of sex steroid hormones on bone homeostasis

3.2.1. The effect of estrogen on bone resorption

The following mechanisms by which estrogen suppresses bone resorption have been suggested in previous studies: inhibition of RANKL production, suppression of pro-resorptive cytokine production, and direct suppression of osteoclast as shown in Fig. 1.

Before discussion of the first mechanisms, the receptor activator of the NF-kB ligand (RANKL)/RANK/osteoprotegerin system should be reviewed [25]. RANKL and osteoprotegerin are secreted from osteoblast precursor cells and RANK is located in osteoclastic precursor cells. The binding of RANKL to RANK activates the proliferation and survival of osteoclasts [26]. Osteoprotegerin is a decoy receptor for RANKL, therefore, osteoprotegerin can neutralize RANK mediated osteoclast activation [27]. RANKL/RANK/osteoprotegerin signaling is also important in immune and vascular systems [28].

Studies have shown that estrogen suppresses RANKL production and increases osteoprotegerin production, which inhibits osteoclast activation [25,28,29].

The second mechanism is through the reduction of pro-resorptive cytokines. In estrogen deficiency, the levels of cytokines, such as interleukins (IL-1, IL-6) [30], macrophage-colony stimulating factor (M-CSF) [31], tumor necrosis factor (TNF)-α [30], and prostaglandin E_2 are increased [28]. Additionally, estrogen supplements can reverse the increase in cytokines levels. Moreover, cytokines, such as transforming growth factor (TGF)-β, which induces apoptosis of osteoclasts, is increased by estrogen [32], and estrogen itself can induce apoptosis through the estrogen receptors in osteoclasts [33].

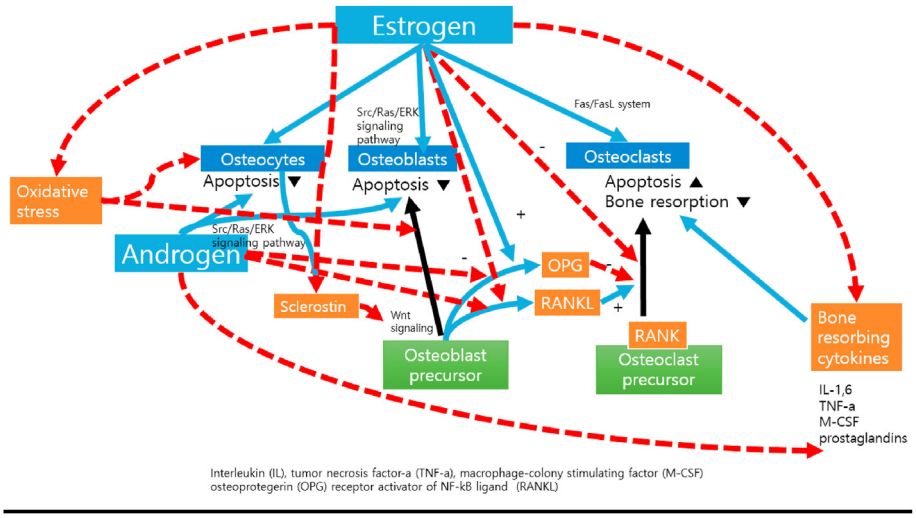

Fig. 1. Mechanisms showing how sex steroids affect bone remodeling.

Another mechanism is through direct suppression of the osteoclast's lifespan. Induction of the Fas/FasL system in osteoclasts by estrogen has been shown [34,35]. Fas/FasL system is one of the major pathways that regulate apoptosis. Further, estrogen reduces the osteoclast's lifespan by inducing its apoptosis.

3.2.2. The effect of estrogen on bone formation

In light of currently available evidence, the effects of estrogen on osteoblasts can be summarized into 4 categories. The first is through direct effect by reducing apoptosis of osteoblasts, the second is by decreasing oxidative stress, the third is by increasing NF-kB, and the last is through suppression of sclerostin production.

Estrogen's antiapoptotic action on osteoblasts via an Src/Ras/ERK signaling pathway has been shown [36]. Kousteni et al [37] demonstrated that ovariectomy in mice increased vertebral osteoblast apoptosis by 10-fold. Estradiol (E2) or 5a-dihydrotestosterone (DHT) inhibited osteoblast apoptosis in a dose-dependent manner through E2-or DHT-induced ERK phosphorylation. This ERK phosphorylation was blocked by the Src family tyrosine kinase inhibitor, indicating that ERK phosphorylation and Src kinase activity are required for the antiapoptotic effects of the 2 sex steroids. Therefore, it is considered that estrogen's anti-apoptotic effects on osteoblasts are medicated via an Src/Ras/ERK signaling pathway.

The second mechanism by which estrogen affects bone formation is mediated through oxidative stress. Low levels of estrogen increase oxidative stress that suppresses osteoblastogenesis, reduces the lifespan of osteoblast/osteocyte, and increases osteoclast generation, function, and survival. It is speculated that the mechanism by which oxidative stress suppresses bone formation is achieved by suppressing Wnt signaling in osteoblasts [38]. Therefore, the bone loss accelerated by estrogen deficiency can be reversed by the use of anti-oxidants [39].

The third mechanism is through suppression of NF-kB activity by estrogen [40]. In estrogen deficiency, the NF-kB activity of osteoblasts increases, and suppression of NK-kB activity inhibits bone loss. This indicates that NF-kB activity mediates the influence of estrogen on osteoblasts. Suppressing the NK-kB level increases Fos-related antigen-1 (Fra-1), which is the transcription factor required for bone matrix formation.

The last mechanism is mediated via the inhibition of sclerostin production by estrogen. In a human study, it was seen that when estrogen was replaced in both men and women, the level of sclerostin decreased [41]. Sclerostin inhibits Wnt signaling, and suppression of Wnt signaling leads to suppression of osteoblast differentiation [42,43]. Inhibition of sclerostin production by estrogen is considered one of the key mechanisms by which estrogen affects osteoblasts.

3.2.3. The effect of androgen on bone homeostasis

A study conducted in elderly men in whom the levels of sex steroids were depleted due to gonadotropin-releasing hormone (GnRH) agonist and an aromatase inhibitor, and who underwent replacement of estrogen or/and testosterone or neither showed that estrogen accounts for more than 70% of the total effect of sex steroid hormones on bone, whereas testosterone accounted for no more than 30% of the effect [44].

The above study has shown that estrogen, not testosterone, is the key regulator in male bone. However, androgen also affects the bone, and the mechanisms can be summarized as follows: first, androgen is converted to estrogen by aromatase, which in turn through the mechanisms described above, exerts its effects on the bone. Second, androgen exerts its direct effect on the bone through androgen receptors on the bone cells. Third, androgen indirectly affects the bone by reducing pro-resorptive cytokines similar to estrogen.

Similar to estrogen, androgen suppresses RANKL production [25,29]. However, while estrogens increase the production of osteoprotegerin [45], androgens suppress osteoprotegerin production [46]. This difference explains the decreased effect on the bone by androgen compared to estrogen.

Androgen suppresses pro-resorptive cytokines (e.g., IL-1, IL-6, and PGE2) similar to estrogen [47–49].

3.2.4. The effect of androgen on bone formation

Androgens also exhibit antiapoptotic action on osteoblasts via an Src/Ras/ERK signaling pathway [36].

Both testosterone and dihydrotestosterone, the most potent form of androgen, which is converted from testosterone by 5 α reductase, activate the proliferation of osteoclast precursors via androgen receptor signaling [50]. Also, the binding of androgens with androgen receptors promotes osteoblast's differentiation and maturation [48].

3.3. Exogenous steroid replacement therapy – ONJ

3.3.1. Estrogen replacement therapy

A large number of studies have shown that estrogen deficiency causes bone loss. However, the effects on the bone with supraphysiological estrogen levels are less researched. Moreover, only 1 study on the association between ONJ and exogenous estrogen use was found [51]. In this study, 89 patients with idiopathic ONJ were tested for factor V Leiden mutation, the most common cause of thrombophilia, and 76 of these patients received exogenous estrogen (oral contraceptive or postmenopausal hormone therapy). In patients with factor V Leiden mutation, ONJ was reported more frequently than the patients without mutation despite the use of a standard dose of estrogen (13/16 (81%) vs 23/60 (38%), $P = 0.002$). It is well known that estrogen replacement is associated with a thrombotic event. It is believed that by supplying exogenous estrogen (oral contraceptive, postmenopausal estrogen supplement) in individuals with thrombophilia, thrombus formation occurs, resulting in intravascular occlusion and necrosis of the bone. If the pathophysiology in which bisphosphonate-related ONJ (BRONJ) occurs is a chronic decrease in healing processes due to long-term BP use, ONJ due to exogenous estrogen has a distinctly different pathophysiology. However, if the pathophysiology of ONJ is viewed as compromised blood supply, then ONJ occurring due to exogenous estrogen supplement shares a similar mechanism.

3.3.2. Androgen replacement therapy

How androgen works differently on the bone from estrogen was reviewed. Estrogen replacement therapy is common in menopausal women, while androgen replacement therapy is not common in elderly men. Whereas menopause is absolute estrogen deficiency, andropause, which is a term describing gonadal function decline with aging, is relative testosterone deficiency. As men age, the decrease in testicular function is gradual. Therefore, there are fewer symptoms and fewer cases requiring treatment than women.

There are 2 case reports regarding ONJ in hypogonadal men receiving testosterone replacement therapy [52,53]. These case reports also reported that testosterone replacement causes venous thrombus in patients with thrombophilia (inherited or acquired), leading to increased intraosseous venous pressure, reduced arterial flow, and finally bone ischemia. One patient was a 32-year-old hypogonadal Caucasian male with ONJ after 8 months of testosterone therapy 50 mg/day. He denied having any history of trauma to the jaw, alcohol abuse, long-term steroid use, and bisphosphonate treatment. Coagulation studies revealed heterozygosity for the Factor V Leiden mutation and the lupus anticoagulant. The other patient was a 55-year-old Caucasian male who was prescribed testosterone,

AndroGel 50 mg/day, to improve impaired sexual performance since the age of 54. Because he had 4 myocardial infarction events starting at the age of 50, his cardiologist found his estradiol level was abnormally high and administered anastrozole (1 mg/day) to reduce his estradiol level. After 6 months of testosterone-anastrozole, the patient developed severe jaw pain, which was diagnosed as ONJ. He denied smoking and heavy alcohol drinking and had never received bisphosphonates or long-term steroid therapy. His coagulation studies showed he was heterozygous for the Factor V Leiden mutation and homozygous for MTHFR C677T. In addition, high B2 glycoprotein IgM levels and high anticardiolipin antibody IgM were revealed, indicating antiphospholipid antibody syndrome. The 2 patients ceased their testosterone replacement therapy, and the jaw pain disappeared without using enoxaparin. Similar to estrogen, if the pathophysiology of ONJ is considered to be due to compromised blood supply, it can be seen that ONJ caused by testosterone supplements occurs similarly.

3.3.3. Androgen excess status due to polycystic ovarian syndrome

Several studies have reported the effect of the polycystic ovarian syndrome (PCOS)-related androgen excess on the bone in young women [54–61]. PCOS is a relatively common endocrine disorder in reproductive-age women and is diagnosed if the following 2 criteria are met: oligo-ovulation or anovulation, clinical and/or biochemical hyperandrogenism, and polycystic ovaries on an ultrasound scan. In a 1988 paper that first examined the effect of PCOS related androgen excess on bone, the bone mineral density (BMD) of trabecular (lumbar) bone and cortical (radial) bone were compared in the PCOS related androgen excess group (n = 19) and normal group (n = 27) [54]. In this paper, the PCOS-related androgen excess group recruited only women with regular menstruation cycles to prevent BMD differences due to estrogen deficiency. It was confirmed that there were no statistically significant differences between the 2 groups in age, height, body weight, smoking history, amount alcohol consumption, parity, the age of menarche, and basal estradiol level, which are known to affect BMD. The trabecular bone density was statistically significantly higher than that of the normal group in the androgen access group, but there was no significant BMD difference in the cortical bone between the 2 groups. This paper concluded that supraphysiological levels of endogenous androgens are associated with increased trabecular bone density in young women.

In another group's paper published in 1989, unlike the previous paper, PCOS women with oligomenorrhea (n = 32) and normal women with regular menstrual cycles (n = 32) were compared. Although the oligomenorrhea group had lower estradiol levels than the normal group, there was no difference in bone mass [55]. The authors considered that even at the low estradiol level due to oligomenorrhea or amenorrhea, the presence of androgen excess in PCOS women resulted in maintaining the bone mass.

In 1992, a study was conducted to compare women with amenorrhea due to PCOS (n = 266) and women vs with amenorrhea for other reasons than PCOS (n = 207), and BMD was higher in the group with amenorrhea due to PCOS [56]. However, this study was criticized because the results were not adjusted with age, duration of amenorrhea, and body weight, and the amenorrhea group for other reasons than PCOS was so heterogeneous to make a simple comparison.

There were follow-up studies that supplemented these shortcomings. In 1993, PCOS with women regular menstruation cycles (n = 30), PCOS women with amenorrhea (n = 9), and normal women (n = 22) were compared, and the mean BMI of the 3 groups were similar [57]. In PCOS women with a regular menstruation cycle, BMD was higher than that of normal women, and in women who were amenorrhea due to PCOS, BMD was similar to normal women. Therefore, the authors concluded that women with hyperandrogenic amenorrhea seemed to be spared from osteopenia. In 1996, women who were nonobese, hirsute, and oligomenorrhea/amenorrhea (n = 27), women who were hirsute and eumenorrhea (n = 25), women who were non-hirsute and oligomenorrhea/amenorrhea (n = 17), and women who were non-hirsute and eumenorrhea (n = 25) were compared [62]. After adjustment of BMI and age, hirsute women with eumenorrhea had the highest BMD, non-hirsute women with oligomenorrhea/amenorrhea had the lowest BMD, and amenorrhea women with androgen overproduction had similar BMD with eumenorrhea women without androgen overproduction. It was considered that the deleterious effect on the bone of amenorrhea was balanced by androgen overproduction. Therefore, some studies have shown that treatment that reduces androgen such as spironolactone and flutamide has a negative effect on bone mass [63,64].

In conclusion, androgen overproduction in the case of PCOS is served as a protecting factor in terms of bone mineral density in young women.

However, there was no case report on ONJ due to androgen excess related to PCOS.

3.4. Sex steroid deficiency – ONJ

3.4.1. Selective estrogen receptor modulators (SERMs)

SERMs are a type of medication that selectively stimulates or inhibits estrogen-like activity in various tissues [65]. Raloxifene, one of the drugs categorized as SERM, is used in osteoporosis because of the evidence that suggested a spine fracture risk reduction of 30–40% seen at a dose of 60 mg. Raloxifene is also associated with 60–70% breast cancer risk reduction, thus making it a drug of choice for breast cancer survivors diagnosed with osteoporosis. The first paper reporting raloxifene could also be related to ONJ was published in 2014 [66]. The study population was the Taiwanese population during January 2000 and April 2012 who were treated with alendronate or raloxifene for osteoporosis. In 1869 people who had no alendronate exposure and used only raloxifene, 1 person had ONJ, whereas, in 6485 people who used alendronate and/or raloxifene, 39 people had ONJs (15 of which had alendronate and raloxifene exposure and the others used alendronate only). Since then, 3 more case reports on raloxifene-associated ONJ have been reported [67–69]. The first case was published in 2015, and it was a 67-year-old woman complaining of numbness of her lower lip, jaw pain, and areas of exposed mandibular bone. Her medical history included hypertension, hyperlipidemia, hypothyroidism, type 2 diabetes mellitus, rheumatoid arthritis, cirrhosis, and osteoporosis. She was taking metoprolol, levothyroxine, acetylsalicylic acid, folic acid, and raloxifene. Raloxifene treatment was maintained at 60 mg/day for 18 months, and before the onset of raloxifene, she had been treated with alendronate treatment (Fosamax, 70 mg/week) for 2 years. Ten months after starting raloxifene treatment, she received multiple teeth extraction and had maintained raloxifene treatment since then. Since alendronate accumulates in the bone and can affect for 12 years in humans, it is difficult to say that the treatment duration of alendronate (2 years) was too short to cause ONJ. However, the authors recommended caution with raloxifene. The second and third case reports were those who had not previously received bisphosphonate treatment. The second case published in 2018 was a 64-year-old female presenting with jaw pain and gingival purulent. Her medical history included osteoporosis, depression, gastritis, and labyrinthitis. She had been taking raloxifene 60 mg per day for 4 years. However, she had not received

bisphosphonate, corticosteroids, or radiation therapy to the jawbone. She was started on antibiotics therapy, and 10 days after, the bone exposure disappeared. In the third case published in 2021, the patient's medical history revealed that there was no prior exposure to a bisphosphonate. She was a 67-year-old African American and visited the hospital with jaw swelling and fever, which began 4 days ago. Her medical history included hypertension, type 2 diabetes, rheumatoid arthritis, myocardial infarction, osteoporosis, and post-traumatic stress disorder. She was taking carvedilol, citalopram, clopidogrel, donepezil, quetiapine and raloxifene. She had been taking raloxifene for 2 years and had been using dentures. There was a bone tissue expansion in the left alveolar bridge accompanied by pain, and the mucosa covering it was thin and accompanied by redness, but there was no bone exposure or suppuration. Large, irregular, dense, and bony masses were found on the X-ray taken on the first day of the visit, suspected of fluid cemento-osseous dysplasia (FCOD). FCOD is found in middle-aged Black women's jaws with dense, highly mineralized, and almost acellular cemeto-osseous tissue, which does not require special treatment. Surgical debridement on the affected body area for ONJ treatment was performed and the pathologist confirmed FCOD. The authors mentioned that FCOD was accidentally discovered, diagnosed ONJ with clinical and radiological evidence, and that it is not yet known whether FCOD is a risk factor for ONJ. The patient has no history of exposure to a bisphosphonate, hence the use of raloxifene may cause ONJ, and therefore caution should be taken to the use of raloxifene.

A recent head to head comparative study comparing effectiveness and safety of alendronate versus raloxifene in osteoporosis patients has shown that the incidence of raloxifene related ONJ 0.06 events per 1000 person-year [70]. This study was a retrospective large scale multicenter study including more than 300 million patients. It included 40,463 patients who were newly diagnosed with osteoporosis and treated with raloxifene firstly and counted the number of events for fracture, esophageal cancer and ONJ. According to the study, raloxifene is a safe and effective alternative to alendronate.

3.4.2. Aromatase inhibitors

An aromatase inhibitor is a drug that reduces estrogen levels by inhibiting aromatase, an enzyme that converts androgen into estrogen. In menopause women, estrogen is mainly produced by aromatase in peripheral fat tissue. Therefore, the use of aromatase inhibitors in postmenopausal women completely inhibits estrogen production. However, in premenopausal women, estrogen deficiency induced by aromatase inhibitor stimulates the secretion of gonadotropin by the hypothalamus-pituitary-ovary axis, increasing the production of ovarian estrogen. Then, the secretion of gonadotropin is suppressed again by the negative feedback of estrogen on the pituitary, resulting in the growth of a single follicle, which is sometimes used in ovulation induction. A few studies have stated that in postmenopausal women using aromatase inhibitor is related to bone loss. BMDs were compared in the group after 2 years of letrozole use ($n = 122$) and placebo ($n = 104$) in breast cancer patients who used tamoxifen for 5 years [71]. Significant decrease in hip BMD (-3.6% vs -0.61%, $P = 0.044$) and lumbar spine BMD (-5.35% vs -0.70%, $P = 0.008$) in letrozole groups. N-telopeptide, which is a bone resorption marker, was measured at 6, 12, and 24 months. Letrozole increased urine N-telopeptide at 12 and 24 months with statistical significance ($P = 0.001$ and $P = 0.008$, respectively). The authors conclude that although letrozole usage in breast cancer patients after 5-year-use of tamoxifen reduces breast cancer recurrence, it increases bone resorption and decreases spine and hip BMD.

One paper was found stating that the aromatase inhibitor is related to ONJ. The paper was published in 2014 and included 93 patients with BRONJ. Since female dominance was observed among BRONJ patients [72], the author postulated that estrogen deficiency may not be neutral to the side effects of bisphosphonate such as BRONJ [73]. Therefore, this prospective study was started with the question of whether BRONJ would recur more if breast cancer patients had been receiving antiestrogen therapy except for tamoxifen. The reason for excluding tamoxifen as it has a weak estrogenic effect on bone, whereas other aromatase inhibitors have an antagonist effect on bone. When ONJ occurred using bisphosphonate due to an underlying disease other than breast cancer, the relapse rate was statistically significantly less than when receiving anti-estrogen treatment due to breast cancer. The authors conclude when bisphosphonate is released ONJ occurs, and estrogen deficiency due to antiestrogen therapy plays a synergistic role. Rather than assuming that ONJ occurs as the effect of the aromatase inhibitor itself, it was assumed that using aromatase inhibitors together with bisphosphonates increases the risk of ONJ.

Then, it was searched whether the existence of a paper examining the association with ONJ by the aromatase inhibitor itself. A paper published in 2020 argues that the aromatase inhibitor itself is not related to ONJ. According to the paper, looking at those reported that the aromatase inhibitor is related to ONJ, in many cases bisphosphonate or denosumab was used together when excluding those cases, the aromatase inhibitor itself is not related to ONJ [74].

3.4.3. Gonadotropin releasing hormone agonist

Gonadotropin-releasing hormone (GnRH) agonist is used in various conditions, such as delayed or precocious puberty, infertility, prostatic and breast cancer, benign prostatic hyperplasia, polycystic ovarian syndrome, endometriosis, uterine fibroids, and fertility preservation during gonadotoxic chemotherapy to suppress gonadal function. As the term shows, an initial agonist action (as known as the flare effect) lasts for 1–3 weeks. After that, desensitization and down-regulation of the pituitary are pursued resulting in hypogonadotropic hypogonadism.

There are several studies reporting BMD decrease after use of GnRH agonist. If GnRH agonist is used short for less than 6 months, BMD reduction is reversible, and if it is used long-term for more than 6 months, BMD reduction becomes irreversible [75,76].

In endometriosis patients, GnRH agonist is the treatment of choice since endometriosis is a disease in which endometrial tissue exists outside the uterus. Using GnRH agonist, cessation of menses is associated with pain relief [77] and endometriosis volume reduction [78]. BMD reduction in trabecular bone was observed after 6 months of GnRH agonist use [79–81], and the reduction was observed as early as 3 months of treatment [80]. To attenuate bone loss with GnRH agonist treatment in endometriosis patients, hormonal add-back therapy can be used to decrease side effects related to estrogen deficiency without sacrificing treatment efficacy [82–84].

In conditions such as prostate or breast cancer, long-term GnRH agonist treatment is required. There are numerous studies stating bone density reduction due to GnRH agonist treatment in prostate [85–87] or breast cancer [88,89]. Also, large-scale studies state even increase in fracture risk due to GnRH agonist treatment in the prostate [90]. In turn, randomized clinical trials were done to investigate how to prevent GnRH agonist-induced bone loss. Intravenous pamidronate [91], zoledronic acid [92] and denosumab [93] are options to choose.

However, there is no report stating GnRH is associated with ONJ.

3.5. Combination of hormone replacement therapy and anti-resorptive – ONJ

In the aromatase inhibitor section, estrogen deficiency was considered a risk factor for BRONJ [73]. However, no study has

Table 3
Summary of various medications affecting sex steroids and association with decreased bone mineral density (in humans) and association with ONJ.

Medication (Trade name)	Category	Impact on sex steroids	Impact on BMD	Association with ONJ
Spironolactone (Aldactone®)	Antiandrogen	Reduction	Conflicting - decrease [63] - protective effect [64]	–
Flutamide (Eulexin®)	Antiandrogen	Reduction	Decrease [64]	–
Raloxifene (Evista®)	SERM	–	Increase [117]	Case reports [67–69] Retrospective cohort study [66,70]
Letrozole (Femara®)	Aromatase inhibitor	Reduction	Decrease [71]	
Anastrozole (Arimidex®)	Aromatase inhibitor	Reduction	Decrease [71]	
Exemestane (Aromasin®)	Aromatase inhibitor	Reduction	Decrease [71]	
Leuprorelin (Leuplin®)	GnRH agonist	Reduction	Decrease [78]	
Goserelin acetate (Zoladex®)	GnRH agonist	Reduction	Decrease [88]	

ONJ, osteonecrosis of the jaw; BMD, bone mineral density; SERM, selective estrogen receptor modulator; GnRH, gonadotropin releasing hormone

reported a reduced risk of developing ONJ with estrogen replacement therapy in osteoporosis patients receiving bisphosphonate or denosumab. Further study is needed.

4. Discussion

Since 2003, when the first ONJ report was published, the use of anti-resorptive medications, anti-cancer drugs, and immunosuppressants has been associated with ONJ. The prevalence of ONJ differs with the use of each drug with the highest prevalence being reported with the use of high dose intravenous bisphosphonate in cancer patients. Although rare, ONJ is a serious adverse event that causes severe pain and decreases the quality of life. The pathophysiology of ONJ remains unclear. Several systemic and local factors (trauma, immunodeficiency, oral hygiene) are considered to play a role in its pathogenesis. Initially, cessation of bone remodeling caused by the inhibitory effect of anti-resorptive medications on the osteoclasts was the main mechanism identified to cause ONJ. However, since not only anti-resorptive agents but also angiogenesis inhibitors and immunosuppressants are related to ONJ, other hypotheses have been suggested such as compromised microcirculation and impairment of defense mechanism toward local infection.

Bone remodeling is largely affected by sex steroid hormones including estrogens and androgens that have a protective effect on the bone. The sex steroid hormones exert their effects either directly by binding to the estrogen and androgen receptors of the bone cells or indirectly by various kinds of cytokines. If sex hormones are important in maintaining bone homeostasis, the use of sex hormones or drugs that affect sex hormone levels may increase the risk of ONJ, a complication caused by broken bone homeostasis.

Exogenous estrogen or androgen replacement therapy was associated with ONJ in the case of thrombophilia patients. The thrombotic event caused by sex steroid hormone replacement causes avascular necrosis of the jaw. In PCOS patients, androgen overproduction serves as a protective factor in maintaining the bone mineral density in young women. However, no study reported androgen overproduction as a cause of ONJ.

Few reports were available on patients with estrogen deficiency induced by drugs such as SERM, aromatase inhibitors, and GnRH agonists. Two out of the 3 reported cases of SERM were not influenced by any previous bisphosphonate usage. Aromatase inhibitors are known to decrease BMD, and it was speculated that estrogen deficiency status caused by the use of aromatase inhibitors in breast cancer patients receiving bisphosphonates were more prone to develop ONJ; however, no study reported the occurrence of ONJ with isolated use of aromatase inhibitors. Further, GnRH agonists are also well-known drugs to decrease the BMD; however, no ONJ report by GnRH agonists was found. In summary, Table 3 shows various medications affecting sex steroids and their association with ONJ.

The reason why there is no ONJ case in GnRH agonist treatment in endometriosis patients is because the young women do not share the risk factors of ONJ. The known risk factors are poor oral

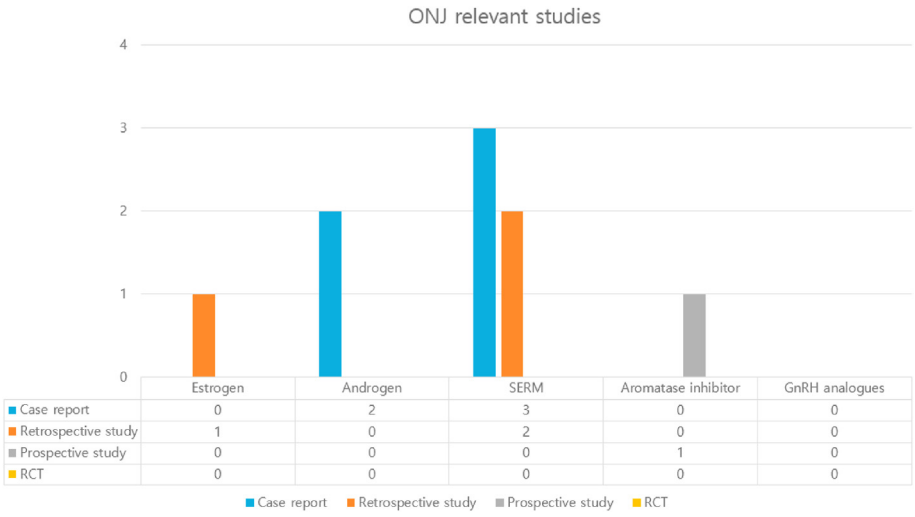

Fig. 2. Reference – classified by sources
ONJ, osteonecrosis of the jaw; SERM, selective estrogen receptor modulator; GnRH, gonadotropin releasing hormone; RCT, randomized clinical trial.

health, uncontrolled diabetes mellitus, smoking, extended bisphosphonate use (more than 4 years), prior or current glucocorticoid exposure. Usually, women patients are not vulnerable to infection and less likely to receive trauma such as implant and extraction.

This review is the first report assessing the association between drugs affecting sex steroids levels and ONJ. However, this review is largely based on several case reports and retrospective studies, and high-level evidence such as randomized clinical trials was not included. The references used in this article are classified by sources in Fig. 2.

If estrogen deficiency is a risk factor for MRONJ, studies comparing the incidence of ONJ in osteoporosis patients with estrogen replacement and ones without estrogen therapy tell us 1 possible prevention method for ONJ. However, the exact mechanism of ONJ is not known, and caution is needed in the area of sex steroid replacement in the elderly since it has known side effects such as breast and prostate cancer, and thromboembolism.

In conclusion, little are known about sex steroid roles in the development of ONJ. Further studies are needed to prevent ONJ by finding the exact role of sex steroids in bone homeostasis and ONJ progression.

CRediT author statement

Ranhee Kim: Conceptualization, Formal analysis, Writing - Original Draft. **Sung Woo Kim**: Methodology, Validation, Formal analysis, Data Curation. **Hoon Kim**: Methodology, Validation, Formal analysis, Data Curation. **Seung-Yup Ku**: Investigation, Resources, Writing - Review & Editing.

Declaration of competing interest

The authors declare no competing interest.

Acknowledgments

This study was supported by the grant of Ministry of Science, Technology and ICT (2020R1A2C1010293) of government of the Republic of Korea.

ORCID

Ranhee Kim: 0000-0001-6841-1234. Sung Woo Kim: 0000-0003-4689-1323. Hoon Kim: 0000-0002-5623-6368. Seung-Yup Ku: 0000-0002-6423-854X.

References

[1] Syed F, Khosla S. Mechanisms of sex steroid effects on bone. Biochem Biophys Res Commun 2005;328:688–96.
[2] Albright F. Postmenopausal osteoporosis. Trans A Amer Phys 1940;55:298–305.
[3] Yarom N, Shapiro CL, Peterson DE, Van Poznak CH, Bohlke K, Ruggiero SL, et al. Medication-related osteonecrosis of the jaw: MASCC/ISOO/ASCO clinical practice guideline. J Clin Oncol 2019;37:2270–90.
[4] Marx RE. Pamidronate (Aredia) and zoledronate (Zometa) induced avascular necrosis of the jaws: a growing epidemic. J Oral Maxillofac Surg 2003;61:1115–7.
[5] Khan AA, Morrison A, Hanley DA, Felsenberg D, McCauley LK, O'Ryan F, et al. Diagnosis and management of osteonecrosis of the jaw: a systematic review and international consensus. J Bone Miner Res 2015;30:3–23.
[6] Barasch A, Cunha-Cruz J, Curro FA, Hujoel P, Sung AH, Vena D, et al. Risk factors for osteonecrosis of the jaws: a case-control study from the CONDOR dental PBRN. J Dent Res 2011;90:439–44.
[7] Kyrgidis A, Vahtsevanos K, Koloutsos G, Andreadis C, Boukovinas I, Teleioudis Z, et al. Bisphosphonate-related osteonecrosis of the jaws: a case-control study of risk factors in breast cancer patients. J Clin Oncol 2008;26:4634–8.
[8] Vahtsevanos K, Kyrgidis A, Verrou E, Katodritou E, Triaridis S, Andreadis CG, et al. Longitudinal cohort study of risk factors in cancer patients of bisphosphonate-related osteonecrosis of the jaw. J Clin Oncol 2009;27:5356–62.
[9] Soutome S, Hayashida S, Funahara M, Sakamoto Y, Kojima Y, Yanamoto S, et al. Factors affecting development of medication-related osteonecrosis of the jaw in cancer patients receiving high-dose bisphosphonate or denosumab therapy: is tooth extraction a risk factor? PLoS One 2018;13:e0201343.
[10] Hasegawa T, Hayashida S, Kondo E, Takeda Y, Miyamoto H, Kawaoka Y, et al. Medication-related osteonecrosis of the jaw after tooth extraction in cancer patients: a multicenter retrospective study. Osteoporos Int 2019;30:231–9.
[11] Kamimura M, Taguchi A, Komatsu M, Koiwai H, Ashizawa R, Ichinose A, et al. Long waiting time before tooth extraction may increase delayed wound healing in elderly Japanese. Osteoporos Int 2019;30:621–8.
[12] Soutome S, Otsuru M, Hayashida S, Murata M, Yanamoto S, Sawada S, et al. Relationship between tooth extraction and development of medication-related osteonecrosis of the jaw in cancer patients. Sci Rep 2021;11:17226.
[13] Otto S, Troltzsch M, Jambrovic V, Panya S, Probst F, Ristow O, et al. Tooth extraction in patients receiving oral or intravenous bisphosphonate administration: a trigger for BRONJ development? J Cranio-Maxillo-Fac Surg 2015;43:847–54.
[14] Rosella D, Papi P, Giardino R, Cicalini E, Piccoli L, Pompa G. Medication-related osteonecrosis of the jaw: clinical and practical guidelines. J Int Soc Prev Community Dent 2016;6:97–104.
[15] Shibahara T. Antiresorptive agent-related osteonecrosis of the jaw (ARONJ): a twist of fate in the bone. Tohoku J Exp Med 2019;247:75–86.
[16] Cardemil C, Omar OM, Norlindh B, Wexell CL, Thomsen P. The effects of a systemic single dose of zoledronic acid on post-implantation bone remodelling and inflammation in an ovariectomised rat model. Biomaterials 2013;34:1546–61.
[17] Santini D, Schiavon G, Angeletti S, Vincenzi B, Gasparro S, Grilli C, et al. Last generation of amino-bisphosphonates (N-BPs) and cancer angiogenesis: a new role for these drugs? Recent Pat Anticancer Drug Disc 2006;1:383–96.
[18] Allegra A, Oteri G, Nastro E, Alonci A, Bellomo G, Del Fabro V, et al. Patients with bisphosphonates-associated osteonecrosis of the jaw have reduced circulating endothelial cells. Hematol Oncol 2007;25:164–9.
[19] Antonuzzo L, Lunghi A, Giommoni E, Brugia M, Di Costanzo F. Regorafenib also can cause osteonecrosis of the jaw. J Natl Cancer Inst 2016;108:djw002.
[20] Allam E, Allen M, Chu TM, Ghoneima A, Jack Windsor L. In vivo effects of zoledronic acid on oral mucosal epithelial cells. Oral Dis 2011;17:291–7.
[21] Kunzmann V, Bauer E, Feurle J, Tony FWH-P, Wilhelm M. Stimulation of γδ T cells by aminobisphosphonates and induction of antiplasma cell activity in multiple myeloma. Blood 2000;96:384–92.
[22] Kos M, Junka A, Smutnicka D, Bartoszewicz M, Kurzynowski T, Gluza K. Pamidronate enhances bacterial adhesion to bone hydroxyapatite. Another puzzle in the pathology of bisphosphonate-related osteonecrosis of the jaw? J Oral Maxillofac Surg 2013;71:1010–6.
[23] Gkouveris I, Soundia A, Gouveris P, Zouki D, Hadaya D, Tetradis S. Macrophage involvement in medication-related osteonecrosis of the jaw (MRONJ): a comprehensive, short review. Cancers 2022;14:330–44.
[24] Otto S, Aljohani S, Fliefel R, Ecke S, Ristow O, Burian E, et al. Infection as an important factor in medication-related osteonecrosis of the jaw (MRONJ). Medicina (Kaunas) 2021;57:463–75.
[25] Eghbali-Fatourechi G, Khosla S, Sanyal A, Boyle WJ, Lacey DL, Riggs BL. Role of RANK ligand in mediating increased bone resorption in early postmenopausal women. J Clin Invest 2003;111:1221–30.
[26] Lacey D, Timms E, Tan H-L, Kelley M, Dunstan C, Burgess T, et al. Osteoprotegerin ligand is a cytokine that regulates osteoclast differentiation and activation. Cell 1998;93:165–76.
[27] Simonet W, Lacey D, Dunstan C, Kelley M, Chang M-S, Lüthy R, et al. Osteoprotegerin: a novel secreted protein involved in the regulation of bone density. Cell 1997;89:309–19.
[28] Hofbauer LC, Schoppet M. Clinical implications of the osteoprotegerin/RANKL/RANK system for bone and vascular diseases. JAMA 2004;292:490–5.
[29] Kawano H, Sato T, Yamada T, Matsumoto T, Sekine K, Watanabe T, et al. Suppressive function of androgen receptor in bone resorption. Proc Natl Acad Sci Unit States Am 2003;100:9416–21.
[30] Pacifici R, Brown C, Puscheck E, Friedrich E, Slatopolsky E, Maggio D, et al. Effect of surgical menopause and estrogen replacement on cytokine release from human blood mononuclear cells. Proc Natl Acad Sci 1991;88:5134–8.
[31] Tanaka S, Takahashi N, Udagawa N, Tamura T, Akatsu T, Stanley ER, et al. Macrophage colony-stimulating factor is indispensable for both proliferation and differentiation of osteoclast progenitors. J Clin Invest 1993;91:257–63.
[32] Hughes DE, Dai A, Tiffee JC, Li HH, Mundy GR, Boyce BF. Estrogen promotes apoptosis of murine osteoclasts mediated by TGF–β. Nat Med 1996;2:1132–6.
[33] Kameda T, Mano H, Yuasa T, Mori Y, Miyazawa K, Shiokawa M, et al. Estrogen inhibits bone resorption by directly inducing apoptosis of the bone-resorbing osteoclasts. J Exp Med 1997;186:489–95.
[34] Nakamura T, Imai Y, Matsumoto T, Sato S, Takeuchi K, Igarashi K, et al. Estrogen prevents bone loss via estrogen receptor alpha and induction of Fas ligand in osteoclasts. Cell 2007;130:811–23.
[35] Ukon Y, Makino T, Kodama J, Tsukazaki H, Tateiwa D, Yoshikawa H, et al. Molecular-based treatment strategies for osteoporosis: a literature review. Int J Mol Sci 2019;20:2557.
[36] Kousteni S, Bellido T, Plotkin L, O'brien C, Bodenner D, Han L, et al. Nongenotropic, sex-nonspecific signaling through the estrogen or androgen receptors: dissociation from transcriptional activity. Cell 2001;104:719–30.

[37] Migliaccio A, Castoria G, Domenico M, Falco Ad, Bilancio A, Auricchio F. Src is an initial target of sex steroid hormone action. Ann N Y Acad Sci 2002;963:185–90.
[38] Manolagas SC, Almeida M. Gone with the Wnts: beta-catenin, T-cell factor, forkhead box O, and oxidative stress in age-dependent diseases of bone, lipid, and glucose metabolism. Mol Endocrinol 2007;21:2605–14.
[39] Almeida M, Han L, Martin-Millan M, Plotkin LI, Stewart SA, Roberson PK, et al. Skeletal involution by age-associated oxidative stress and its acceleration by loss of sex steroids. J Biol Chem 2007;282:27285–97.
[40] Chang J, Wang Z, Tang E, Fan Z, McCauley L, Franceschi R, et al. Inhibition of osteoblastic bone formation by nuclear factor-kappaB. Nat Med 2009;15:682–9.
[41] Modder UI, Clowes JA, Hoey K, Peterson JM, McCready L, Oursler MJ, et al. Regulation of circulating sclerostin levels by sex steroids in women and in men. J Bone Miner Res 2011;26:27–34.
[42] van Bezooijen RL, Roelen BA, Visser A, van der Wee-Pals L, de Wilt E, Karperien M, et al. Sclerostin is an osteocyte-expressed negative regulator of bone formation, but not a classical BMP antagonist. J Exp Med 2004;199:805–14.
[43] Long F. Building strong bones: molecular regulation of the osteoblast lineage. Nat Rev Mol Cell Biol 2011;13:27–38.
[44] Falahati-Nini A, Riggs BL, Atkinson EJ, O'Fallon WM, Eastell R, Khosla S. Relative contributions of testosterone and estrogen in regulating bone resorption and formation in normal elderly men. J Clin Invest 2000;106:1553–60.
[45] Hofbauer LC, Khosla S, Dunstan CR, Lacey DL, Spelsberg TC, Riggs BL. Estrogen stimulates gene expression and protein production of osteoprotegerin in human osteoblastic cells. Endocrinol 1999;140:4367–70.
[46] Hofbauer LC, Hicok KC, Chen D, Khosla S. Regulation of osteoprotegerin production by androgens and anti-androgens in human osteoblastic lineage cells. Eur J Endocrinol 2002;147:269–73.
[47] Bellido T, Jilka RL, Boyce BF, Girasole G, Broxmeyer H, Dalrymple SA, et al. Regulation of interleukin-6, osteoclastogenesis, and bone mass by androgens. The role of the androgen receptor. J Clin Invest 1995;95:2886–95.
[48] Clarke BL, Khosla S. Androgens and bone. Steroids 2009;74:296–305.
[49] Pilbeam CC, Raisz LG. Effects of androgens on parathyroid hormone and interleukin-1-stimulated prostaglandin production in cultured neonatal mouse calvariae. J Bone Miner Res 1990;5:1183–8.
[50] Kasperk CH, Wakley GK, Hierl T, Ziegler R. Gonadal and adrenal androgens are potent regulators of human bone cell metabolism in vitro. J Bone Miner Res 1997;12:464–71.
[51] Glueck CJ, Mcmahon RE, Bouquot JE, Triplett D, Gruppo R, Wang P. Heterozygosity for the Leiden mutation of the factor V gene, a common pathoetiology for osteonecrosis of the jaw, with thrombophilia augmented by exogenous estrogens. J Lab Clin Med 1997;130:540–3.
[52] Pandit RS, Glueck CJ. Testosterone, anastrozole, factor V Leiden heterozygosity and osteonecrosis of the jaws. Blood Coagul Fibrinolysis 2014;25:286–8.
[53] Jarman MI, Lee K, Kanevsky A, Min S, Schlam I, Mahida C, et al. Case report: primary osteonecrosis associated with thrombophilia-hypofibrinolysis and worsened by testosterone therapy. BMC Hematol 2017;17:1–6.
[54] Buchanan JR, Hospodar P, Myers C, Leuenberger P, Demers LM. Effect of excess endogenous androgens on bone density in young women. J Clin Endocrinol Metabol 1988;67:937–43.
[55] Dixon JE, Rodin A, Murby B, Chapman MG, Fogelman I. Bone mass in hirsute women with androgen excess. Clin Endocrinol 1989;30:271–7.
[56] Di Carlo C, Shoham Z, MacDougall J, Patel A, Hall ML, Jacobs HS. Polycystic ovaries as a relative protective factor for bone mineral loss in young women with amenorrhea. Fertil Steril 1992;57:314–9.
[57] Preželj J, Kocijančič A. Bone mineral density in hyperandrogenic amenorrhoea. Calcif Tissue Int 1993;52:422–4.
[58] Dagogo-Jack S, Al-Ali N, Qurttom M. Augmentation of bone mineral density in hirsute women. J Clin Endocrinol Metab 1997;82:2821–5.
[59] Adami S, Zamberlan N, Castello R, Tosi F, Gatti D, Moghetti P. Effect of hyperandrogenism and menstrual cycle abnormalities on bone mass and bone turnover in young women. Clin Endocrinol 1998;48:169–73.
[60] Good C, Tulchinsky M, Mauger D, Demers LM, Legro RS. Bone mineral density and body composition in lean women with polycystic ovary syndrome. Fertil Steril 1999;72:21–5.
[61] Zborowski JV, Talbott EV, Cauley JM. Polycystic ovary syndrome, andorgen excess, and the impact on bone: obstet Gynecol Clin North Am, vol. 28; 2001. p. 135–51.
[62] Castelo-Branco C, Pons F, de Osaba MJM, Garrido J, Fortuny A. Menstrual history as a determinant of current bone density in young hirsute women. Metabolism 1996;45:515–8.
[63] Preželj J, Kocijančič A. Antiandrogen treatment with spironolactone and linestrenol decreases bone mineral density in eumenorrhoeic women with androgen excess. Horm Metab Res 1994;26:46–8.
[64] Moghetti P, Castello R, Zamberlan N, Rossini M, Gatti D, Negri C, et al. Spironolactone, but not flutamide, administration prevents bone loss in hyperandrogenic women treated with gonadotropin-releasing hormone agonist. J Clin Endocrinol Metab 1999;84:1250–4.
[65] Seeman E. Raloxifene. J Bone Miner Metab 2001;19:65–75.
[66] Chiu WY, Chien JY, Yang WS, Juang JM, Lee JJ, Tsai KS. The risk of osteonecrosis of the jaws in Taiwanese osteoporotic patients treated with oral alendronate or raloxifene. J Clin Endocrinol Metab 2014;99:2729–35.
[67] Baur DA, Altay MA, Teich S, Schmitt Oswald M, Quereshy FA. Osteonecrosis of the jaw in a patient on raloxifene: a case report. Quintessence Int 2015;46:423–8.
[68] Pontes HAR, de Souza LL, Uchôa DCC, Cerqueira JMM. Mandibular osteonecrosis associated with raloxifene. J Craniofac Surg 2018;29:e257–9.
[69] Bindakhil M, Shanti RM, Mupparapu M. Raloxifene-induced osteonecrosis of the jaw (MRONJ) with no exposure to bisphosphonates: clinical and radiographic findings. Quintessence Int 2021:2–7. 0.
[70] Kim Y, Tian Y, Yang J, Huser V, Jin P, Lambert CG, et al. Comparative safety and effectiveness of alendronate versus raloxifene in women with osteoporosis. Sci Rep 2020;10:11115.
[71] Perez EA, Weilbaecher K. Aromatase inhibitors and bone loss. Oncology 2006;20:1029–48.
[72] Ruggiero S, Gralow J, Marx RE, Hoff AO, Schubert MM, Huryn JM, et al. Practical guidelines for the prevention, diagnosis, and treatment of osteonecrosis of the jaw in patients with cancer. J Oncol Prac 2006;2:7–14.
[73] Vaszilko M, Kovacs E, Restar L, Balla B, Cseplo K, Kosa J, et al. Potential significance of antiestrogen therapy in the development of bisphosphonate related osteonecrosis of the jaw. J Cranio-Maxillo-Fac Surg 2014;42:1932–6.
[74] Neha R, Beulah E, Anusha B, Vasista S, Stephy C, Subeesh V. Aromatase inhibitors associated osteonecrosis of jaw: signal refining to identify pseudo safety signals. Int J Clin Pharm 2020;42:721–7.
[75] Wallach EE, Fogelman I. Gonadotropin-releasing hormone agonists and the skeleton. Fertil Steril 1992;57:715–24.
[76] Nawroth F. GnRH agonist. In: Wolff Mv, Nawroth F, editors. Fertility preservation in oncological and non-oncological diseases : a practical guide. first ed. Cham, Switzerland: Springer; 2020. p. 215–21.
[77] Brown J, Pan A, Hart RJ. Gonadotrophin-releasing hormone analogues for pain associated with endometriosis. Cochrane Database Syst Rev 2010:CD008475.
[78] Gerhard I, Schindler A, Bühler K, Winkler U, Meinen K, Mancarella D, et al. Treatment of endometriosis with leuprorelin acetate depot: a German multicentre study. Clin Ther 1992;14:3–16.
[79] Dawood MY, Lewis V, Ramos J. Cortical and trabecular bone mineral content in women with endometriosis: effect of gonadotropin-releasing hormone agonist and danazol. Fertil Steril 1989;52:21–6.
[80] Dodin S, Lemay A, Maheux R, Dumont M, Turcot-Lemay L. Bone mass in endometriosis patients treated with GnRH agonist implant or danazol. Obstet Gynecol 1991;77:410–5.
[81] Whitehouse R, Adams J, Bancroft K, Vaughan-Williams C, Elstein M. The effects of nafarelin and danazol on vertebral trabecular bone mass in patients with endometriosis. Clin Endocrinol 1990;33:365–73.
[82] Kiilholma P, Tuimala R, Korhonen M, Hagman E. Comparison of the gonadotropin-releasing hormone agonist goserelin acetate alone versus goserelin combined with estrogen-progestogen add-back therapy in the treatment of endometriosis. Obstetrical & gynecological survey 1996;51:177–9.
[83] Sagsveen M, Farmer JE, Prentice A, Breeze A. Gonadotrophin-releasing hormone analogues for endometriosis: bone mineral density. Cochrane Database Syst Rev 2003:CD001297.
[84] Surrey ES, Judd HL. Reduction of vasomotor symptoms and bone mineral density loss with combined norethindrone and long-acting gonadotropin-releasing hormone agonist therapy of symptomatic endometriosis: a prospective randomized trial. J Clin Endocrinol Metab 1992;75:558–63.
[85] Maillefert J, Sibilia J, Michel F, Saussine C, Javier R, Tavernier C. Bone mineral density in men treated with synthetic gonadotropin-releasing hormone agonists for prostatic carcinoma. J Urol 1999;161:1219–22.
[86] Morote J, Morin JP, Orsola A, Abascal JM, Salvador C, Trilla E, et al. Prevalence of osteoporosis during long-term androgen deprivation therapy in patients with prostate cancer. Urology 2007;69:500–4.
[87] Stoch SA, Parker RA, Chen L, Bubley G, Ko Y-J, Vincelette A, et al. Bone loss in men with prostate cancer treated with gonadotropin-releasing hormone agonists. J Clin Endocrinol Metab 2001;86:2787–91.
[88] Jonat W, Kaufmann M, Sauerbrei W, Blamey R, Cuzick J, Namer M, et al. Goserelin versus cyclophosphamide, methotrexate, and fluorouracil as adjuvant therapy in premenopausal patients with node-positive breast cancer: the Zoladex Early Breast Cancer Research Association Study. J Clin Oncol 2002;20:4628–35.
[89] Kim EH, Jeon YK, Pak K, Kang T, Kim KE, Kim SJ, et al. Effect of tamoxifen with or without gonadotropin-releasing hormone analog on DXA values in women with breast cancer. Sci Rep 2021;11:3407.
[90] Shahinian VB, Kuo Y-F, Freeman JL, Goodwin JS. Risk of fracture after androgen deprivation for prostate cancer. N Engl J Med 2005;352:154–64.
[91] Smith MR, McGovern FJ, Zietman AL, Fallon MA, Hayden DL, Schoenfeld DA, et al. Pamidronate to prevent bone loss during androgen-deprivation therapy for prostate cancer. N Engl J Med 2001;345:948–55.
[92] Michaelson MD, Kaufman DS, Lee H, McGovern FJ, Kantoff PW, Fallon MA, et al. Randomized controlled trial of annual zoledronic acid to prevent gonadotropin-releasing hormone agonist-induced bone loss in men with prostate cancer. J Clin Oncol 2007;25:1038–42.
[93] Lee RJ, Saylor PJ, Smith MR. Treatment and prevention of bone complications from prostate cancer. Bone 2011;48:88–95.
[94] Kim SH, Lee YK, Kim TY, Ha YC, Jang S, Kim HY. Incidence of and risk for osteonecrosis of the jaw in Korean osteoporosis patients treated with

bisphosphonates: a nationwide cohort-study. Bone 2021;143:115650.
[95] Eiken PA, Prieto-Alhambra D, Eastell R, Abrahamsen B. Surgically treated osteonecrosis and osteomyelitis of the jaw and oral cavity in patients highly adherent to alendronate treatment: a nationwide user-only cohort study including over 60,000 alendronate users. Osteoporos Int 2017;28:2921–8.
[96] Ishimaru M, Ono S, Morita K, Matsui H, Hagiwara Y, Yasunaga H. Prevalence, incidence rate, and risk factors of medication-related osteonecrosis of the jaw in patients with osteoporosis and cancer: a nationwide population-based study in Japan. J Oral Maxillofac Surg 2022;80:714–27.
[97] Cummings SR, Martin JS, McClung MR, Siris ES, Eastell R, Reid IR, et al. Denosumab for prevention of fractures in postmenopausal women with osteoporosis. N Engl J Med 2009;361:756–65.
[98] Orwoll E, Teglbjærg CS, Langdahl BL, Chapurlat R, Czerwinski E, Kendler DL, et al. A randomized, placebo-controlled study of the effects of denosumab for the treatment of men with low bone mineral density. J Clin Endocrinol Metab 2012;97:3161–9.
[99] Bone HG, Wagman RB, Brandi ML, Brown JP, Chapurlat R, Cummings SR, et al. 10 years of denosumab treatment in postmenopausal women with osteoporosis: results from the phase 3 randomised FREEDOM trial and open-label extension. Lancet Diabetes Endocrinol 2017;5:513–23.
[100] Watts NB, Grbic JT, Binkley N, Papapoulos S, Butler PW, Yin X, et al. Invasive oral procedures and events in postmenopausal women with osteoporosis treated with denosumab for up to 10 Years. J Clin Endocrinol Metab 2019;104:2443–52.
[101] Smith MR, Saad F, Oudard S, Shore N, Fizazi K, Sieber P, et al. Denosumab and bone metastasis–free survival in men with nonmetastatic castration-resistant prostate cancer: exploratory analyses by baseline prostate-specific antigen doubling time. J Clin Oncol 2013;31:3800.
[102] Troeltzsch M, Woodlock T, Kriegelstein S, Steiner T, Messlinger K, Troeltzsch M. Physiology and pharmacology of nonbisphosphonate drugs implicated in osteonecrosis of the jaw. J Can Dent Assoc 2012;78:1–7.
[103] Cosman F, Crittenden DB, Adachi JD, Binkley N, Czerwinski E, Ferrari S, et al. Romosozumab treatment in postmenopausal women with osteoporosis. N Engl J Med 2016;375:1532–43.
[104] Nicolatou-Galitis O, Razis E, Galiti D, Vardas E, Tzerbos F, Labropoulos S, editors. Osteonecrosis of the jaw in a patient with chronic myelogenous leukemia receiving imatinib-a case report with clinical implications. Forum Clin Oncol; 2013.
[105] Viviano M, Rossi M, Cocca S. A rare case of osteonecrosis of the jaw related to imatinib. J Korean Assoc Oral Maxillofac Surg 2017;43:120–4.
[106] Gupta L, Dholam K, Janghel Y, Gurav SV. Osteonecrosis of the jaw associated with imatinib therapy in myeloproliferative neoplasm: a rare case report. Oral Surg Oral Med Oral Pathol Oral Radiol 2021;131:e157–62.
[107] Garuti F, Camelli V, Spinardi L, Bucci L, Trevisani F. Osteonecrosis of the jaw during sorafenib therapy for hepatocellular carcinoma. Tumori 2016;102:S69–70.
[108] Patel V, Sproat C, Kwok J, Tanna N. Axitinib-related osteonecrosis of the jaw. Oral Surg Oral Med Oral Pathol Oral Radiol 2017;124:e257–60.
[109] Jung T-Y. Osteonecrosis of jaw after antiangiogenic agent administration in a renal cell carcinoma patient. Oral and Maxillofacial Surgery Cases 2017;3:27–33.
[110] Marino R, Orlandi F, Arecco F, Gandolfo S, Pentenero M. Osteonecrosis of the jaw in a patient receiving cabozantinib. Aust Dent J 2015;60:528–31.
[111] Abel Mahedi Mohamed H, Nielsen CEN, Schiodt M. Medication related osteonecrosis of the jaws associated with targeted therapy as monotherapy and in combination with antiresorptives. A report of 7 cases from the Copenhagen Cohort. Oral Surg Oral Med Oral Pathol Oral Radiol 2018;125:157–63.
[112] Giancola F, Campisi G, Russo LL, Muzio LL, Di Fede O. Osteonecrosis of the jaw related to everolimus and bisphosphonate: a unique case report? Ann Stomatol 2013;4:20.
[113] Lee C, Lee K, Hirata K, Suzuki J. Medication-related osteonecrosis of the jaw with the mTOR inhibitor everolimus in a patient with estrogen-receptor positive breast cancer: a case report. Int J Oral Dent Health 2016;2:33.
[114] Yamamoto D, Tsubota Y, Utsunomiya T, Sueoka N, Ueda A, Endo K, et al. Osteonecrosis of the jaw associated with everolimus: a case report. Mol Clin Oncol 2017;6:255–7.
[115] Nifosì A, Nifosì L, Nifosì G. Osteonecrosis of the jaw in a patient treated with denosumab and temsirolimus. SAJ Case Rep 2017;4:401.
[116] Henien M, Carey B, Hullah E, Sproat C, Patel V. Methotrexate-associated osteonecrosis of the jaw: a report of two cases. Oral Surg Oral Med Oral Pathol Oral Radiol 2017;124:e283–7.
[117] Palomba S, Orio Jr F, Morelli M, Russo T, Pellicano M, Nappi C, et al. Raloxifene administration in women treated with gonadotropin-releasing hormone agonist for uterine leiomyomas: effects on bone metabolism. J Clin Endocrinol Metab 2002;87:4476–81.