Review article

The impact of sex steroids on osteonecrosis of the jaw

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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.

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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 osteoclastic 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.

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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, and 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.

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...
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 E2 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].

![Mechanisms showing how sex steroids affect bone remodeling.](image-url)
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-κB, and the last is through suppression of sclerostin production.

Estrogen’s antiapoptotic effect 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 5α-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 mediated 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-κB activity by estrogen [40]. In estrogen deficiency, the NF-κB activity of osteoblasts increases, and suppression of NK-kb activity inhibits bone loss. This indicates that NF-κB activity mediates the influence of estrogen on osteoblasts. Suppression of 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 5α 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 sub-physiological 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 intravascular 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 antithrombin 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 compared 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 andralonate 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, levethoxyrine, acetalsalicly 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 tooth 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
biphosphonate, 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 biphosphonate. 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 considered treatment. Surgical debridement on the affected body area for ONJ treatment was performed and the pathologist considered the presence of fluid cemento-osseous dysplasia (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 biphosphonate, hence the use of raloxifene may cause ONJ, and therefore caution should be taken to use 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, resulting in 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 antagonistic 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
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.

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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 health and smoking, which are common in this population.

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 | Increase [117] | – |
| Letrozole (Femara®) | Aromatase inhibitor | Reduction | Decrease [71] | Case reports [67-69] |
| Anastrozole (Arimidex®) | Aromatase inhibitor | Reduction | Decrease [71] | Retrospective cohort study [66,70] |
| Exemestane (Aromasin®) | Aromatase inhibitor | Reduction | Decrease [71] | |
| Leuprolide (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.

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 steroid 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 and ones without estrogen therapy.

In conclusion, little are known about sex steroid roles in the progression.

Declaration of competing interest

The authors declare no competing interest.

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