J Contemp Med 2017; 7(4): 418-427
DOI: 10.16899/gopctd.315052

REVIEW
DERLEME

The Critical Role of Estrogen in Menopausal Osteoporosis

Menapoz Osteoporozunda Östrojenin Kritik Rolü

Mrinali Sharma[1], Sathees B. Chandra[1]

[1] Biomedical Sciences Program, College of Nursing and Health Sciences, Barry University, Miami, FL

ÖZ

Osteoporoz, kemik dokusunun kütlesinde ve yoğunluğunda azalmaya neden olan ve iskelet kırıklarının ortaya çıkma ihtimalini artıran bir kemik bozukluğudur. Bu kemik hastalığı, menopozdaki kadınlar için özellikle önemlidir. Bu genel prevalansa bağlı olarak osteoporoz hastaları için, farmakolojik ve tıbbi endüstride daha iyi tedavi seçenekleri için sürekli girişim gerektirir. Osteoporoz için birçok bilimsel araştırma çalışmasının odak noktası, östrojen olmuştur. Bir hormon olarak, östrojen kadının vücudunda değişken bir kapasite sergiler ve kadınların neden menopozdan sonra osteoporoz geliştiğine ilişkin elverişli bir açıklama olduğu şeklinde suçlanıyor.

Bu yazının amacı, östrojenin menopoz osteoporozu tedavi etme kapasitesini yorumlamaktır. Bu nedenle, bu makalede, östrojenin kemik sağlığında, farklı şekillerde, türevlerde ve östrojen kombinasyonlarında osteoporoz tedavisinde etkinlik açısından önemi, incelenmektedir.

Anahtar Kelimeler: osteoporoz, menopoz, östrojen, kemik, kırıklar

ABSTRACT

Osteoporosis is a bone disorder, which causes a reduction in the mass and density of bone tissue, and implants a greater possibility for skeletal fractures to occur. This bone disease is especially relevant for women suffering from menopause. Due to this general prevalence, osteoporosis requires continual intervention in the pharmacological and medicinal industry for better treatment alternatives for patients. A focal point for many scientific research studies for osteoporosis has been estrogen. As a hormone, estrogen exhibits a fluctuating capacity in the woman's body, and this has been proclaimed to be a qualifying explanation as to why women develop osteoporosis after menopause.

The purpose of this paper is to interpret estrogen's capacity to treat menopausal osteoporosis. Thus, in this article, estrogen's significance in bone health and different forms, derivatives, and the combinations of estrogen is examined in terms of efficiency in treating osteoporosis.

Keywords: osteoporosis, menopause, estrogen, bone, fractures

Corresponding Author: Sathees B. Chandra, Ph.D

Address Associate Professor of Biomedical Sciences Director for Biomedical Sciences Program College of Nursing and Health Sciences Barry University 11300 NE Second Ave Miami, FL 33161, USA

E-mail: schandra@barry.edu

Başvuru Tarihi/Received: 19-05-2017

Kabul Tarihi/Accepted: 18-08-2017

Introduction

With growing age, both women and men experience loss of neuromuscular function and bone weakening. As this condition prolongs and continues its coverage throughout the aging body, it becomes known as osteoporosis (1). Not only does this age-related bone disease reduce bone mass and density, but it also produces a high susceptibility for skeletal fractures to occur. Just in the United States, 2 million bone fractures are caused by osteoporosis, with an estimate of 550,000 vertebral fractures and 300,000 hip fractures (2). Presently, 10 million people in the United States are suffering from osteoporosis, and approximately 200 million women in the entire world (3). Women have a higher probability of having osteoporosis than men because of a lower peak bone mass; whereas, men have a peak bone mass 10-15% higher than women (4). The peak bone mass is a term used to describe the mass and strength observed in bone tissue at the end of puberty. Even though both male and females share the same magnitude of bone density, men exhibit a greater bone size than females because of a greater periosteal deposition. Due to this indifference, men have a stronger ability to resist mechanical forces than women (5). However, different peak bone mass does not necessarily indicate osteoporosis, but it explains why women are a greater probable candidate of osteoporosis.

Estrogen deficiency is the dominant factor in osteoporosis analysis, which common in both males and females; but, similar to the peak bone mass indifference, estrogen levels are found to be much lower in women than in men (6). Its deficiency increases the life of cells that degrade bone tissue - osteoclasts; whereas, it decreases the longevity of osteoblasts, which function to build bone tissue (3). However, when estrogen is at its optimal level, it protects osteoblasts via estrogen receptors found in the polymorphic sites of the bone tissue. These receptors function in sustaining the development of osteoblasts. Thus, when an estrogen deficiency takes place, these receptors are inactivated, and the growth of osteoblasts is impacted (7). In contrast, the cytokine RANKL is stimulated by declining estrogen levels and promotes osteoclastogenesis or the production of osteoclasts (8). RANKL can be predicted based on the levels of its antagonist osteoprotegerin (OPG). When RANKL/OPG ratio is high, an estrogen deficiency is in place. However, when RANKL/OPG ratio is low, estrogen is present at an optimal level, and RANKL is inhibited (9). With estrogen's regulatory mechanisms in mind, researchers have further progressed to develop a procedure to combat osteoporosis known as the estrogen replacement therapy (ERT). This treatment uses estrogen to inhibit the action of osteoclasts and also decrease their production in the bone tissue (10.). Consequently, this reduces bone loss and the risk of osteoporotic fractures. Despite ERT's efficacy, the treatment is known to produce fatal side effects. Thus, ERT has to be modified for each menopausal patient by duration, age, ethnicity, and lifestyle to prevent unwanted repercussions and to achieve long-term benefits from the therapy (11).

The purpose of this article is to present a thorough analysis of estrogen's crucial role in the treatment of menopausal osteoporosis. Therefore, a deeper understanding of the pathophysiological process of osteoporosis effects on the bone tissue is presented, and the physiological aspect of estrogen concerning bone metabolism is evaluated. Lastly, ERT is investigated by the type, form, dosage, and administration, to gauge its credibility to treat of menopausal osteoporosis in comparison to other alternatives.

The Pathophysiology and Diagnosis of Osteoporosis

The pathophysiological process of osteoporosis is described in regards to the function of osteoclasts and osteoblasts. When osteoclastic cells are more numerous than

osteoblastic cells, they possess a stronger force and accelerate the degradation and resorption of bone tissue. As a result, the inhibition of osteoblasts over time leads to an imbalance known as osteoporosis (12, 63). Osteoporosis is diagnosed by the incidence of osteoporotic fractures, or by the World Health Organization's bone mineral density (BMD) criteria. An osteoporotic fracture is a low-level trauma injury that occurs due to a fall experienced from a lower height. These fractures usually take place after a sustained reduction in BMD with a decrease in the quality of the bone tissue (13). When diagnosing osteoporosis using the BMD diagnostic exam, an approximation of bone strength is quantified as a T-score and a Z-score and with this the risk of fracture can be determined (14,15). The T-score is a quantitative measurement of the difference of standard deviations (SD) of the average BMD obtained from a normal adult population. If the T score is higher than 2.5 SD, the patient is confirmed to have osteoporosis. However, a limitation of the T-score method is that it cannot be used to determine osteoporosis in patients younger than 50 years. Therefore, in the cases that are younger than 50 years, the Z-score is used to screen for osteoporosis (13, 15). Unlike the T-score that compares results to a normal adult population, the Z-score calculates the mean BMD by the patient's age and gender. Although the BMD diagnostic exam does predict fracture incidence from bone mass, a threshold at which a fracture is most likely to occur has not been established yet (16).

Osteoporotic fractures usually occur in sites like the ribs, spine, and wrists. However, the hip fractures are considered the most common and fatal osteoporotic injury. It has been reported that 10% of patients with osteoporotic hip injury die within 30 days of surgery, and the other 30% die within one year (17). These types of complications arise because osteoporotic fractures are more challenging to heal because the bone tissue tends to be more displaced and unstable. The bone is displaced due to the weakened the screw fixation. The screws in bone tissue are responsible for keeping the bone tissue in place and lifted. However, with decreasing BMD, the bone itself becomes fragile, which causes the screws to lose its ability to keep the bone tissue in place (18). Another difficulty faced with osteoporotic fractures is that they take a longer time to heal because of decreased levels of mesenchymal stem cells (19). The mesenchymal stems cells are significant in the fracture repair process, where they travel to the fracture site and incite proliferation and differentiation of osteogenic precursors; to stimulate the growth of bone tissue. Thus, the unavailability of mesenchymal stem cells significantly slows down the recovery process in a patient suffering from an osteoporotic fracture (17,20). However, in cases where osteoporotic fractures do heal, the repaired bone tissue cells are found to be much weaker than they were previously, and the tolerance for mechanical stress is also reduced (21). Therefore, due to their association with morbidity, mortality, and problematic healing, most treatments for osteoporosis are fixated just to prevent osteoporotic fractures (22).

Estrogen's operational role in the Human Body

Estrogen is a sexual hormone that is found both in males and females. However, women have a higher level of estrogen than men, due to its presence in important bodily functions, such as the menstrual cycle. Three forms of estrogen exist in women: estradiol, estriol, and estrone. Estradiol originates in the ovaries of childbearing females. However, when the ovaries stop producing estradiol during menopause, androstenedione is converted into estrone in the adipose tissue. Whereas, the placenta produces estriol during pregnancy, but is still present in small quantities in non-pregnant females. However, out of the three forms of estrogen, estradiol is known to be the most potent form, and it also exhibits the

highest affinity for cell receptors (23, 24). Estrogen is a critical operating unit for many functions that take place in the body at the organ, tissue, and cellular and is responsible for skeletal proliferation and maturation (25). It begins pubertal growth of the bone and is responsible for closing the epiphyseal growth plate, which ceases the continuing development of long bones (26). Additionally, estrogen regulates bone metabolism by directing activities in the immune system, through oxidative_stress, and by influencing bone cells (27). Thus, estrogen is known as the major systemic regulator of bone tissue metabolism (28).

Estrogen regulates bone metabolism through the bone tissue repair and remodeling process. The human skeleton is consistently remodeling and repairing minor cracks that appear in spongy bones due to various reasons, such as mechanical strain. The remodeling of the bone tissue begins in the core multicellular units (BMUs), which comprises of osteoblasts, osteoclasts, and osteocytes (28). In a BMU, osteoclasts and osteoblasts work in a close and simultaneous manner. Osteoclasts begin the bone remodeling process by attaching to the target bone tissue and resorbing the bone by acidification and proteolytic digestion. Once they finish their work, osteoclasts depart from the resorption site and call upon osteoblasts to enclose and conceal the resorbed cavity. This cavity ultimately develops into mineralized bone tissue. Estrogen influences this cycle by accelerating the activity of osteoblasts by preventing osteoblast apoptosis (15, 29, 30). However, this takes place by modifying the activity of osteoclasts in such way that it enhances the function of osteoblasts. Estrogen does this by suppressing the RANKL ability to bind to RANK on the precursors found on osteoclasts, and this leads to the inhibition of osteoclast differentiation. In this process, RANKL functions as an activator of the nuclear factor kappa B ligand and stimulates osteoclast differentiation and growth. Whereas, osteoprotegerin (OPG) is the natural inhibitor of RANKL and functions to protect bone tissue from the loss caused by RANKL binding to RANK (31). For osteoblasts, estrogen regulates the ratio of RANKL and OPG by decreasing the levels of RANKL and maintaining the levels of OPG (32). Another way estrogen decreases the levels of RANKL is by repressing the T cell tumor necrosis factor (TNF) production. Similar to osteoclasts, estrogen represses the activity by controlling the differentiation of T cells in organs like the bone marrow, thymus, and peripheral lymphoid organs. As a result, this reduces the_number of stem cells in the bone marrow via an IL-7 mediated mechanism. Thus, the T cell precursors travel to the thymus to differentiate and grow. However, once again, estrogen inhibits the activation of T cells indirectly by suppressing the production of IL-7 and IFN-γ and does this by increasing the levels of TFG-β. The result of these mechanisms will ultimately reduce the levels of TNF. In turn, low levels of TNF will also reduce RANKL levels (33). However, through this pathway, OPG levels are not increased and just maintained. Therefore, the suppression of RANKL will not change to the total cell number, and only the ratio of RANKL/OPG will be impacted (34).Where estrogen can inhibit osteoblasts apoptosis from taking place, it also has the power to promote osteoclast apoptosis by stimulating the expression of the Fas ligand (34). The Fas is a death receptor that induces apoptosis by progressing as FasL. This mechanism is conducted in an autocrine manner and begins in the pre-osteoclast stage. In this reaction, estrogen regulates the appearance of FasL in osteoclasts by working through osteoblastic cells; thereby it controls the lifespan of each osteoblast (23, 35).

Estrogen performs all of the mechanisms in the bone tissue with the help of estrogen receptors (ER): ERα and ERβ (27). These two functional estrogen receptors are nuclear receptors of transcriptional factors and are involved in cell growth and differentiation. Both ERα and ERβ identified in different

genes located on separate chromosomes, and each receptor also distributes differently in tissues. ERα originates in the uterus, liver, breast, and kidney; whereas, ERβ occupies the brain, bone, urinary tract, vasculature, and in the reproductive tissues (36, 37). However, ERα is the primary estrogen receptor in a female skeleton and promotes stimulatory effects on bone mass (38). The nuclear receptor positively influences bone growth by acting on the osteoblast progenitor and stimulating the Wnt pathway. The Wnt pathway is imperative in osteoblast production and bone tissue growth (39). The pathway begins by stabilizing β-catenin, which proceeds to activate the TCF/lymphoid enhancer factor transcription factor family. As a result, they are now able to incite the expression of Osx-1 gene by the osteoblast progenitors (40). The Wnt pathway is stimulated in response to mechanical strain encountered by the bone tissue. The ability to withstand mechanical pressure or bone loading is associated with the presence of ERα, and without it, the pathway will not proceed (41). Therefore, to maintain the integrity of the bone tissue, ERα is essential. Additionally, since this mechanism involves mechanical loading, ERα induces the Wnt signaling pathway independent of estrogen or ligand and does not require estrogen to activate receptor proteins (39, 40). The activity ERα is regulated by ERβ, which acts to restrain its functionality. Studies concluded that the inhibitory ability of ERβ is only exclusive in females and not in males. Although the reason for this selectivity for women has not been determined, it has been proposed that ERβ inhibition of ERα consist of specific transcription factors that stimulate the degradation of ERα (36, 38, 63).

The medicinal significance of estrogen

From the analysis above, it is sure that estrogen is a multifaceted hormone that has the ability control various aspects of the human body. Hence, many studies are driven to evaluate estrogen's medicinal capabilities. In recent times, significant pharmacological intervention has taken place, and estrogen has now become the primary active ingredient in 6 out of the 100 medications mostly prescribed medications today in the United States (23). Estrogen versatility is visible in drugs like ethynylestradiol for fertility, and Premarin for menopausal treatment (27). However, to receive a better understanding of estrogen's usage as a medication for menopausal osteoporosis, it is important to examine its potency and metabolic functionality.

Estrogen originates from the steroid class of hormones. Three different types of steroids exist mineralocorticoids, glucocorticoids, and gonadocorticoids. With a steroidal structure of C18 and phenol structure in ring A, estrogen is classified as gonadocorticoids. Additionally, since estrogen is a steroid, it is capable of traveling far in the bloodstream because its lipid solubility characteristic allows it to diffuse through cell membranes quickly (23, 39). Nevertheless, non-steroidal estrogens do exist, such as diethylstilbestrol and its derivatives, as well as phytoestrogens. However, a major drawback of non-steroidal estrogens is that they are unable to produce the same biological effects as steroidal estrogen; since they do not associate with the ligand-binding domain of the receptor protein as strongly as steroidal estrogen does. As a result, structural differences arise and, there is a difference in function. For instance, phytoestrogens lack similarity with the structure of estrogen, and this causes them to have decreased binding affinity for ERα and ERβ. As a hormone and a drug in action, it is essential to have a high binding similarity for the estrogen receptors to produce any effect. Because, when estrogen binds to its receptors, it leads to an initiation of intercellular signal cascades in the cells, and a stimulation of reactions (39). However, coactivator recruitment is a way to influence the ligand binding capacity directly. Coactivators support molecules that are both structural different and don't have a competitive ligand-binding

capacity by activating the ligand complex (27). Along with ligand-binding affinity and coactivator recruitment, the concentration of estrogen inside the cell also determines the level dominance the molecule has on the cell. However, the level of estrogen is determined by its metabolic activity (42). The metabolism of estrogen drug formulations is a task undertaken by cytochrome P450 enzymes, which are found in tissues designated for estrogen action, such as the mammary gland, uterus, and brain. In the metabolism of estrogen, cytochrome P450 enzymes hydroxylate estrogen found in the particular tissue. As a result, the metabolites are produced near, or at the receptors. The location of the metabolites is imperative to determine if the product is functionally active or inactive, and it can lead to altercations in estrogen's activity in the tissue (43). Hence, the metabolism of estrogen is vital in predicting its action, and it also determines how estrogen is formulated in medications.

For oral administration routes, estrogen has to be produced into water-soluble compounds to transit in and out of the body. However, if the estrogen compound is designed to enter the cell, it has to be lipid soluble (23). Since lipid solubility is an original characteristic of estrogen, it is not the challenge faced by researchers. The challenge is to have estrogen appear water soluble for oral medications, and this is accomplished by sulfates and glucuronides. These two compounds are highly water-soluble and help transit estrogen inside the cell (39). This pharmacological pathway works through a first pass mechanism, which essentially reduces the level of estrogen circulating in the body. For instance, oral administration of estrogen is metabolized into estrone by the gut and liver, and this causes a decrease of estrogen in circulation. Oral medications are made in a microcrystalline form to defend the estrogen from the first pass effect. The microcrystalline structure functions to enlarge the compound surface, and increase resorption and bioavailability of estrogen (23, 39)

Estrogen Replacement Therapy (ERT) Benefits and Risks Profile

As stated previously, estrogen deficiency can result in bone loss and eventually osteoporosis. Hence, for osteoporosis, researchers have found a protocol to maintain the levels of estrogen from falling by treating the issue with ERT (23). In regards to osteoporosis, this therapy can decrease the incidence of osteoporotic bone fractures in women under the age of 60 and within ten years after menopause onset. After the age of 60, there is a higher risk to be subjected to long-term complications, including the risk of certain types of cancers like breast cancer. Another drawback of ERT is that its effect on bone tissue declines after the treatment is stopped; thus, the patient is again subjected to the risk of osteoporotic fractures (44). Despite the limitations and associated risks, ERT has been proven to work very well. Statistical data conducted suggest that ERT given in the first five years of menopause can reduce the incidence of fracture in women by at least 50%. The most popular form of estrogen utilized in ERT is 17β- Estradiol (45). Research studies have found substantial evidence of 17β- Estradiol' s ability to reduce menopausal bone loss in the lumbar spine area. Nonetheless, an investigation on ERT' s ability to prevent bone loss in other types of bone tissue still has to be conducted to evaluate its full potential (46).

Although ERT has proven their efficacy and capability of treating menopausal osteoporosis, the long-term side effects present medical professionals with uncertainty on prescribing them to patients. Due to the safety concerns, the U.S. Food and Drug Administration (FDA) has introduced regulations that require all products with estrogen or combined with progestin to issue a warning about the associated risk factors, including the risk of breast cancer, blood clots,

stroke and heart attack. FDA also recommends physicians to prescribe topical products to treat most menopausal symptoms. However, for osteoporosis, FDA does not place any regulations on it, as long as the doctor recognizes the health risk to outweigh the potential risks associated with the medication (47).

A lighter version of ERT with reduced dosage and strength

Due to the potential hazards and FDA regulations in place, scientific studies have investigated lower doses of 17β- estradiol combined with progestogens to preserve the efficacy of the treatment and reduce the fatal side effects (46). In a previous study, 17β-estradiol was solely administrated in varying doses from 0.25 mg/day to 2 mg/day. The study concluded that 0.5 mg/day is enough for a reduction to be seen in symptoms related to osteoporosis (48). Nevertheless, 17β- estradiol in combination with a progestogen, such as norethisterone acetate enhances the response in bone tissue with a low dosage of estrogen. (14). Norethisterone is a 19-nortestosterone derived progestogen has been potentially beneficial for bone turnover. Also, it has been found that norethisterone acetate can reduce the concentration of bone resorption markers found in bone tissue, which triggers bone formation. Additionally, clinical trials have reported combinations of 1 mg 17β- estradiol with 0.25-0.5 mg of norethisterone acetate can prevent bone loss and stabilize the bone turnover and bone markers back to premenopausal levels (46).

Metabolic Characteristics of Transdermal ERT in contrast to Oral ERT

Since a comparable alternative to ERT is still not found, transdermal ERT is a reliable option to ERT, rather than having to do away with it all together (49). While oral regimens are the most popular form of ERT prescribed, it is believed that oral estrogen can have adverse effects on the liver, increases clotting factors, triggers gastrointestinal problems and causes inflammation. Transdermal administration of estrogen is capable of avoiding these complications, and functions by being directly absorbed into the capillaries in the skin and by being processed via hepatic metabolism (29,50). This delivery method is equivalent with oral regimens effectiveness of treating menopausal osteoporosis. Studies have found that transdermal ERT in lower dosages produces a steady and substantial increase in BMD and also decreases bone turnover markers (51). Transdermal ERT is found to be more consistent in its levels of estrogen than oral ERT (29). Since absorption through the skin occurs gradually, it avoids fluctuations which are a common occurrence in oral ERT products. Transdermal ERT products are usually distributed in dosages of 0.025 to 0.1 mg/day and instructed to be applied twice a week (50).

To measure the risk-benefit profile of transdermal ERT; a case study was conducted between transdermal estrogen patch users versus oral estrogen user. The study revealed oral estrogen to increase the risk of deep vein thrombosis and pulmonary embolism by at least three folds. Whereas, the transdermal estrogen patch users observed no increase in risk at all (52). Currently, transdermal ERT is commonly prescribed to women with hypertension, diabetes mellitus, obesity, cardiovascular issues, and other health concerns. Also, based on the findings from the study, transdermal ERT is the only option that is recommended for women above the age of 60 because of the risks of deep vein thrombosis and stroke with oral ERT (49).

A “natural” alternative to synthetic estrogen used in ERT

Despite being FDA approved, raloxifene could not be comparable to ERT in regards to efficacy. Hence, instead of an estrogen antagonist, the idea of "natural estrogen" is introduced as Bioidentical Hormone Therapy (BHT). BHT is advertised

as a natural hormone treatment, which consists of plant-derived hormone formulations of 17β-estradiol, estrone, or estriol. Their products are available at most pharmacies, and many of them are FDA approved. A likely benefit of BHT is that these medications can be compounded to according to the patient's needs (53,54). Bioidentical compounded estrogen formulations are usually prescribed in a combination of 2 or 3 forms of estrogen, and bi-est and tri-est are the most popular bioidentical formulations. Compounded BHT consists of varying percentages of estradiol, estrone, and estriol. For instance, Bi-est is composed of about 80% estriol; but 17β-estradiol makes up the remaining 20% and accounts for most of the functionality (55). Also, one thing to keep in mind is that compounded BHT products cannot be tested for safety and efficacy because they are compounded from the results of saliva tests or blood sera levels. These tests are against evidence-based guidelines protocol, which state that compounded hormone medications can only be compounded based on the symptoms present. Hence, it is difficult to estimate a compounded dose that is equivalent to the standard estrogen formula (53, 55, 56).

While BHT is proclaimed to be a natural and safe substitute for treating menopausal osteoporosis, till now, no scientific evidence suggests BHT to be more beneficial or safer than FDA-approved manufactured drugs (55,56). Although, a few studies have found that BHT is effective in decreasing mood symptoms that occur in menopause (57). Also, studies report that bioidentical hormones can be prescribed for patients who are unable to consume FDA-approved manufactured drugs, or require a more personalized formulation. However, BHT should be followed by the same guidelines and expect the same results and side effects as found in ERT (55).

Estrogen's Agonist Raloxifene's efficacy compared with ERT

Although, the perception behind prescribing lower doses of ERT is to prevent the undesirable side effects associated with ERT; however, by reducing the dosage of ERT, the effectiveness of estrogen's ability to combat menopausal osteoporosis is also decreased (58). By keeping this in mind, studies were conducted to find a chemical compound that has similar efficacy as estrogen but was safer and free from unpleasant side effects. Hence, raloxifene was introduced as an alternative to ERT.

A nonsteroidal benzothiophene, raloxifene is categorized as a second-generation selective estrogen receptor modulator (SERM), and it was the first SERM to be approved by the FDA to treat menopausal osteoporosis. SERM classifies compounds that have tissue selectivity but differ in activity from estrogen. Thus, staying true to the definition, raloxifene produces agonist effects against estrogen by competitively binding to estrogen receptors (59). Raloxifene utilizes its antiresorptive function to bind to estrogen receptors with 17β- estradiol and thereby reduces bone degradation (30,60). This medication therapy has given patients relief from menopausal osteoporosis and is found to be very effective in reducing vertebral fractures (61). Thus, FDA has approved 60mg/day of raloxifene, which is enough to provide a 2.6% increase in BMD (62). Nonetheless, research findings do indicate that ERT produces a higher increase in BMD than raloxifene. Also, ERT decreases bone turnover more than raloxifene does (58). Despite the discrepancy in results, raloxifene is still upholding its ability to treat menopausal osteoporosis safely and being free from the risk of obtaining cancer after usage. Although, raloxifene does incite other repercussions, such as deep vein thrombosis, pulmonary embolism, retinal vein thrombosis, hot flashes and leg cramps. These risks are considered mild in regards to ERT repercussions. However, one drawback of raloxifene is that it does not extend its protection to the bone tissue after the treatment is stopped, similar to ERT (62).

Future Directions:

In conclusion, we have established the mechanisms by which estrogen influences bone reformation and bone tissue maintenance. Furthermore, we understand the vitality of harmonizing these processes to prevent bone loss and osteoporosis. However, as a drug, estrogen's potency to treat menopausal osteoporosis calls for more intervention with minimal side effects. Scientific studies began with ERT, which led to the discovery of raloxifene, BHT, and transdermal ERT. Out of the three treatment options, it can be inferred that raloxifene is the safest alternative, but more research is necessary to conclude regarding the efficacy. Additionally, both BHT and transdermal ERT require further clinical investigations to understand how safe these treatments are as well as to comprehend the potential risks of each

References

1. Cummings SR, Melton LJ. Epidemiology and outcomes of osteoporotic fractures. The Lancet. 2002;359(9319):1761-1767.
2. Li, G., Thabane, L., Papaioannou, A., Ioannidis, G., Levine, M. A., & Adachi, J. D. An overview of osteoporosis and frailty in the elderly. BMC Musculoskeletal Disorders. 2017;18(1):46.
3. Lane, N. E. (2006). Epidemiology, etiology, and diagnosis of osteoporosis. AM J Obstet Gynecol. 2006; 194(2): S3-S11.
4. World Health Organization. (1994). Assessment of fracture risk and its application to screening for postmenopausal osteoporosis: report of a WHO study group [meeting held in Rome from 22 to 25 June 1992].
5. Bonjour, J. P., Chevalley, T., Ferrari, S., & Rizzoli, R.The importance and relevance of peak bone mass in the prevalence of osteoporosis. Salud publica de Mexico. 2009; 51: s5-s17.
6. Kuchuk, N. O., Van Schoor, N. M., Pluijm, S. M., Smit, J. H., De Ronde, W., & Lips, P. The association of sex hormone levels with quantitative ultrasound, bone mineral density, bone turnover and osteoporotic fractures in older men and women. Clin Endocrinol. 2007; 67(2): 295-303.
7. Shoukry, A., Shalaby, S. M., Etewa, R. L., Ahmed, H. S., & Abdelrahman, H. M. Association of estrogen receptor β and estrogen-related receptor α gene polymorphisms with bone mineral density in postmenopausal women. Mol Cell Biochem. 2015; 405(1-2): 23-31.
8. Eghbali-Fatourechi, G., Khosla, S., Sanyal, A., Boyle, W. J., Lacey, D. L., & Riggs, B. L. Role of RANK ligand in mediating increased bone resorption in early postmenopausal women. J Clin Invest. 2003; 111(8): 1221-1230.
9. Hofbauer, L. C., Kuhne, C. A., & Viereck, V. The OPG/RANKL/RANK system in metabolic bone diseases. J Musculoskelet Neuronal Interact. 2004; 4(3): 268.
10. Bruder, J. Newer Therapies in the Management of Osteoporosis. Geriatrics and aging. 2002:5: 14-17.
11. Felson, D. T., Zhang, Y., Hannan, M. T., Kiel, D. P., Wilson, P., & Anderson, J. J. The effect of postmenopausal estrogen therapy on bone density in elderly women. N Engl J Med.1993; 329(16): 1141-1146.
12. Rountree, R. (2014). Roundoc Rx: Natural Approaches to Preventing and Managing Osteoporosis. J Altern Complement Ther. 2014, 20(2), 65-72.
13. Qaseem, A., Snow, V., Shekelle, P., Hopkins, R., Forciea, M. A., & Owens, D. K. Screening for osteoporosis in men: a clinical practice guideline from the American College of Physicians. Ann Intern Med. 2008; 148(9): 680-684.
14. Gambacciani, M., Cappagli, B., Ciaponi, M., Pepe, A., Vacca, F., & Genazzani, A. R. Ultra low-dose hormone replacement therapy and bone protection in postmenopausal women. Maturitas. 2008; 59(1): 2-6.
15. Kling, J. M., Clarke, B. L., & Sandhu, N. P. Osteoporosis prevention, screening, and treatment: a review. J Womens Health. 2014; 23(7): 563-572.
16. Brunader, R., & Shelton, D. K. Radiologic bone assessment in the evaluation of osteoporosis. Am Fam Phys. 2002; 65(7): 1357-1366.
17. Giannoudis, P. V., & Schneider, E. Principles of fixation of osteoporotic fractures. Bone Joint J. 2006; 88(10): 1272-1278.
18. Hollevoet, N., Verdonk, R., Kaufman, J. M., & Goemaere, S. Osteoporotic fracture treatment. Acta Orthop Belg. 2011; 7(4): 441-7.
19. Cheung, W. H., Miclau, T., Chow, S. K. H., Yang, F. F., & Alt, V. Fracture healing in osteoporotic bone. Injury. 2016; 47: S21-S26.
20. Haasters, F., Docheva, D., Gassner, C., Popov, C., Böcker, W., Mutschler, W. et al. Mesenchymal stem cells from osteoporotic patients reveal reduced migration and invasion upon stimulation with BMP-2 or BMP-7. Biochem Biophys Res Commun. 2014; 452(1): 118-123.
21. Sterck, J. G., Klein-Nulend, J., Lips, P., & Burger, E. H. Response of normal and osteoporotic human bone cells to mechanical stress in vitro. Am J Physiol Endocrinol Metab.1998; 274(6): E1113-E1120.
22. Burge, R., Dawson-Hughes, B., Solomon, D. H., Wong, J. B., King, A., & Tosteson, A. Incidence and economic burden of osteoporosis-related fractures in the United States, 2005–2025. J Bone Miner Res. 2007; 22(3): 465-475.
23. Novack, D. V. Estrogen and bone: osteoclasts take center stage. Cell metab. 2007; 6(4): 254-256.
24. What Is Estrogen & What Does It Do? Hormone Health Network. http://www.hormone.org/diseases-and-conditions/womens-health/what-is-estrogen. Accessed May 6, 2017.
25. Riggs, B. L., Khosla, S., & Melton III, L. J. Sex steroids and the construction and conservation of the adult skeleton. Endocr Rev. 2002; 23(3): 279-302.
26. Turner, R. T., Riggs, B. L., & Spelsberg, T. C. (1994). Skeletal effects of estrogen. Endocr Rev. 1994; 15(3): 275-300.
27. Jeyakumar, M., Carlson, K. E., Gunther, J. R., & Katzenellenbogen, J. A. Exploration of dimensions of estrogen potency parsing ligand binding and coactivator binding affinities. J Biol Chem. 2011; 286(15): 12971-12982.
28. Khosla, S., Oursler, M. J., & Monroe, D. G. Estrogen and the skeleton. Trends Endocrinol Metab. 2012; 23(11): 576-581.
29. Kim, H. J., Oh, Y. K., Lee, J. S., Lee, D. Y., Choi, D., & Yoon, B. K. Effect of transdermal estrogen therapy on bone mineral density in postmenopausal korean women. J Menopausal Med. 2014; 20(3):111-117.
30. Kim, J., Shin, J. Y., Lee, J., Song, H. J., Choi, N. K., & Park, B. J. Comparison of the prescribing pattern of bisphosphonate and raloxifene in Korean women with osteoporosis: from a national health insurance claims database. PloS one. 2015;10(6): e0127970.
31. Boyce, B. F., & Xing, L. Functions of RANKL/RANK/OPG in bone modeling and remodeling. Arch Biochem Biophys. 2008; 473(2):139-146.

32. Oursler, M. J. (2003). Direct and indirect effects of estrogen on osteoclasts. J MUSCULOSKELET AND NEURONAL INTERACT; 3(4): 363-366.

33. Weitzmann, M. N., & Pacifici, R. Estrogen deficiency and bone loss: an inflammatory tale. The J Clin Invest. 2006; 116(5): 1186-1194.

34. Manolagas, S. C., O'brien, C. A., & Almeida, M. The role of estrogen and androgen receptors in bone health and disease. Nat Rev Endocrinol. 2013; 9(12): 699-712.

35. Krum, S. A., Miranda-Carboni, G. A., Hauschka, P. V., Carroll, J. S., Lane, T. F., Freedman, L. P., & Brown, M. Estrogen protects bone by inducing Fas ligand in osteoblasts to regulate osteoclast survival. The EMBO J. 2008; 27(3): 535-545.

36. Heldring, N., Pike, A., Andersson, S., Matthews, J., Cheng, G., Hartman, J., ... & Gustafsson, J. Å. Estrogen receptors: how do they signal and what are their targets. Physiol Rev. 2007; 87(3): 905-931.

37. Ruggiero, R. J., & Likis, F. E. Estrogen: physiology, pharmacology, and formulations for replacement therapy. J Midwifery Women's Health. 2002; 47(3):130-138.

38. Ohlsson, C., & Vandenput, L. The role of estrogens for male bone health. Eur J Endocrinol. 2009; 160(6): 883-889.

39. Kuhl, H. Pharmacology of estrogens and progestogens: influence of different routes of administration. Climacteric. 2005; 8(sup1): 3-63.

40. Armstrong, V. J., Muzylak, M., Sunters, A., Zaman, G., Saxon, L. K., Price, J. S., & Lanyon, L. E. (2007). Wnt/β-catenin signaling is a component of osteoblastic bone cell early responses to load-bearing and requires estrogen receptor α. J Biol Chem, 282(28), 20715-20727

41. Almeida, M., Iyer, S., Martin-Millan, M., Bartell, S. M., Han, L., Ambrogini, E. et al. Estrogen receptor-α signaling in osteoblast progenitors stimulates cortical bone accrual. J Clin Invest, 2013; 123(1): 394-404.

42. Kuhl, H. Pharmacology of estrogens and gestagens. Menopause–andropause: hormone replacement therapy through the ages. New cognition and therapy concepts. Krause & Pachernegg, Glabitz. 2001; 33-50.

43. Zhu, B. T., & Conney, A. H. Functional role of estrogen metabolism in target cells: review and perspectives. Carcinogenesis. 1998; 19(1): 1-27.

44. Gambacciani, M., & Levancini, M. Hormone replacement therapy and the prevention of postmenopausal osteoporosis. Prz Menopauzalny. 2014; 13(4): 213-20.

45. Giske, L. E., Hall, G., Rud, T., & Landgren, B. M. The Effect of 17β-Estradiol at Doses of 0.5, 1 and 2 mg Compared with Placebo on Early Postmenopausal Bone Loss in Hysterectomized Women. Osteoporosis international. 2002; 13(4): 309-316.

46. Delmas, P. D., Confavreux, E., Garnero, P., Fardellone, P., de Vernejoul, M. C., Cormier, C. et al. A combination of low doses of 17β-estradiol and norethisterone acetate prevents bone loss and normalizes bone turnover in postmenopausal women. Osteoporosis Int. 2002;11(2): 177-187.

47. Stephenson, J. FDA orders estrogen safety warnings. Jama. 2003; 289(5): 537-538.

48. Stute, P., Becker, H. G., Bitzer, J., Chatsiproios, D., Luzuy, F., von Wolff, M. et al. Ultra-low dose–new approaches in menopausal hormone therapy. Climacteric. 2015; 18(2): 182-186.

49. L'Hermite, M. HRT optimization, using transdermal estradiol plus micronized progesterone, a safer HRT. Climacteric. 2013; 16(sup1): 44-53.

50. iu, J., & Minkin, M. Advances in transdermal estrogen-only therapy for vasomotor symptoms. Clin. Rev. 2013

51. Shulman, L. P. Transdermal hormone therapy and bone health. Clin Interv Aging. 2008; 3(1): 51.

52. Shulman, L. P. The menopausal transition: how does route of delivery affect the risk/benefit ratio of hormone therapy?. J Fam Pract. 2004; 53(7): SS13-SS13.

53. Publications HH. What are bioidentical hormones? Harvard Health. http://www.health.harvard.edu/womens-health/what-are-bioidentical-hormones. Accessed May 4, 2017.

54. Velentzis, L. S., Banks, E., Sitas, F., Salagame, U., Tan, E. H., & Canfell, K. Use of Menopausal Hormone Therapy and Bioidentical Hormone Therapy in Australian Women 50 to 69 Years of Age: Results from a National, Cross-Sectional Study. PloS one. 2016; 11(3): e0146494.

55. Files, J. A., Ko, M. G., & Pruthi, S. (2011, July). Bioidentical hormone therapy. In Mayo Clinic Proceedings (Vol. 86, No. 7, pp. 673-680). Elsevier.

56. Cirigliano, M. Bioidentical hormone therapy: a review of the evidence. J Womens Health. 2007; 16(5): 600-631.

57. Ruiz, A. D., Daniels, K. R., Barner, J. C., Carson, J. J., & Frei, C. R. Effectiveness of compounded bioidentical hormone replacement therapy: an observational cohort study. BMC womens health. 2011; 11(1): 27.

58. Dane, C., Dane, B., Cetin, A., & Erginbas, M. Comparison of the effects of raloxifene and low-dose hormone replacement therapy on bone mineral density and bone turnover in the treatment of postmenopausal osteoporosis. Gynecol Endocrinol. 2007; 23(7): 398-403.

59. Cranney, A., & Adachi, J. D. Benefit-risk assessment of raloxifene in postmenopausal osteoporosis. Drug Safety. 2005; 28(8): 721-730.

60. Scott, J. A., Da Camara, C. C., & Early, J. E. Raloxifene: a selective estrogen receptor modulator. Am Fam Phys. 1999; 60(4): 1131-1139.

61. Rey, J. R. C., Cervino, E. V., Rentero, M. L., Crespo, E. C., Álvaro, A. O., & Casillas, M. Raloxifene: mechanism of action, effects on bone tissue, and applicability in clinical traumatology practice. The open orthop J. 2009; 3(1).

62. Gluck, O., & Maricic, M. Skeletal and nonskeletal effects of raloxifene. Cur Osteoporos Rep. 2003; 1(3): 123-128.

63. Camacho, PM., Binkely N., Harris, ST., Kleerekoper, M., Miller, PD., Pollock, RP., Wimalawansa, SJ., & Watts, N. American Association of Clinical Endocrinologists and American College of Endocrinology Clinical practice guidelines for the diagnosis and treatment of postmenopausal osteoporosis. AACE/ACE Guidelines. 2016:22:1-42.