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Postmenopausal Osteoporosis: A Primary Women Health Concern

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Abstract: Osteoporosis is the chronic condition of bone associated with decreased bone density, quality of bones and increased risks of fractures. Postmenopausal osteoporosis deals with increased bone resorption that results in loss of bone and fragility over 45 years of women. One of the leading causes of postmenopausal osteoporosis is the reduction of estrogen production in the ovaries of females. Lack of estrogen triggers several bone turnover pathways that result in osteoporosis. The drop of estrogen in the postmenopausal transition period, causes more bone resorption as compared to bone formation resulting in postmenopausal osteoporosis. Osteoporotic fractures is the major threat to the health of the women due to postmenopausal osteoporosis and hormone therapy is considered the first line therapy against this disease. To date, several pharmacological and non-pharmacological approaches have been designed to treat postmenopausal osteoporosis. Bone turnover markers help in the monitoring of osteoporosis treatment and in the assessment of fracture risk. Besides these conventional therapies, novel and advanced strategies have been constructed for the treatment of osteoporosis. Probiotics Choice and Ovarian Follicular Pool have opened a new avenue to treat osteoporosis. This review shed light on the biochemical perspective of postmenopausal osteoporosis, novel methods for its treatment, and management therapies to treat postmenopausal osteoporosis.

Keywords: Postmenopausal Osteoporosis, Estrogen, Bone Turnover Markers, Probiotics, Ovarian Follicular Pool

1. Introduction

Osteoporosis is a diseased condition in which bone strength decreases led to an increased risk of fractures. It is a major global health concern especially for women; it is considered a 'silent' disease because bone loss silently occurs. It is reported that one in three women have osteoporosis worldwide. Fractures that are related to osteoporosis basically associated with pain, disability, and increased risk of mortality and morbidity in women. Studies reported different causes of osteoporosis i.e. calcium deficiency, vitamin D deficiency, and postmenopausal. Postmenopausal women are at high risk for developing osteoporosis. [1]

The maximum defeat of bone mass arises in women through perimenopause and relates to estrogen deficiency, a situation of menopause. The mutual effects of estrogen deficiency and elevate FSH creation cause a clear inspiration of bone resorption and a stage of increased bone loss which triggers postmenopausal osteoporosis [2]. All these processes are under the bone turnover markers. The level of growth hormones also decreases with age along with the decrease in bone formation level. As a result, an increase in the bone resorption process and causes osteoporosis.

For the treatment of osteoporosis different novel methods have been proposed by researchers. One of the novel methods is the use of Probiotics. The living microbes such as lactobacillus, gut microbiota, and several bacterial strains have been used for this purpose. Probiotics have been proved very effective and cheap method for the treatment of osteoporosis [3]. Another method Ovarian Follicular Pool advances to postpone menopause. In which cryopreserving ovarian tissue at an earlier age of a girl is done that results in the increase of natural menopause duration. This also results in enhanced fertility and prevent osteoporosis. [4]

The risk of postmenopausal osteoporosis can also be reduced with different strategies by using several pharmacological and non-pharmacological therapies. All these strategies are used to combat post-menopausal osteoporosis. [5]

2. Main Body

Studies reported different biochemical causes of osteoporosis in women. Estrogen deficiency, abnormalities in Parathyroid hormone secretion, and Bone resorption related to PTH are some of the highlighted causes of osteoporosis in women.

2.1. Estrogen Deficiency

Women are at high risk for developing osteoporosis, especially after menopause. It is just because of a reduced level of estrogen (female hormone). Osteoporosis begins after menopause due to loss of estrogen. [6] Estrogen deficiency increases the sensitivity of bone to the parathyroid hormone released by the parathyroid gland in a result, calcium loss continuously occurs from bone and less absorption occurs from the intestines due to PTH, and this calcium ultimately released in the urine. Due to this process of bone turnover increases and bone remodeling decreases. [7]

2.2. Secondary Hyperparathyroidism

Besides estrogen deficiency, less renal function and less intestinal function due to aging are major contributors to the cause of secondary hyperparathyroidism and ultimately osteoporosis in women. With aging, less calcium is conserved by the kidneys, less absorbed by the intestines that led to the cause of low blood calcium levels [8]. This low calcium level would release the parathyroid for a longer time as a result parathyroid hormone becomes hyperactive and cause progressively the process of bone resorption that causes the loss of bone strength and density and women become affected with osteoporosis [9].

2.3. Bone Resorption in Postmenopausal Women

At menopause, the process of bone resorption increases while the process of bone formation decreases. This bone resorption process is age-associated in postmenopausal women that linked with the decreased production of growth hormones and factors, like insulin-like growth factors, transforming growth factor-β by osteoblastic cells. The decreased level of these paracrine growth factors diminishes the process of bone formation. At this stage, bone resorption is more prevalent that causes the loss of calcium level and ultimately osteoporosis. (Figure 1) [10].
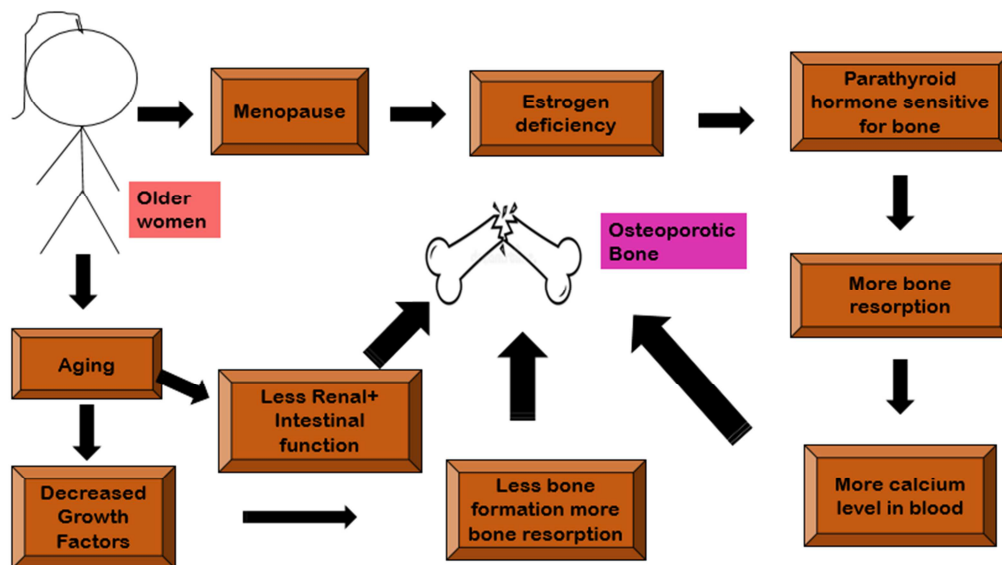

Figure 1. *Demonstration of Osteoporosis in Women linked with various factors.*

2.4. Bone Turnover Markers

Bone turnover markers (BTMs) are proteins/fragments creating from osteoblast or osteoclast activity or produced during the synthesis or degradation of the collagen of type-I (CTX). These peptides may be larger or smaller, large ones can be detected by blood test and the smaller ones can be filtered into the urine. These markers can be used for the calculation of the bone turnover rate. But these markers cannot be taken for diagnosis and screening of diseases, affected by different kinds of pathological and physiological factors. Bone turnover markers (BTM) also used to predict the risk of fracture, and changes induced by treatment in specific markers used for the reduction of fracture risk. [11]

Markers of bone turnover (BTMs) are commonly classified as markers of formation and resorption. Formation markers can be enzymes of osteoblastic or the breakdown products e.g. procollagen-type 1- amino-propeptide (P1NP) marker is more specific for the synthesis of bone collagen as compared to carboxy- propeptide. Markers of enzymes are less precise, stable and discontinued. [12] Osteocalcin provides more information about the use of CTX and P1NP.

It is an abundant non-collagenous matrix protein in bone produced by osteoblasts. Some of the OC fragments are tested in urine and shown the degradation of bone matrix. Therefore, OC represents the degree of bone resorption. Resorption markers may be osteoclastic enzymes or products of collagen degradation e.g. carboxy- telopeptide which are crosslinks of type I collagen (CTX) and peptidyl bound and released into the circulation. [13]

2.5. Bone Formation Markers

Bone formation markers like matrix components of osteoid and type I collagen are products of osteoblasts and their activity. Bone formation markers can be measured in the serum blood and show different steps of bone formation, but they all are not definite to osteoblasts.

2.5.1. Propeptides of Type I Procollagen
During the formation of bone, osteoid is produced. Almost 90% of the osteoid consists of type I collagen, which is shown by osteoblasts. The synthesis of type I collagen needs cleavage of the propeptides of type I procollagen-terminal (PINP) and C-terminal (PICP) then these are released into the blood circulation and can be calculated as bone formation markers. [12, 14]

2.5.2. Alkaline Phosphatase
The serum alkaline phosphatase contains many isoforms. But alkaline phosphatase specified for bone is formed in osteoblasts and shows the activity of osteoblast during the bone formation. This alkaline phosphatase of bone is not commonly measured due to less cost-effectiveness and its concentration is specifically associated with the risk of bone fracture irrespective of the density of bone mineral in postmenopausal females.

2.5.3. Osteocalcin
Osteocalcin is a protein formed by osteoblasts and binds within the bone matrix to hydroxyapatite. Its main function is to regulate bone remodeling via a negative feedback mechanism. Osteocalcin becomes unstable after its collection due to its testing is not broadly offered. However, a low level of osteocalcin has been related to the high risk of bone fractures.

2.6. Bone Resorption Markers

Markers of resorption are the degradation products of type I collagen and it demonstrates the rate of breakdown of bone matrix and the active osteoclasts number. Other markers are the non-collagenous proteins which are linked with the activity of osteoclast.

2.6.1. Pyridinoline and Deoxypyridinoline Cross-links
Pyridinoline and deoxypyridinoline are known as cyclic amino groups having small structures of the linking collagen peptide chains. In the process of resorption, these molecules are released in the blood circulation and detected in urine in bounded form. This concentration shows the degradation rate of collagen. Concentrations of collagen crosslinks are precisely measured in urine by the high-performance liquid chromatography; 6–9 and free deoxypyridinoline calculated by ELISA.

2.6.2. Telopeptides
During bone resorption, the N- and C-terminals of collagen can be detected in the blood circulation. However, N-terminal telopeptide expressed in serum, but C-terminal telopeptide serum concentrations of mature collagen are more valuable in measuring the degree of progress in bone resorption and osteoporosis in multiple myeloma. High concentration reflects the high risk of fractures which is independent of the bone mineral density. The measurement may also be helpful in monitoring the response to antiresorptive drugs e.g. bisphosphonates. Moreover, testing of early morning fasting of the blood sample is suggested. [15]

Bone turnover markers are formed during normal bone turnover but their concentrations may increase during metabolic bone diseases (e.g. osteoporosis), during physiological processes like growth spurts and fracture healing. These Bone turnover markers are not specific to any disease. Therefore, cannot be used for diagnosis and screening of specific bone diseases but their patterns and concentrations can be used by specialist units for monitoring of the disease progression and treatment response in the disease of metabolic bone-like postmenopausal osteoporosis. Many factors affect the concentration of bone turnover markers in urine and blood such as sex, age, menstrual cycle, fasting or non-fasting, exercise history, circadian rhythms, and medical history. The interpretation can be optimized by taking more careful specimen collection and clinical history under the standard conditions.

Currently, two markers are used in clinical practice e.g. amino-terminal propeptide of type I collagen and serum C-terminal telopeptide. These specific markers show the formation and resorption rates. But, other markers such as parathyroid hormone, alkaline phosphatase, and 25-hydroxyvitamin D could be used but they have limited clinical use. They do not reflect the fracture risk and not valid for the screening tests in common clinical practice. [13]

There are some Limitations of BTWs as they show the bone turnover but they do not reflect the reason and cannot replace the process of imaging for diagnosis. The lack of broader utility of BTMs may be qualified to earlier analytical faults and less appreciation of the issues of pre-analytical.

2.7. Probiotics Choice to Treat Osteoporosis

Currently, the probiotics as a promoter of health proved as an innovative method for the treatment of several inflammatory disorders like bone health. Probiotics are defined as the living microbes feed extras that administered in suitable quantities give many health benefits to the organism which is the host [16].

Various strains of Lactobacillus had been reported having the therapeutic effect in experimental models of inflammatory bowel disease, atopic dermatitis, rheumatoid

arthritis (RA). Several species of Lactobacillus like L. salivarius Ls-33 and L. acidophilus-NCFM entirely protected SCID mice from colitis. Various strains of Lactobacillus are used as efficient therapeutics for treating many diseases such as osteoporosis, as the use of some probiotics reduces bone loss which commonly follows ovariectomy [17]. This method can be very priceless for inhibition of more bone joint devastation in patients having the inflammation. Where bone loss could not be prohibited by well-known older methods. The procedure of probiotics on bone health had been an important topic of study in the last few years, unexpectedly some studies have completely divided this nexus. However, the clinical method of ordering probiotics may be an innovative method for the treatment of bone loss in the disorder of osteoporosis from the modulated immunity of the host [18]. This method of probiotics encouraged the reduction of inflammation, thus can prove a cheap and effective alternative for the future therapeutics of this field [16].

Recently, the use of gut microbiota (GM) for health and disorders has been extensively studied. The GM consist of trillions of bacteria, which comprise more 150- fold genes than the human genome. It is developed at birth and, though a different thing, it has evidently co-evolved with the human genome. [17]. The structure of the GM is moderated by several effective factors such as environmental factors, antibiotics, s, and diet [19]. The agitated microbial structure has been assumed to be tangled in a variety of inflammatory circumstances, internal and external the gut [20]. An experiment showed that the absence of GM in mice is related to the decrease of bone resorption and transformed immune status in the bone. Colonization of GF (germ-free) mice with a usual gut microbiota directed to regulation of bone mass and the immune system in bone marrow [21]. An important part of the GM in bone mass is maintained by antibiotic treatment sub-therapeutically in primary life induce bone mass in young mice [22].

Probiotics bacteria act by varying the arrangement or the metabolic action of the GM [23]. The recommended causal mechanisms for the probiotic's contribution to health are various such as more solubility, enhanced barrier function, absorption of minerals, and variation of immune status. Consequently, Ovx in mice is related to the boneless, transformed immune status which resembles postmenopausal osteoporosis. [24]

The probiotic strains of the bacteria used, L. paracasei DSM13434 (L. para) or a combination of three different strains like L. paracasei DSM13434, L. Plantarum DSM 15312, and DSM 15313 denoted as L. mix. Their selection was based on the anti-inflammatory nature. Treatment with this L. para or the L. mix stops ovx-induced cortical bone loss and signpost that these probiotic treatments modify the immune position in the bone as verified by decreased expression of inflammatory cytokines and increased expression of Osteoprotegerin (OPG), resulting in reduced bone resorption in ovx mice. This experiment results in the therapeutic potential of probiotics in the treatment of postmenopausal osteoporosis. [25]

2.8. Ovarian Follicular Pool to Treat Osteoporosis

At present countless women leading to increase menopause-related diseases like cardiovascular disease, osteoporosis, and lack of well-being. Hence financial and medical burden increases for treating menopause-related conditions by increasing life expectancy. Mainly menopausal effect tackled by means of hormone replacement therapy (HRT). It only postponed the menopausal for a short period of time and for a longer period new strategies developed [26]. Now in new strategies freezing ovarian tissue allow menopause to postpone. For this ovarian tissue firstly cryopreserve then transplant for purpose of providing continued menstrual cycle. The method used for preservation developed from the last two decades ago and may be used for menopause postponing [27].

Ovaries of new girls have almost one million eggs in their resting follicles and only one will be chosen for new offspring. From stage of puberty to menopause a woman will ovulate 450 times while all other follicles go through degeneration. Moreover, woman with one ovary remains as fertile as with two ovaries [28]. Mainly, a woman, has one ovary enter menopause earlier as compare to a woman who has two ovaries. It is found that cryopreservation keeps follicles that maintain the menstrual cycle upon transplantation [29]. Present experience shows that tissues remain active for a long period of time. In the experiment, four patients had their first tissue transplantation. The first patient keeps ovarian activity after the first transplant almost for 11 years. The second patient maintains activity after having 55% of ovary transplantation for almost 7 years. The third patient has an activity for 6 years with all transplanted tissues. And the last patient has 62% of one ovary transplanted show almost regular menstrual cycle. Till the tissues remain active and patients also have the ability to undergo one additional transplantation [30].

It is shown that tissues in these patients transplanted for purpose of providing fertility that needs a large follicular pool as compared to the menstrual cycle alone. So that if the aim was to postpone menopause then the longevity of tissue is required. In the case of normal females, it has been observing that the number of resting follicles decreases towards menopause although maintain the capacity of pre-ovulatory follicles so that overall the degeneration of the overall follicular reduced. Moreover, ovarian tissue from one ovary separated into pieces then grafting these pieces that expand the sex steroid period. Then ovarian tissues start to work by means of local anesthesia in the body. In this way, fertility provided and senior females prevented pregnancy [31]. In conclusion, a new method develops to postpone menopause. By means of cryopreserving ovarian tissue at a younger age then the time to natural menopause becomes prolonged. The advantages of cryopreserving consist of providing a concentration of sex steroids for a long period of time that does not reduce fertility. Hence the chief goal of cryopreservation is the preservation of fertility, frozen

ovarian tissue transplantation that may serve to prevent legacy of the osteoporosis in the aging population.

2.9. Management of Postmenopausal Osteoporosis by Pharmacological and Non-pharmacological Strategies

Including in management of postmenopausal osteoporosis pharmacological and non-pharmacological interventions suggested that depend on the lead of risk measurement. If there is a low risk of disease then providing better lifestyle advice and ensure the intake of vitamin D 800IU and calcium of 1200mg. In addition to lifestyle, advice medication may be considered. After considering any therapy first thing that is most important is that it must discuss with the patient to reduce the further risk [32].

In case of high risk, there must be the addition of pharmacological treatment. In this type of risk, the patients that have hip and other fragility fractures are included. [33].

2.9.1. Pharmacological Strategy

Pharmacological therapy is suggested if the post-menopausal female has vertebral or hip fractures and has the BMD values equal to or worse than -2.5 at the femoral neck, lumbar spine, or the hip region. These females have a greater risk of developing spine, shoulder, wrist, and hip fractures. These interventions prevent bone resorption and form new bone formation [33]. Several FDA approved drugs are available to hit osteoporosis (Table 1) [28].

Table 1. *Drugs used in the treatment of postmenopausal osteoporosis.*

Drugs Name	Post-menopausal female follow
Alendronate oral	Prevent hip, vertebral and non-vertebral fractures.
Raloxifene oral (Evista)	Reduce vertebral fractures.
Denosumab SC	Prevent hip and nonvertebral fractures.
HRT	Reduces vertebral, hip and non-vertebral fractures.
Zolendroni acid IV (Reclast)	Prevent vertebral and non-vertebral fractures.

2.9.2. Non-Pharmacological Strategy

The non-pharmacological approach based on calcium and vitamin-D supplements. Studies suggested that for women there at least a daily intake of 1,200 mg of calcium affected with osteoporosis. [34] The NOF recommends 800 to 1,000 IU of vitamin D daily for individuals 50 years and older. In the management of post-menopausal osteoporosis the following pharmacological interventions are involved (Table 2).

Table 2. *Supplements based non-pharmacological treatment for Postmenopausal osteoporosis.*

Non-Pharmacological management	
Calcium	Daily 1200mg is recommended.
Vitamin D	800IU per day of vitamin D3.
Protein	1kg per day is recommended.
Exercise	Regular exercise of weight bearing and muscle strengthening.
Alcohol	Intake of 3 or more units per day.

3. Conclusion

Osteoporosis is one of the primary women's health concerns globally, it is associated with an increased risk of disability, morbidity, pain, and mortality due to several biochemical changes observed after menopause. With the advancement in the field of science, scientists currently proposed novel approaches to treat postmenopausal osteoporosis. Probiotics and Ovarian follicular pool are some of the novel methods for the treatment of osteoporosis. Different non-pharmacological strategies have also been strongly recommended. All these measurements reduced the risk level of the disease.

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