A study of the role of calcium and oxidative stress in pathophysiology of osteoporosis in postmenopausal women-a review

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Abstract

The aim of this review was to identify the role of calcium and oxidative stress as factors associated with osteoporosis in postmenopausal women. There are many diseases related to post-menstruation in women, the most important of which is osteoporosis. Calcium levels remains stable until menopause, when the bone resorption rate increases in association with the decrease in ovarian estrogen production that effect the intestinal calcium absorption. On the other hand, studies support that oxidative stress is directly involved in the genesis and development of osteoporosis. However, Oxidative stress blocks the activation of osteoblasts and activates the differentiation of osteoclasts which led to increased resorption rate without adequate and proper bone formation. In conclusion, Physiological changes in postmenopausal women lead to fluctuations in calcium metabolism and oxidative stress, which may lead to the occurrence or development of osteoporosis.

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Keywords: Osteoporosis; Calcium; Oxidative stress; Menopause.

1. Introduction

Menopause (as defined by the World Health Organization) is the permanent cessation of menstruation due to loss of ovarian follicular activity (World Health Organization, 1981). And as the last menstrual period followed by at least twelve months of amenorrhea (no menstrual bleeding) (Shailendra, 2011). Usually occurs between the ages of 45 and 55 years (Southern, 2019). Menopause was an important selective trait in human evolution, as women who became infertile many years before death would be better able to care for existing children (Takahashi et al., 2017). In the other hand, calcium is an essential element; therefore, the bioavailability in the organism is generally insured by the food stuff (Kass-Wolff, 2004). Calcium status depends on the state of calcium metabolism, which is regulated by mechanisms including hormonal homeostasis, intestinal absorption, renal reabsorption and bone turnover. The hormonal part of regulation mechanism is based on parathyroid hormone (PTH), dihydroxyvitamin D, ionized calcium itself, and their corresponding receptors in the gut, kidney and bone (Derouiche and Kechrid, 2018). Calcium levels remains stable until menopause, when the bone resorption rate increases in association with the decrease in ovarian estrogen production that effect the intestinal calcium absorption (North American Menopause Society, 2006). Osteoporosis is a disease that is characterized by low bone mass, deterioration of bone tissue, and disruption of bone microarchitecture: it can lead to compromised bone strength and an increase in the risk of fractures (Zerzour et al., 2020). Osteoporosis, a multifactorial systemic skeletal disease, is characterized by low bone mineral density (BMD) and micro-architectural deterioration of bone tissue resulting in bone fragility. osteoporosis is the most prevalent disease in menopausal women, and is strongly associated with low quality of life (Ji and Yu, 2015). Many of recent landmarks in scientific research have shown that in human beings, Oxidative stress is an important factor causing

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metabolic and physiological alterations and various diseases in the body (Kaouachi and Derouiche, 2018), it is as a consequence of increase a reactive oxygen species and decrease in antioxidant defenses in prevalent in many health problems (Derouiche et al., 2019). In light of these data, the aim of this review was to identify the role of calcium and oxidative stress as factors associated with osteoporosis in postmenopausal women.

2. Calcium and Risk factors of Osteoporosis

In 2001, the National Institutes of Health has defined osteoporosis as "a skeletal disorder characterized by compromised bone strength predisposing a person to an increased risk of fracture (Gullberg et al., 1997). Osteoporosis is generally a disease of older adults because the cumulative effects of slow bone mineral loss take time to deplete the skeleton (Power et al., 2000). Physical activity/inactivity show good evidence that, among both women and men, physical inactivity is a risk factor for osteoporosis as well as for fractures (Cummings, 1955). Previous fractures are a major risk factor for new fractures (Kanis, 2004) And low weight is a higher risk for both osteoporosis and fractures (Brot et al., 1977). Also smoking decreases bone density and increases the risk of fractures (Forsen, 1994). And low exposure to sunlight leads to poor uptake of vitamin D (Johnell and Hertzman, 2006). Treatments with cortisone reduce bone density and increase the risk of fractures (Espallargues, 2001). Calcium is essential in maintaining total body health (Derouiche and Kechrid, 2013). When blood Ca levels drop too low, it is borrowed from the bones and returned to the bones from Ca supplied through the diet (Pravina et al., 2013). Thus, the effects of calcium deficiency may escape notice for a considerable time, until they manifest as skeletal weakness or fractures (Fischer et al., 2018). In fact, low dietary calcium intake is associated with low bone density, and calcium deficiency cause age-related bone loss, therefore, osteoporosis (Kim, 2014).

3. Pathophysiology of Osteoporosis

Once the peak bone mass is achieved, bone regulation takes place by local remodeling which is regulated by RANK (or receptor activator of nuclear factor-kb), RANKL (RANK Ligand) and OPG (Osteoprotegerin) (Kearns et al., 2008). RANK is present in the osteoclasts and causes the increase in their activity. RANKL is synthetized by osteoblasts and it binds with the RANK receptor on the osteoclasts. OPG is also synthetized by the osteoblasts and prevents the binding of the RANK to the RANK Ligand by itself binding to the RANKL (Wu et al., 2020). Hence, the activity of the osteoclasts and in turn the bone remodeling depends upon the interplay between the RANK and the OPG. This interplay is controlled by hormonal and local factors (Vikram et al., 2017). Imbalance in bone remodeling lead to decreased skeletal mass. In most individuals, bone mass peaks in the third decade, after which bone resorption exceeds bone formation. Failure to reach a normal peak bone mass or acceleration of bone loss can lead to osteoporosis (Varacallo and Fox, 2014).

4. Osteoporosis in menopausal women

A decline in estrogen has been shown to play a major role in the decreasing bone mass during the menopause, especially because it has a variety of protective effects on bone marrow and bone cells (Manolagas et al., 2013). This hormone allows for increased bone formation by reducing the production and function of the osteoclasts as well as increasing osteoclast apoptosis (Jilka et al., 1999). This effect on the osteoclastic cells of the bone is facilitated via estrogen's inhibition of a signaling molecule, RANKL, which is involved in osteoclast differentiation and survival. However, due to the estrogen deficiency during menopause, this beneficial effect on the bone is lost causing osteoporosis (Doshi and Agarwal 2013). Also, menopause has been linked to an increase in inflammatory cytokines within the serum specifically tumor necrosis factor (TNF- α), which negatively impacts the bone by contributing to increased osteoclast formation. Additionally, the high levels of FSH during menopause stimulate osteoclast differentiation and TNF- α production, both of which play an important role in osteoporotic bone loss (Graziana et al., 2013).



Fig. 1. A model of the effects of estrogen deficiency on bone loss, prostaglandin E2 and Osteoprotegerin (Wolfgang et al., 2009)

5. Oxidative stress and osteoporosis

Oxidative stress is defined as an imbalance in the balance between antioxidants and pro-oxidants in favor of antioxidants (Derouiche et al., 2017; Boulaares et al., 2020). The overproduction of free radicals can cause oxidative damage to biomolecules (lipids, proteins, DNA), eventually leading to many chronic diseases such as cancer, diabetics, cardiovascular diseases, chronic inflammation, aging and osteoporosis (Derouiche et al., 2018).

5.1. Oxidative stress during menopause

Menopause creates a redox imbalance and subsequent oxidative stress due to the decline of the natural antioxidant hormone estrogen (Sankar et al., 2017). Specifically, at high concentrations, estrogen tends to have a beneficial antioxidant effect by inhibiting the 8-hydroxylation of guanine DNA bases (Doshi and Agarwal, 2013), also by increasing the activities of antioxidant enzymes, such as glutathione peroxidase, and causing an increase in antioxidant vitamin levels (Atoussi et al., 2018; chetehouna et al., 2020). However, an increasing number of studies have recently shown another activity of estrogens as important pro-oxidants at physiological concentrations (Victorino et al., 2013) and changes in the lipid profile and the increase of lipoperoxidation (Montoya-Estrada et al., 2020). Additionally, serum concentrations of inflammatory cytokines and pro-oxidant biomarkers such as glutathione, 4-hydroxynenal, and malonaldehyde were found to be higher in postmenopausal women than in premenopausal women (Agarwal et al., 2005). The elevation of cytokines and pro-oxidant makers suggests that there is a high degree of oxidative stress in the postmenopausal state (Derouiche, 2020).

5.2. Oxidative stress and osteoporosis

Oxidative stress activates the differentiation of osteoclasts which led to a significant increase in the number and activity of these cells. Also, ROS induce the apoptosis of osteoblasts and osteocytes, by activating numerous signaling

pathways (Domazetovic et al., 2017). The oxidative stress blocks the activation of osteoblasts and thus the production of OPG; under this condition, the action of RANKL prevails, and the differentiation and activity of osteoclasts are induced. Thereafter, the turnover of the bone remodeling process increases due to increased resorption rate without adequate and proper bone formation; this event has been related to osteoporosis (Domazetovic et al., 2017). Antioxidants have opposing effects, they contribute to the differentiation of osteoblasts and bone formation, while reduce the osteoclast differentiation and their activity (Agidigbi and Kim, 2019).



Fig. 2. Effect of ROS and antioxidants on the activity of bone cells in bone remodelling (Domazetovic et al., 2017).

Reactive oxygen species (ROS) are free radicals resulting from the metabolism of oxygen (Derouiche et al., 2020) which activate osteoclast differentiation and osteocyte apoptosis (+), while inhibit osteoblast activity (-) inducing bone resorption; antioxidants activate osteoblast differentiation (+) and inhibit osteoclast activity and osteocyte apoptosis (-) inducing bone formation (figure) (Almeida, 2012).

6. Conclusion

Physiological changes in postmenopausal women lead to fluctuations in calcium metabolism and oxidative stress, which may lead to the occurrence or development of osteoporosis. On the other hand, oxidative stress is essential factor in the development and complication of the osteoporosis and therefore it is necessary to take into account the mitigation of these phenomena in any approved treatment program which contributes to the prevention or limitation of disease development.

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