



Antioxidants as a novel way to alleviate the adverse effects of oxidative stress in osteoporosis

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Abstract

Bone is a dynamic organ undergoing remodeling through the coordinated resorption and formation activities between osteoblasts and osteoclasts. Osteoporosis is regarded as degenerative disease that is one of the biggest problems in elderly people. Osteoporosis is a multi-factorial disease. Age-related oxidative stress causes osteoporosis via adversely affecting both osteoblasts and osteoclasts. On the other hands, one of defense mechanisms against reactive oxygen species is antioxidant. Fruits and vegetables are the sources of antioxidants alleviating osteoporosis caused by oxidative stress. Hence, the aim of this review article is to illustrate the favored effects of antioxidants therapy to mitigate osteoporosis caused by oxidative stress.

Keywords: Antioxidants, Oxidative stress, Osteoporosis

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Introduction

Bone tissue is undergoing a process of both renewal and repair called “bone remodeling” (1). The two bone cell types, that are responsible for bone remodeling, are osteoblasts for bone formation and osteoclasts for bone resorption (2). Osteoblasts are differentiated from bone marrow stromal cells (3). On the other hand, osteoclasts are cells of hemopoietic origin differentiating from the precursors in the monocyte lineage (4). When bone cells are damaged or old, osteoclasts removed these bone cells via the secretion of acid or proteolytic enzyme during bone remodeling. After that, osteoclasts migrate away from the bone surface and consequently osteoblasts are replaced (5,6). Bone homeostasis is derived from the coordination of osteoblasts and osteoclasts (5). Hence, osteoporosis is linked to either inappropriate formation of bone or the extreme bone resorption (6). Lerner et al (7) concluded that the increased occurrence of resorption cavities by osteoclasts and the decreased ability of osteoblasts participate in the decrease in bone mass and hence bone strength.

Since osteoporosis is a degenerative disease and is not recognized until it shows fragility structure, so it is important to control or to treat it. On the other hand, osteoporosis is affected by many factors. One of its causes is oxidative stress related to age. Antioxidant systems present in the body prevent oxidative stress, but it seems that system is not effective alone. Thus, the aim of this study is to clarify the effect of antioxidant therapy on alleviation of osteoporosis induced by oxidative stress.

Materials and Methods

While, oxidative stress is one of the causes of aggravation of osteoporosis, hence, the aim of this review article is to determine the effects of antioxidant therapy as a new treatment strategy on the alleviation of osteoporosis. For this review, we used a diversity of sources by searching through PubMed/Medline, Scopus, EMBASE, EBSCO and directory of open access journals (DOAJ). The search was conducted, using combination of the following key words and or their equivalents; antioxidants, free radicals, oxidative stress, free radical scavengers, reactive oxygen species, osteoporosis, osteoblasts, bone remodeling and Nitric oxide

Osteoporosis

Osteoporosis refers as a degenerative disease especially in elderly people as determined by decline in bone mass and density that prone patients to have skeleton fragility and also to increase the risk of fracture (8,9). Osteoporosis is known as the “silent thief”, because there are no marked symptoms until it manifests in the form of fragility fracture (10). Unfortunately, approximately 30% of women over the age of 50 have fragility fracture (11). Moreover the prevalence of hip fractures is estimated nearly 1.6 million each year, notably this outbreak will reach to 4.5 million to 6.3 million by 2050 (11). Notably, it is estimated that approximately \$14 billion is spent each year for treatment of bone fractures (12).

There are two types of osteoporosis known as two

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■ Implication for health policy/practice/research/medical education

Osteoporosis is regarded as degenerative disease that is one of the biggest problems in elderly people. Osteoporosis is a multi-factorial disease. Age-related oxidative stress causes osteoporosis via adversely affecting both osteoblasts and osteoclasts. On the other hands, one of defense mechanisms against reactive oxygen species is antioxidant. Fruits and vegetables are the sources of antioxidants alleviating osteoporosis caused by oxidative stress.

subtypes:

- 1) Type I osteoporosis (primary) that is a bone disorder in postmenopausal women resulting from estrogen deficiency as the consequence of menopause. The primary osteoporosis is occurred because postmenopausal women are exposed the increased rate of bone turnover; consequently, it negatively affects the bone microarchitecture; thus, it is related to the increased risk of osteoporotic fractures (13).
- 2) Type II osteoporosis (secondary) that is mainly attributable to aging either in women or men (6). The secondary osteoporosis is considered to be as the results of many factors including medical conditions, changes in physical activity, and also pharmacological therapeutics (6,7).

The risk factors of osteoporosis

Osteoporosis is referred as a multi-factorial disease. In this regard, two main factors could cause it, categorized as non-modifiable risk factors and modifiable risk factors. The non-modifiable factors are those that cannot be changed such as age, sex, family history and early menopause (14-17). Women are more susceptible to bone loss rather than men as the result of estrogen deficiency; because estrogen participates in bone remodeling resulting in the increased osteoblast activity and bone formation (18). One of the reasons in terms of osteoporosis in elderly women is a decrease in sexual hormone like estrogen contributing to protect bone against reactive oxygen species via functioning as an antioxidant (19,20). The increased bone resorption exerts the important role for bone loss in the acute estrogen deficiency; because there is evident that bone cells including osteoblasts, osteocytes, and osteoclasts express estrogen receptors (21). It is well known that the stimulation of estrogen receptors especially in osteoblasts by estrogen causes their anabolic activities and consequently decreases the pathway that osteoblasts activate osteoclasts activity (7). Notably, estrogen possessing antioxidant property protects women from cardiovascular disease and activates osteoblastic function and hence stimulates bone growth (22).

Later, those are changeable including geographical region and lifestyle like alcohol intake, smoking, exercise or diet (23-26). It has been demonstrated that there is the increased frequency of osteoporosis in people who live in northern countries when compared to those living in southern countries (23,25). Moreover, smoking accelerates the free radical levels responsible for stimulation of

bone resorption (27).

A diet deficient in calcium leads to the increase in synthesis and secretion of parathyroid hormone; consequently, it activates osteoclast activity. So, this elevates bone resorption (26). In this regard, it is recommended that for Canadian women over the age of 50 years to intake 800 to 2000 IU of vitamin D and 1200 mg of calcium daily to prevent the induction of osteoporosis (28,29). Notably, the deficiencies of vitamin K, C and B are classified as modifiable risk factors of osteoporosis especially in elderly people.

The adverse effects of reactive oxygen species on cellular disturbances

Oxidative stress has been considered as an imbalance between the production of reactive oxygen species and antioxidant activity (30). Oxidative stress induces many chronic and degenerative diseases for instance osteoporosis, cancer, Alzheimer disease and Parkinson disease (31-33).

Since there is high concentration of unsaturated fatty acids in cellular membranes, they are very susceptible to oxidation (34) which is known as lipid peroxidation. The lipid peroxidation marker, malondialdehyde, has been served as osteoclast function (35); because osteoclasts produce O_2^- causing the lipid peroxidation.

Reactive oxygen species contribute to protein disorders including damage to specific side-chain, alteration in their tertiary structure and degradation (36,37).

Reactive oxygen species react with DNA and hence, they induce changes in DNA bases, the increase in susceptibility to lose purines and the damage in the deoxyribose sugar. Interestingly, all ROS cannot damage DNA for example OH^- and H_2O_2 (38). Notably, the DNA disturbances derived from reactive oxygen species cause various chronic diseases for instance osteoporosis (39,40).

Oxidative stress and osteoporosis

Reactive oxygen species is considered to be by-products of respiration and oxidase enzyme activity in the mitochondria and also of the cellular response to external stimuli resulting from inflammatory cytokines (6). The two groups of reactive oxygen species are radicals and non-radicals. The radicals have one or more unpaired electrons; so, they donate or obtain another electron to become stable (38). Radical group include nitric oxide, superoxide ion, hydroxyl, peroxy, and alkoxy radicals (41). Non-radical group include hypochlorous acid, hydrogen peroxide, organic peroxides, aldehydes, and ozon (41). Reactive oxygen species adversely affect cell structures including lipids, proteins, DNA and also some enzymes (42).

Nitric oxide synthesized from L-arginine is considered to be associated with the prevalence of osteoporosis especially in postmenopausal women (43); because it is an important molecule in the regulation of bone metabolism (44). Nitric oxide participates in both the function of osteoclasts and the differentiation and proliferation of osteoblasts (43). Its level in blood is linked to estrogen levels during the menstrual cycle (45). It seems that nitric oxide

regulates the effects of estrogen on bone remodeling via restraining osteoclast-mediated bone resorption and activating osteoblasts (46). Nitric oxide exerts the inhibitory effect on osteoclasts via both the inhibition of osteoclast formation and modification of cathepsin K responsible for bone resorption mechanism by degrading bone collagen (47,48). Percival et al (49) and Arai et al (50) reported that oxidative stress induced by hydrogen peroxide inhibits osteoblast differentiation and causes the apoptosis in osteoblastic cells.

Altindag et al (51) reported that oxidative stress caused an increase in osteoclastic activity and a decline in osteoblastic activity. Notably, the increased osteoclastic activity derived in bone disturbances led to the elevated generation of reactive oxygen species that is responsible for higher serum malondialdehyde levels (52). The increased reactive oxygen species has been found to be responsible for the decreased osteoblastogenesis and therefore bone formation (53). Evidence showed that reactive oxygen species activate osteoclasts and increase bone resorption (39). Sontakke and Tare (35) reported that there is association between malondialdehyde and osteoclasts. In this respect, experiments showed that there is correlation between superoxide radical generation and osteoclast-mediated bone resorption (54,55). Similarly, in the study by Garrett et al (56), they found that the generation of superoxide radicals by osteoclasts is linked to their ability to resorb bone; in turn, they increase the formation of osteoclasts. Furthermore, Yang et al (57) and Dreher et al (58) reported that reactive oxygen species contribute to bone resorption via involvement in osteoclast-generated superoxide and bone degradation. Interestingly, exposure to hydrogen peroxide reduced osteoblasts viability (59). Interestingly, osteoblasts produce antioxidant including glutathione peroxidase and exert the key role in depression of bone resorption (58). The generation of reactive oxygen species caused by osteoclasts contributes to hastening disorder in calcified tissue and bone remodeling (60).

The increased reactive oxygen species generation as the form of superoxide is attributable to osteoclastic activity in bone disturbance, as characterized by the high serum malondialdehyde levels (61). Sontakke and Tare (35) reported that an increase in malondialdehyde level and a reduction in glutathione peroxidase activity were obtained in osteoporotic people as compared to healthy controls. Maggio et al (62) also found a decrease in antioxidant capacity in women with osteoporosis. Sendur et al (52) studied serum antioxidant enzymes level in postmenopausal women with osteoporosis. Interestingly, they found that the enzyme activity of glutathione reductase and malondialdehyde concentration was lower and higher in women with osteoporosis rather than non-osteoporotic healthy subjects, respectively. Additionally, Oveisi et al (63) studied the levels of antioxidants in serum in Iranian osteoporotic women. They found that serum levels of vitamin C, catalase were lower in osteoporotic women in comparison with control group, whereas the serum superoxide dismutase and glutathione reductase were higher in osteopo-

rotic group. In addition, Cervellati et al (20) reported that oxidative stress increased serum levels of lipid peroxidation marker and decreased bone mineral density.

Sharma et al (64) reviewed the correlation between oxidative stress and bone mineral density in postmenopausal osteoporotic women. They found that serum glutathione peroxidase, superoxide dismutase and catalase were lower in osteoporotic postmenopausal women rather than control group. However, Wolf et al (65) observed that serum antioxidants level is not associated with bone mineral density.

Antioxidants and anti-osteoporosis activity

One of the main lines of defense against reactive oxygen species is antioxidant (66). The natural antioxidant systems existed in the body could be enzymatic and non-enzymatic including metal chelating proteins and the endogenous antioxidant enzymes including catalase, glutathione peroxidase, and superoxide dismutase (66). Indeed, antioxidant serves as singlet oxygen quenchers, radical scavengers and radical chain suppressors (66,67). These prevent oxidation of cellular components including proteins, lipids and DNA (68). In this respect, Smetana et al (69) showed that oxidative stress induced by superoxide dismutase deficiency decreased bone stiffness and strength. Another antioxidant defense is the dietary antioxidants (57,70). New research has been focused on the supplementation of natural antioxidants including photochemical, carotenoids, flavonoids, vitamins C and E existed in the vegetables and fruits and also herbal medicine (68,71,72). Melhus et al (73) reported that inadequate dietary antioxidant intake accelerates the risk of hip fractures in smokers. Sandukji et al (61) and Shuid et al (74) reported that intake of vitamin E, as the form of α -tocopherol, prevent osteoporosis and assist in healing of bone fracture due to the increased antioxidant enzyme activities, as evidenced by higher α -tocopherol levels in vitamin E treatment rather than control group. Some studies reported that dietary intake of vitamin C is correlated with bone mineral density in postmenopausal osteoporotic women (75,76). Rivas et al (77) found that there is positive correlation between dietary intake of vitamin C and selenium (dietary antioxidants) and bone mineral density. Ascorbic acid has been found to influence markers of osteoblast activity (78). Simon and Hudes (79) showed that dietary intake of ascorbic acid is linked to bone mineral density in premenopausal women. Nevertheless, some early studies reported that there is association between ascorbic acid deficiency and osteoporosis in Black South African men (80,81). Chavan et al (82) studied the effects of dietary intake of 500 mg of vitamin C and 400 mg of vitamin E on osteoporosis induced by oxidative stress. They found that dietary treatments improved antioxidant capacity (as reflected by the increased serum superoxide dismutase activity and glutathione level) and decreased the serum malondialdehyde level in osteoporotic subjects. Moreover, they showed that intake of vitamin C and E improved whole bone status in osteoporosis.

Kono et al (83) and Yan et al (57) found that the active components of fruits of *Prunus mume* resulted in the stimulation of pre-osteoblastic cells differentiation to elevate collagen synthesis and mineralization of osteoblasts. In the study by Mackinnon et al (70) in terms of the effect of lycopene administration on oxidative stress and bone of postmenopausal women, they found that intake of lycopene decreased the oxidative stress markers and bone resorption in women. Similarly, Rao et al (84) studied the effects of lycopene administration on the risk of osteoporosis. They found that intake of lycopene enhances antioxidant capacity and consequently reduced oxidative stress; hence, it decreased the risk of osteoporosis in postmenopausal women.

Moreover, Wang et al (59) reported that curculigoside, a bioactive phenolic component, manifests anti-osteoporosis activity due to the potent antioxidant property. They found that curculigoside supplement significantly decreased the generation of reactive oxygen species and enhanced the antioxidant enzyme activities including superoxide dismutase and glutathione peroxidase in osteoblasts caused by hydrogen peroxide (59). Additionally, Deyhim et al (85) observed that intake of grapefruit juice increased bone mineral deposition and improved bone density, probably via the stimulation of antioxidant enzyme activity.

There is evident that intake of green tea due to its bioactive components mitigates bone loss and therefore the risk of osteoporosis as determined by improving osteoblastic activities and decreasing osteoclastic activities (86,87).

Effendy and Shuid (88) found that oral administration of 100 mg/kg of *Labisia pumila* in ovariectomized rats increased the superoxide dismutase and glutathione peroxidase levels and decreased serum malondialdehyde concentration.

Spilmont et al (89) observed that consumption of pomegranate peel extract prevented the decrease in bone mineral density and bone microarchitecture impairment in ovariectomized mice.

Several studies have been found that flavonoids including genistein and oleuropein inhibit osteoclast differentiation and activate osteoblast formation both in vitro and in vivo (90-93).

Conclusion

Taken together, osteoporosis is one of the growing problems especially in elderly men and women. There are many factors affecting osteoporosis including age, sex, oxidative stress, family history and early menopause, geographical region and also lifestyle. Postmenopausal women always show osteoporosis of hip and vertebral fracture as the result of alterations in osteoblastic and osteoclastic activities. As mentioned above, age-related oxidative stress is one of the causes of osteoporosis in people. Oxidative stress negatively affects osteoblasts activity and viability and also osteoclasts activity. So, researchers have followed to find new alternatives to prevent or control osteoporosis. It seems that antioxidant therapy could ameliorate the

adverse effects of oxidative stress on osteoporosis in particularly in elderly people.

Authors' contribution

EJ prepared the primary draft. First edition done by MK. Final edition done by MRK.

Conflicts of interest

The authors declared no competing interests.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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Since oxidative stress was implicated in pathogenesis of osteoporosis (manifested as deterioration of bone) and antioxidants, such as lycopene and polyphenols have been suggested to benefit the therapy of osteoporosis [17,19,49], we studied the antioxidative potential of the selected DHPs which were 10-fold more effective than uric acid on HOS cells in mild oxidative stress conditions. In recent years, the role of oxidative stress in the pathogenesis of osteoporosis has drawn considerable interests because there is now ample evidence to suggest that ROS-induced oxidative stress is associated with the development of osteoporosis (Baek et al., 2010; Rao & Rao, 2013). Moreover, we outline the effects of antioxidant supplementation on exercise-induced oxidative stress, which have been studied extensively. Finally, the following review briefly summarizes future tasks in the field of redox biology of exercise. In principle, this review covers findings for the whole body, and describes human trials and animal experiments separately. Please select whether you prefer to view the MDPI pages with a view tailored for mobile displays or to view the MDPI pages in the normal scrollable desktop version. This selection will be stored into your cookies and used automatically in next visits. You can also change the view style at any point from the main header when using the pages with your mobile device. Aging, menopause, and osteoporosis are correlated with increased oxidative stress and reduced antioxidant defense mechanisms. We previously demonstrated that oxidative stress induced by a variety of compounds such as xanthine/xanthine oxidase (XXO) and minimally oxidized LDL (MM-LDL) inhibit the osteogenic differentiation of osteoprogenitor cells. We now demonstrate that this osteogenic combination of oxysterols prevents the adverse effects of oxidative stress on differentiation of M2 cells into mature osteoblastic cells. XXO and MM-LDL inhibited the osteogenic differentiation of M2 cells, demonstrated by the inhibition of markers of osteogenic differentiation: alkaline phosphatase activity, osteocalcin expression and mineralization.