Dietary polyphenols and osteoporosis: molecular mechanisms involved

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ABSTRACT

Osteoporosis is related to dysfunction of the crosstalk between osteoblasts and osteoclasts, the cells involved in the formation and resorption of bone, respectively. Oxidative stress and inflammation are involved in the pathogenesis of osteoporosis. Because of their antioxidant and anti-inflammatory properties, natural compounds such as polyphenols extensively present in fruit, vegetables, wine, tea, extra virgin olive oil, and berries, play an important protective role in disorders of bone metabolism, including osteoporosis. A diet rich in polyphenol-rich fruit and vegetables can reduce bone mineral density loss, decreasing the risk of fracture and preserving lifestyle quality. The aim of the present review is to highlight the principal mechanisms involved in the role played by the main dietary polyphenols in the prevention and/or treatment of osteoporosis.

KEYWORDS

Osteoporosis, oxidative stress, dietary polyphenols, bone health.

Introduction

Bone is a dynamic tissue that undergoes continuous remodelling due to the collaborative and highly regulated crosstalk between osteoblasts (bone-forming cells) and osteoclasts (bone-resorbing cells) [1].

Biochemical signalling pathways and various factors, such as hormones and growth factors, are involved in the regulation of the sophisticated mechanism of bone remodelling in which osteocytes, along with osteoblasts and osteoclasts, participate. Osteocytes actively contribute to bone remodelling. Vital osteocytes produce osteogenic factors, while apoptotic osteocytes produce osteoclastogenic factors [2]. Mesenchymal stem cells in bone marrow can differentiate into osteoblasts and osteocytes, whereas osteoclasts derive from the monocyte/macrophage lineage of haematopoietic stem cells. Osteoblasts are involved in bone synthesis and mineralization by producing collagen, osteocalcin, osteopontin, osteonectin and alkaline phosphatase (ALP). In addition, they control osteoclastogenesis by producing the osteoprotegerin (OPG) and the receptor activator of nuclear kappa-B ligand (RANKL), a down-regulator and an up-regulator of osteoclastogenesis, respectively [1]. The binding of RANKL to the receptor activator nuclear factor Kappa-B (RANK), present in osteoclast precursor, triggers differentiation processes mediated by the activation of transcriptional factors, such as nuclear factor Kappa-B (NF-kB) and activator protein-1 (AP-1). On the contrary, the binding of RANKL to the soluble receptor OPG inhibits osteoclastogenesis. The apical membranes of osteoclasts have the ruffled border domain responsible for the secretion of acids and proteases that break down the organic and mineral component of bone leading to its resorption [3].

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Dysregulation of the complex balance between osteoblastogenesis and osteoclastogenesis causes bone disorders, including osteoporosis, which is characterized by an alteration of bone metabolism resulting in a loss of bone mass associated with bone fragility and fracture risk. This impacts quality of life [4]. Osteoporosis is due to excessive activation of osteoclasts associated with defective osteoblast activity and with an increase in osteocyte apoptosis. In women, postmenopausal osteoporosis is caused by hormonal changes involving the loss of estrogens, in addition to aging, inflammation and oxidative stress [5]. In particular, conditions of oxidative stress, which occurs when the excessive production of reactive oxygen species (ROS) is not counterbalanced by the antioxidant systems, contribute to bone loss and osteoporosis, given that redox signalling is involved in bone remodelling and repair [6,7]. The association between oxidative stress and osteoporosis is demonstrated by the evident changes in oxidative stress markers in the plasma of osteoporotic women [8]. Moreover, ROS activate transcription factors, including NF-kB, which induce the production of cytokines, such as tumor necrosis factor alpha (TNFα) and interleukin (IL)-6, resulting in the triggering of inflammatory processes and in amplification of osteoclastogenesis [7,9]. An-

tioxidants play an important role in osteoporosis prevention and several studies have shown that fruit and vegetables rich in polyphenols, which have antioxidant properties, are important for bone metabolism. Daily consumption of dietary polyphenols, secondary metabolites that include flavonoids, phenolic acids, lignans, and stilbenes, widely present in various foods such as red grapes, berries, tea, and extra virgin olive oil, appears to be related to a decreased risk of developing osteoporosis [10].

Intake of polyphenols and osteoporosis

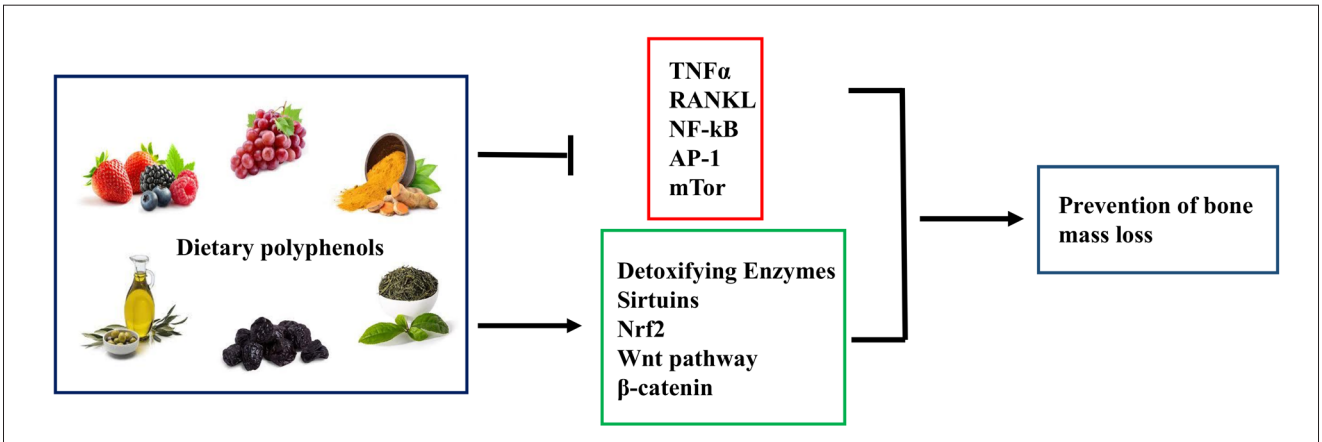
Anti-resorptive drugs, such bisphosphonates, hormone replacement therapy and the selective estrogen receptor modulators, have been approved by the Food and Drug Administration for the prevention and treatment of osteoporosis. However, these therapies are not without side effects and have limited efficacy. Thus, implementing nutrition strategies with foods rich in antioxidants, such as polyphenols, in combination with medical therapies may help to prevent bone mass loss and progression of osteoporosis and reduce fracture risk [11]. Studies in animals and cells in culture show a positive relationship between polyphenol consumption and bone health [12]. Polyphenols, in addition to protecting cells from oxidative stress injury, play an important role in bone metabolism because of their anti-inflammatory properties. They increase osteoblastogenesis and inhibit osteoclastogenesis by activating different signalling pathways linked to bone. Indeed, polyphenols inhibit proinflammatory enzymes, NF-kB, AP-1 and the mammalian target of rapamycin pathway, activate detoxifying enzymes and the nuclear factor-erytroid 2-related factor 2 (Nrf2), which regulates genes encoding antioxidant proteins, and regulate mitogen-activated protein kinase, protein kinase C, Sirtuins (Sirt) and microRNAs (miRNAs). In addition, suppression of osteoclastogenesis by polyphenols is also expressed through reduction of the production of TNFα and RANKL [13-17]. Data from the literature show that polyphenols are also able to mediate their positive effects on osteoporosis by activating the Wnt pathway and up-regulating β-catenin expression [18]. In fact, the Wnt signaling pathway, through the activation of β-catenin, directs the differentiation of bone marrow stromal cells (BMSCs) towards osteogenesis, and therefore its deregulation is linked to osteoporosis. In ovariectomized (OVX) rats, polyphenols exert beneficial effects by enhancing bone mineral density (BMD) and bone mineral content, and by reducing function and differentiation of osteoclasts [19]. Figure 1 summarises the main mechanisms involved in the role of food-introduced polyphenols in the prevention and progression of osteoporosis.

However, there are studies in which polyphenols do not positively affect bone health in OVX rats, and the administration of genistein, quercitin, resveratrol and blueberry extracts is not able to protect against bone loss [20,21]. This can be explained by the use of relatively old animals and the variability in the metabolism of polyphenols in rodents.

Resveratrol and curcumin

Resveratrol (RES), an agonist of the deacetylase Sirt-1 involved in the regulation of various biological processes, belongs to the stilbene family and is present in red wine, berries and peanuts. RES can act as a phytoestrogen and has an anti-osteoporotic effect by inducing osteoblast differentiation and inhibiting osteoclast differentiation, even though the mechanisms involved are not yet very clear. Studies *in vitro* demonstrated that RES exerts its anti-osteoporotic effect by inhibiting the p53 signalling pathway [22], improving the osteogenic differentiation into BMSCs [23] and up-regulating FOXO1 transcriptional activity [24]. OPG and β-catenin are increased by RES that, on the contrary, decreases RANKL by stimulating Sirt-1 expression [24,25]. RES positively regulates osteogenic differentiation by inhibiting the expression of miRNA-338-3p and inhibits osteoclast proliferation by stimulating the expression of miRNA-92-b-3p [26,27]. The oral administration of RES to OVX rats and post-menopausal women improves the bone loss due to estrogen-deficiency, increases bone mass and reduces bone resorption [25]. Moreover, RES intake increases bone mass in women who do not take calcium or vitamin D and strengthens the increase of lumbar BMD in women who take calcium and/or vitamin D [28].

Figure 1 Summary of the main mechanisms involved in the protective role of dietary polyphenols in osteoporosis.



Abbreviations: **TNFα**, tumor necrosis factor alpha; **RANKL**, receptor activator of nuclear kappa-B ligand; **NF-kB**, nuclear factor kappa B; **AP-1**, activator protein-1; **mTor**, mammalian target of rapamycin; **Nrf2**, Nuclear factor erythroid-2 related factor.

Curcumin, abundantly present in the tuberous rhizome of various species of turmeric, especially Curcuma longa, contributes to bone health and regulates bone remodelling by increasing and decreasing apoptosis of osteoclasts and osteoblasts, respectively. The role of curcumin in reducing osteoclastogenic processes also occurs through inhibition of the RANK receptor on osteoclast precursors [29]. The administration of curcumin to osteoporotic rats enhances bone formation by increasing β-catenin and RUNX2 and decreasing nhancer of zeste homologue 2, the histone methyltransferase component of the polycomb repressive complex 2, involved in osteoclast differentiation [30]. Curcumin can play an important role in secondary osteoporosis, as it reduces the loss of bone mass and ameliorates, via the TGFβ/SMAD2/3 pathway, the mechanical properties of bone in rats with type 2 diabetes mellitus [31]. It has been shown that the association of high doses of curcumin with standard doses of alendronate is much more effective than alendronate alone in improving densitometry parameters and biomarkers of bone turnover [32].

Berries

Various studies have highlighted the role of dietary berries, particularly rich in anthocyanins, in bone health as well as the positive correlation between high levels of berry intake and increased bone mass. The mechanisms by which anthocyanins up-regulate osteoblast production and promote bone formation involve the Wnt signalling pathway and MAP38 kinase [33]. In particular, blueberries and cranberries have a significant impact on bone. In OVX rats cranberry juice increases the antioxidant capacity in plasma and red blood cells, while blueberries increase bone mass density and serum ALP [12]. A close correlation, involving in part Sirt-1, between the antioxidant properties of blueberries and the molecular mechanisms related to oxidative stress-induced apoptosis and osteoclastogenesis has been demonstrated in osteocytes. In fact, in conditions of oxidative stress, blueberry juice is able to down-regulate RANKL and sclerostin levels in MLO-Y4 osteocytes and to prevent the oxidative stress-induced cytotoxicity in BMSCs [34]. Moreover, in GSH-depleted SaOs-2 cells, blueberry juice improves the osteogenic differentiation and mineralization processes by redox and non-redox-regulated mechanisms and by increasing Sirt-1 expression. These data indicate that Sirt-1 can be considered a possible anti-resorptive and anabolic target for osteoporosis treatment [35].

Olive oil

Olive oil, characteristic food of the Mediterranean diet, is an important source of polyphenols (e.g., hydroxytyrosol, tyrosol, oleuropein) that, via their anti-oxidant and anti-inflammatory properties, enhance the growth and differentiation of pre-osteoblasts and decrease osteoclast formation. In particular, oleuropein prevents bone loss in osteoporosis by stimulating the growth and differentiation of osteoblasts [36]. Indeed, this polyphenol up-regulates the expression of RUNX2 and osterix, involved in both the initial and later phase of osteoblast formation, increases the levels of osteoblast markers, such as ALP and type I collagen, and enhances the deposition of calcium ions in the extracellular matrix [37]. The administration of virgin olive oil to OVX rats favours an increase in BMD, protects bone health and prevents osteoporosis by mitigating the increase in osteoclasts and the decrease in trabecular thickness [38]. Moreover, intake of olive oil reduces bone mass loss and increases total, trabecular and cortical bone density in women [39].

Green tea

Tea, the most commonly used drink in the world, principally contains flavonoids and catechins, which exert beneficial effects on bone metabolism by positively regulating the differentiation of osteoblasts and inhibiting the activity of osteoclasts [40]. Numerous studies have evaluated the relationship between green tea intake and the risk of osteoporosis. The results obtained are contrasting. A study performed in postmenopausal women demonstrated a positive correlation between green tea intake and increase in BMD, with consequent reduction of osteoporosis and hip fracture risk [41,42]. On the contrary, other studies have shown that habitual green tea consumption has little impact on BMD and does not reduce the risk of fractures [43]. These discrepant results may be due to the constituents of green tea. Indeed, in green tea, in addition to antioxidant polyphenols that ameliorate bone loss by increasing bone formation and reducing bone absorption, caffeine is also present, which negatively affects osteoporosis. In fact, daily caffeine intake higher than that obtained through coffee consumption has been shown to accelerate bone loss in women, decrease the viability of osteoblasts, reduce duodenal calcium absorption, and stimulate calcium excretion [43].

Prunes

Polyphenols found in prunes, such as quercetin, rutin and proanthocyanidins, increase the expression of antioxidant enzymes, inhibit NF-kB activation and pro-inflammatory cytokines, and play a beneficial role in bone by positively affecting bone metabolism [44]. The protective effects of dried plums in bone in postmenopausal women have been confirmed by numerous animal studies. In particular, prune supplementation inhibits bone loss, increases the expression of Nrf2 and suppresses NK-kB activation and the production of pro-inflammatory cytokines in animal models [45]. Moreover, consumption of dried plums positively affects bone health and increases BMD and bone biomarkers, such as ALP and bone-specific ALP, in postmenopausal women [46]. Since daily prune intake prevents loss of hip BMD, this fruit can be considered a non-pharmacological treatment useful for preserving hip BMD and for reducing the risk of hip fracture [47].

Conclusions

Oxidative stress plays an important role in bone loss and is involved in the pathogenesis of osteoporosis. The use of antioxidants and, therefore, the intake of foods rich in polyphenols may contribute to bone health by reducing oxidative stress. In fact, polyphenols have antioxidant properties, reduce inflammation and modulate osteoclastogenesis and osteoblastogenesis. Therefore, fruit and vegetables that contain high concentrations of polyphenols, such as tea, berries, olive oil and red

grapes, can provide benefits in the prevention and treatment of osteoporosis. Polyphenols provide new therapeutic opportunities also in combination with medical therapies to delay the onset and progression of osteoporosis.

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