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Review Article

Main Resveratrol Action Mechanisms in Postmenopausal Osteoporosis

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Abstract

Osteoporosis is a disorder of bone tissue that affects a large part of the population and is related to great morbidity and health spending due to osteoporotic fractures. Among its various types, postmenopausal osteoporosis, related to estrogen deficiency, does not have very satisfactory treatments, since Hormone Replacement Therapy can present harmful effects when used in the long term or in individual specific conditions. In the search for alternative treatments, resveratrol (3,5,4'-trihydroxystilbene), a polyphenol found mainly in grape, emerges as a potential agent, because it's similarity to diethylstilbestrol, a synthetic estrogen. Among its many effects, it has the capacity to act as a cardioprotector and on the bone tissue. *In vitro* and *in vivo* studies indicate that it can protect against the characteristic damages of osteoporosis, mainly in the decrease of the bone mineral density and deterioration of the trabecular microarchitecture of the bone, important factors for the resistance to fractures. Although the mechanisms of action of resveratrol on bone tissue have not yet been fully elucidated, the literature demonstrates that it can interfere with the responsible cells for bone remodeling directly or indirectly, stimulating formation and decreasing bone resorption. With this, we can consider resveratrol a substance capable of treating or preventing damage from postmenopausal osteoporosis. However, further studies involving its antioxidant function and bone tissue may support such a function, allowing the evolution of studies for clinical trials involving postmenopausal osteoporosis.

Keywords: *Resveratrol; Bone Tissue; Estrogen Deficit; Osteoporosis; Phytoestrogens*

Abbreviations

AP-1: Activator Protein-1; BMP-2: Bone Morphogenetic Protein 2; BMP-7: Bone Morphogenetic Protein 7; BW: Body Weight; DVT: Deep Vein Trombosis; FoxO: Forkhead Box O Transcriptional Factor; g: gram; GPX: Glutathione Peroxidase; HRT: Hormone Replacement Therapy; LDL: Low Density Lipoprotein; MAPK: Mitogen-Activated Protein Kinase; mg: milligram; NAD+: Nicotinamide Adenine Dinucleotide; NADPH: Nicotinamide Adenine Dinucleotide Phosphate; NF-κB: Nuclear Factor Kappa B; NF-κB/p65: Nuclear Factor Kappa B Subunit; NOX: NADPH Oxidase; OPG: Osteoprotegerin; RANKL: Receptor Activator of Nuclear Factor-κB Ligand; ROS: Reactive Oxygen Species; Sirt 1: Sirtuin 1; SOD: Superoxide Dismutase; TNFα: Tumor Necrosis Factor α

Introduction

Osteoporosis is a systemic skeletal disorder that affects not only bone metabolism, but also the entire body. In it, multiple pathophysiological mechanisms converge causing the deterioration of trabecular bone microarchitecture and loss of bone density. These damages

lead to increased tissue fragility which, together with the increased risk of characteristic falls in aging, favors a greater number of fractures in osteoporotic patients, especially in senility [1-3]. Still, Osteoporosis is considered a silent disease since it appears asymptomatic until the first fracture with minimal trauma or even without any trauma, indicating the advanced degree of bone fragility [4].

This disease can be classified, summarily, in primary (which refers to bone disorders not associated with other diseases) and secondary (wherein bone loss is associated with specific chronic clinical conditions and/or use of drugs that contribute to this involvement) [5,6]. Among the examples of primary osteoporosis, we have senile osteoporosis and postmenopausal osteoporosis, among which, the reduction of estrogen levels have been the focus of several studies, being the explanation for the increase in the loss of bone mass in women after the menopause since, during this period, ovarian failure leads to a decrease in the production of the hormone [7,8].

In the Caucasian population, it is estimated that approximately 50% of women and 20% of men will experience osteoporotic fractures at some point in their life, being these major causes of morbidity and mortality in the population [4,9]. The prevalence of osteoporotic fractures in the world is about 9 million annually, resulting in costs that exceed € 36 billion in Europe and could double by 2050 if there is no significant treatment [2,10].

Even though Hormone Replacement Therapy (HRT) is a well-indicated treatment and prevention method for postmenopausal women, postmenopausal osteoporosis is still known to lack satisfactory treatments [11]. This is due to the fact that HRT may have harmful effects when used in the long term or in specific conditions (such as genetic predisposition to the development of one of these effects). Some of the most damaging effects are increased risk of breast and endometrial cancer, deep vein thrombosis (DVT), stroke and some coronary heart diseases [12,13].

Therefore, the use of HRT requires a great deal of caution in its use and indication, requiring the search for alternatives with fewer adverse effects in the treatment and prevention of osteoporosis in women. Among the substances with this potential desired effect, such as the SERMs (Selective Estrogen Receptors Modulator) and phytoestrogens, resveratrol (3,5,4'-trihydroxystilbene), a polyphenol found in some plants and fruits, presents itself as a promising substance because of its similarity with diethylstilbestrol (a synthetic estrogen) [14].

Capable of acting selectively on estrogen receptors, resveratrol may act in a beneficial way on osteoprogenitor cell lines, with effects on animal models of osteoporosis. In addition, it is able to prevent the progression of breast cancer cells via estrogen-receptor-independent pathways and has important cardioprotective, anti-inflammatory and eliminating reactive oxygen species (ROS), contributing to other effects of the estrogen deficit [15-21].

Despite the potential action on elements involved in bone metabolism, the mechanisms by which resveratrol acts specifically in this tissue remain uncertain and widespread in the literature, hampering the consolidation of a large knowledge base that can serve as a guide for studies that better consolidate this capacity of the substance and allow the advancement of research for the use of resveratrol in humans with osteoporosis.

Thus, the objective of this work was to review the particularities of resveratrol, its effects on bone tissue, and as well as the mechanisms by which this substance can act positively on the latter, and may serve as the basis for future experimental studies that can further consolidate this substance in the treatment of postmenopausal osteoporosis.

Methods

This study was drawn from a literature review and based on scientific articles, dissertations and theses recorded in the universities of origin. The following databases were used: BIREME, PUBMED, Science Direct and ResearchGate.

Were analysed and included in this review, original or revision articles that addressed postmenopausal osteoporosis and bone tissue, and mainly *in vitro* and *in vivo* studies involving resveratrol and its effects on organism, especially the bone tissue. The keywords used were: resveratrol; postmenopausal osteoporosis; bone tissue; estrogen deficiency; mechanisms of action.

Discussion

Resveratrol (3,5,4'-trihydroxystilbene) is a non-flavonoid polyphenol/phytoalexin, member of the viniferine family of polymers, existing in nature both in the form of trans-resveratrol and cis-resveratrol. It was first isolated in 1939 from the roots of *Veratrum grandiflorum* and in 1976 gained the rank of phytoalexin, a substance whose synthesis is induced by fungal infection in the plant [22].

In 1992, Renaud and De Logeril [24] published an article on "French paradox" which argues that even the French population having a diet rich in saturated fats, they have a low mortality due to coronary and cardiac problems. At that time, such effects were correlated with the high consumption of red wine by the population, but with the deepening of the studies involving the beverage and the discovery of resveratrol as the main biologically active compound in wine, studies involving resveratrol in attempt to consolidate it as one of the main substances involved in this paradox [24,25].

It is found in more than 70 plant species of which the most frequent sources are: *Polygonum cuspidatum* rhizome, red grapes (including leaves, seeds, stems and roots) such as *Vitis vinifera* species (used for winemaking in Europe), *Vitis labrusca* (from North American origin) and *Vitis rotundifolia* (muscadine grapes grown in the southeastern United States for the production of wines, juices and jams), as well as some berries (such as blueberries and cranberries), pine trees, flowers (such as *Veratrum grandiflorum*) and even in dark chocolate and cocoa [26,27].

In our eating habits, the three main sources of resveratrol are grape (0.16 to 3.54 µg/g), grape juice (0.50 mg/L) and red wine (0.10 to 14.3 mg/L). Although red grapes have a concentration of resveratrol similar to that of white grapes, red wine has a higher concentration of resveratrol because during its production the fermentation process takes place in the bark of the grape other than white wine whose fermentation occurs after bark is removed [26].

In the body, resveratrol is rapidly absorbed, with plasma peaks occurring 30 to 45 minutes after administration. Its distribution is quite high, because it has a lipophilic characteristic and its half-life in humans is 30 to 60 minutes [18,28].

Although it has low bioavailability and rapid metabolism when administered orally, there are indications that the metabolites generated by the gastrointestinal and hepatic metabolism may aid in the beneficial functions of the substance, besides serving as a substrate reserve for conjugation of resveratrol and consequent release to the tissues, contributing to the pharmacological effects of the substance [29-32].

Furthermore, other compounds present in the food that contains it may modify its bioavailability, as evidenced by Ortuño., *et al.* [33], who observed that resveratrol is better absorbed when ingested in natural products derived from the grape. In addition, it is observed that the use of lower doses obtained by the consumption of red wine can bring beneficial effects to human health compared to high doses used alone in an experiment, further reinforcing the importance of the food composition of the product that will be administered together with resveratrol [28].

Recently, resveratrol has shown promising effects on a wide range of diseases, having a large number of preclinical studies on cancer, metabolic disorders and cardiovascular diseases [18]. Nevertheless, it presents other effects well elucidated in the literature as: anti--inflammatory; as adjuvant in hypoglycemic treatments in patients with Type 2 Diabetes; and antioxidants (either eliminating Reactive Oxigen Species [ROS] or modulating the endogenous antioxidant system) [18,22,34].

Effects of resveratrol on organism

Due to the fact that it was probably involved with the French Paradox, much was investigated about its effects as a cardioprotector. This fact was reinforced by the fact that, when high concentrations of resveratrol metabolites in urine were found, the prevalence of risk factors for cardiovascular disease in high-risk patients was diminished, directly or indirectly [35,36]. In addition, clinical data demonstrate that the substance is able to increase cerebral blood flow during task performance and increase oxygen extraction in a dose-dependent manner [37].

In obese subjects with borderline hypertension, treatment with resveratrol was able to decrease systolic and mean blood pressure, simulating the effects of caloric restriction [38], besides causing slight changes in diastolic blood pressure also in individuals who, in addition to being obese and hypertensive, had Type 2 Diabetes Mellitus [39].

Still, Fabricio., *et al.* [40] studying the effect of two preventive treatment durations with resveratrol (60 and 90 days, 10 mg RES/kg Body Weight (BW)) in ovariectomized rats at 90 days of age, observed that the treatment of 90 days with resveratrol was able to protect against increased blood pressure and endothelial dysfunction characteristic of estrogen deficiency, possibly through an independent mechanism of nitric oxide, further consolidating the protective effect of this substance in the cardiovascular system, even focusing only on in situations of estrogen deficiency.

On lipid metabolism, Tomé-Carneiro., *et al.* [41], when administering grape extract with resveratrol at a dose of 8 mg per day for 6 months, observed the decrease of Low Density Lipoprotein (LDL) and oxidized LDL, superior to the effects observed in patients who did use of statins.

On glucose metabolism, high doses (1 - 2g once daily after feeding) of resveratrol were able to decrease postprandial glucose peak, area under the glucose curve 3 hours post meal, in addition to reducided insulin sensitivity in elderly subjects with impaired glucose tolerance [39]; intermediate doses (150 mg) administered for 30 days were able to decrease insulin levels and insulin resistance in obese men [38] and low doses (5 mg) given twice a day (after a test meal) were able to lower the maximum glucose level and insulin resistance when compared to placebo [42].

Another much studied and well-established effect of resveratrol is on cancer. Several *in vitro* studies demonstrate the ability of the substance to inhibit the growth, proliferation and viability of cancer cells, as well as to stimulating their apoptosis. These effects occur through several pathways such as: regulation of the activation of the mitochondrial enzyme cascade and caspase; increased expression of cyclin-dependent kinases; decreased expression of survival proteins related to chemoresistance; inhibition/activation of signaling and messengers related to the processes of survival and proliferation of cancer cells; in addition to the antioxidant action on cancer cells, decreasing the production of ROS, which have important function in the cell cycle for cancer progression and metastasis [43].

More specifically on the antioxidant effects, evidence confirms that resveratrol has scavenger ability (ability to neutralize free radicals, in this case, trapping them in its benzene ring); complexation with oxidizing metals, especially iron; preservation of the enzyme paraoxonase; increase of endogenous antioxidants; inhibition of NOX activity and mitochondrial production of reactive species in vascular cells; and modulation of the activity of important enzymes in the antioxidant defense such as superoxide dismutase (SOD), glutathione peroxidase (GPx), hemoxygenase and catalase, via transcription factor Nrf2, Activator Protein-1 (AP-1) or forkhead box O transcriptional factor (FoxO) [36,44-48].

Effects of resveratrol on bone tissue

Due to its similarity with diethylstilbestrol and similar functioning as that of a SERM, acting differently in different estrogen-responsive tissues, resveratrol began to be studied as a possible alternative and preventive treatment for osteoporosis, especially postmenopausal osteoporosis [14].

In vitro studies indicate the ability of resveratrol to affect bone metabolism by showing an osteogenic effect on bone cells, not only by increasing the differentiation of mesenchymal cells in osteoblasts, but also by inhibiting the formation of osteoclasts [20,49-52]. Mizutani., *et al.* [20] analyzing the action of resveratrol on MC3T3-E1 cells (line of rat pre-osteoblasts, used as an osteoblast model in the bone marrow in *in vitro* research), reported the effect of direct stimulation of osteoblast proliferation and differentiation.

Boissy., *et al.* [49] indicated that the substance is also capable of increasing the expression of markers of osteoblasts such as osteopontin and osteocalcin in mesenchymal stem cells. He., *et al.* [21], observed in the colony of RAW264.7 cells (osteoclast progenitor cells) the ability of resveratrol to inhibit the formation of RANKL-dependent osteoclasts and to stimulate apoptosis of the same.

In vivo studies relating the substance to the prevention of bone damage in experimental osteoporosis models showed effects on some bone parameters, mainly bone mineral density and trabecular microarchitecture, factors of great importance to indicate the bone's ability to resist fractures. Liu., *et al.* [53], when treated ovariectomized Wistar rats with resveratrol (0.7 mg/kg BW, via gastric gavage) for 12 weeks, observed that resveratrol may inhibit the reduction of bone mineral density, especially in the epiphyses of the femurs of the animals used.

Habold., *et al.* [54], in a protocol of bone loss by disuse (which shows mechanisms similar to those of postmenopausal osteoporosis) in Wistar rats, observed that oral preventive treatment with resveratrol (400 mg/kg MC) protected against the decrease in bone mineral density volumetric femurs and tibia (with more expressive response in the tibias), cortical bone mineral density in the tibia metaphysis, and protection against microarquiteural deterioration in both bones analyzed.

Zhao., *et al.* [55] reported that twelve weeks of treatment with different doses of resveratrol (between 20 and 80 mg/kg BW) administered through a stomach tube in ovariectomized rats was able to protect against the reduction of areal bone mineral density in the neck and the distal portion of femur (in the two largest doses); partially prevent microarchitectural deterioration of bones at the highest dose; and decrease calcium and phosphorus excretion, which may indicate a decrease in bone resorption.

Still, Casati., *et al.* [56] and Casarin., *et al.* [57] demonstrated that 30-day treatment with resveratrol (10 mg/kg BW) via gastric gavage exerts beneficial effects on the bone in dental implant models and periodontitis, which involves some mediators similar to those of postmenopausal osteoporosis, reinforcing the effects of the substance on the bone tissue.

Possible mechanisms of action

Even though the effects of resveratrol on bone tissue are better consolidated, the exact mechanisms of action of the substance on it, especially in estrogen deficiency, remain uncertain but constantly updated and reported. On bone cells, Dai., *et al.* [58], have described that small concentrations of resveratrol have the ability to induce rapid stimulation of proliferation, osteoblastic differentiation and expression of osteogenic genes by mechanisms involving estrogen receptors, mitogen-activated protein kinase (MAPKs), and essential transcription factors for osteogenesis (Runx2 and Osterix).

He., *et al.* [21] have observed that inhibition of proliferation and differentiation of osteoclast progenitor cells in osteoclasts is not dependent of estrogen receptors but on the inhibition of reactive oxigen species released after stimulation of cells by RANKL, with ROS being considered quite important in osteoclastogenesis.

Similarly, several studies have observed an increase in substances related to increased bone formation (such as alkaline phosphatase) and a decrease in bone resorption-related substances (such as IL1, IL6, NF-κB and TNFα), demonstrating the effect of resveratrol on bone cells indirectly and, consequently, in bone remodeling as a whole [55,59,60]there is no direct evidence supporting its inhibitory effect towards bone loss. In the present study, effects of resveratrol on bone mineral density (BMD. On bone formation, Casarin., *et al.* [57], analyzing the effect of resveratrol treatment on bone repair after calvarial defects in Wistar rats, observed that the substance was able to stimulate the early stages of ossification by increasing the expression of Bone Morphogenetic Protein 2 and 7 (BMP-2 and BMP-7), genes important for stimulating this process.

Regarding bone resorption, Boissy., *et al.* [49], showed that resveratrol is able to act directly on RANKL receptors in precursor cells of osteoclasts, decreasing the activation of NF-κB and, consequently, decreasing osteoclastogenesis. Lei, Liu and Liu [61] investigating the

effects of resveratrol on interleukins in chondrocyte-derived bone marrow mesenchymal cell culture, have also shown that resveratrol acts as an inhibitor of NF-κB factor, indicating a protective effect in this cell type via inhibition of interleukins, mediated by integrins.

More recent studies also relate resveratrol as a potent activator of Sirtuin 1 (Sirt1), a NAD^+-dependent deacetylase involved with a number of biological functions [62,63]. Iyer., *et al.* [64], in a study involving the deletion of Sirt1 in mouse osteoblast progenitor cells, found that this deletion led to a decrease in the cortical contingent on the endocortical surface of bones resulting from decreased bone formation. Studying further, the authors have suggested that this protein is able to deacetylate β-Catenin and FoxO factor, preventing binding between them and aiding bone formation. Since FoxO is related to β-Catenin sequestration and inactivation of the Wnt/β-Catenin pathway [64,65], blocking this binding by Sirt1 would be able to stimulate bone formation, and resveratrol stimulating such a protein may also enhance such activity.

Sirt1 may also exert an effect on NF-κB factor through its association with the p300 substance (an acetyltransferase, responsible for nuclear acetylation and translocation of NF-κB), rendering it useless [50]. Wang, Chen and Peng [63], when analyzing the effect of resveratrol at doses of 5, 25 and 45 mg kg body weight in a osteotomy model of male Wistar rats, found that the two higher doses of the substance were able to increase the expression of Sirt1 and decrease NF-κB/p65 expression in the animals compared to the ovariectomized control group. Since the activation of NF-κB depends on the phosphorylation of NF-κB/p65 [66], the decrease in the expression of the latter is able to mitigate the effects of osteoporosis on the bone mediated by this protein.

Knowing that increased ROS can lead to increased bone resorption, and since estrogen has the ability to stimulate the production of antioxidant enzymes and even to collect (and later assist in eliminating) ROS [67-69], we can assume that the excess of EROs is involved with osteoporosis due to estrogen deficiency. Nevertheless, resveratrol is considered a potent antioxidant [18,24], making it possible to make deeper relationships in the mechanism of action of the substance on bone tissue affected by osteoporosis.

However, the lack of a direct and strong relationship between the involvement of bone tissue and oxidative stress limits the development of this important topic while making it interesting to study the relationship between resveratrol, ROS and postmenopausal osteoporosis, allowing it to be better consolidated in the future, another mechanism by which the substance can act on bone tissue.

Conclusion

Postmenopausal osteoporosis is a multifactorial disorder that affects a large part of the world's population of women and is associated with high hospitalization, treatment, and morbidities related to osteoporotic fractures. Also, the most appropriate treatment for this disease can present adverse effects in individuals with specific conditions, which prevents it from being a treatment with a global effect, able to stop the growth of the number of people affected by this affection.

With this, the need to find alternative treatments and with the minimum of adverse effects becomes more and more important. In this situation, resveratrol has emerged as a substance with great potential to fill this gap.

This research has proposed to deepen the studies on resveratrol, its effects on the body and, more specifically, on the bone tissue, as well as the mechanisms by which the latter can occur.

Thus, the beneficial effects of resveratrol on the whole body were established, allowing the substance to act on estrogen deficient effects not related to bone tissue such as vascular dysfunction and lipid metabolism.

On bone tissue, it was found that the substance is able to treat or prevent bone damage by controlling substances that stimulate bone formation and resorption, control of the differentiation of the cells responsible for bone remodeling and by stimulating the production of substances which may affect all bone metabolism such as Sirtuin 1.

However, the effects of oxidative stress (caused by estrogen deficiency) on bone are not yet studied, and since resveratrol, which has an excellent antioxidant capacity, can affect tissue through these pathways. Thus, the emergence of further studies involving oxidative stress, bone tissue and resveratrol may further underpin this substance as a good alternative treatment for postmenopausal osteoporosis and for other effects of estrogen deficiency in the body.

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Conflict of Interest

There was no conflict of interest.

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