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Review

Resveratrol supplementation affects bone acquisition and osteoporosis: Pre-clinical evidence toward translational diet therapy☆

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ABSTRACT

Osteoporosis is a major public health issue that is expected to rise as the global population ages. Resveratrol (RES) is a plant polyphenol with various anti-aging properties. RES treatment of bone cells results in protective effects, but dose translation from *in vitro* studies to clinically relevant doses is limited since bioavailability is not taken into account. The aims of this review is to evaluate *in vivo* evidence for a role of RES supplementation in promoting bone health to reduced osteoporosis risk and potential mechanisms of action. Due to multiple actions on both osteoblasts and osteoclasts, RES has potential to attenuate bone loss resulting from different etiologies and pathologies. Several animal models have investigated the bone protective effects of RES supplementation. Ovariectomized rodent models of rapid bone loss due to estrogen-deficiency reported that RES supplementation improved bone mass and trabecular bone without stimulating other estrogen-sensitive tissues. RES supplementation prior to age-related bone loss was beneficial. The hindlimb unloaded rat model used to investigate bone loss due to mechanical unloading showed RES supplementation attenuated bone loss in old rats, but had inconsistent bone effects in mature rats. In growing rodents, RES increased longitudinal bone growth, but had no other effects on bone. In the absence of human clinical trials, evidence for a role of RES on bone heath relies on evidence generated by animal studies. A better understanding of efficacy, safety, and molecular mechanisms of RES on bone will contribute to the determination of dietary recommendations and therapies to reduce osteoporosis. This article is part of a Special Issue entitled: Resveratol: Challenges in translating pre-clinical findings to improved patient outcomes.

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1. Introduction

Resveratrol (RES) is a polyphenolic (3,4′,5-trihydroxystilbene) compound naturally present in red wine and a variety of plant foods such as grapes, cranberries, and nuts [1]. There is a growing body of evidence that RES is an effective therapeutic agent for age-related degenerative diseases such as osteoporosis [2,3]. Osteoporosis is a skeletal disorder characterized by low bone mass, structural deterioration, decreased bone strength, and increased risk of bone fractures [4]. Osteoporosis is a major public issue with a worldwide estimated 9 million bone fractures annually. Additionally, the prevalence of osteoporosis is expected to increase as the global population ages [5].

Throughout life, bone is remodeled by a process involving bone resorption which removes old bone followed by replacement with new bone by the process of bone formation. During the growth stages of childhood, adolescence, and into young adulthood, bone formation exceeds the rate of bone resorption resulting in bone mass acquisition. After this stage, at ~20–30 years of age, bone resorption exceeds bone formation resulting in gradual and progressive bone loss [6]. Therefore, maximizing peak bone mass (PBM) during the growth stage is an important factor for preventing future risk of osteoporosis. This is particularly important for women, who are at greater of risk of osteoporosis than men, due to rapid bone loss resulting from declining estrogen at menopause [7]. Both women and men experience age-related bone loss that is often accelerated by mechanical unloading associated with physical inactivity and prolonged bed rest [8]. Disuse-related bone loss is also observed in young patients confined to prolonged bed rest as a result of injury or immobilization due to spinal cord injury.

RES has estrogenic, anti-inflammatory, antioxidant, and proliferative properties that can influence bone metabolism [9]. No toxicity has been reported for RES intakes of up to 500 mg/d in animals and humans [9,10]. Due to its multiple bioactivities and low toxicity, RES offers the promise of being an efficacious and safe therapeutic agent for osteoporosis. However, due to the lack of human clinical trials, evidence of a therapeutic role of RES on bone relies on *in vitro* studies and animal models of bone loss. The aim of this review is to evaluate the pre-clinical evidence of RES supplementation to enhance bone, to reduce

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risk of osteoporosis, and to determine potential mechanisms of action. A better understanding of the effects of RES on bone will contribute toward the development of dietary recommendations and therapies for preventing bone loss leading to osteoporosis.

2. Bone remodeling

Bone consists of cortical (compact) and trabecular (spongy) components. Cortical bone accounts for ~80% of skeletal mass and is located in the diaphyseal regions of long bones; whereas, trabecular bone is located inside cortical bone in the proximal and distal epiphysis region of long bones and vertebrae [6] (Fig. 1A). Bone is constantly remodeled in a process where old bone is removed (bone resorption) and replaced by new bone (bone formation). The process of bone remodeling is summarized in Fig. 1B. The cell lineages important in bone turnover are osteoblasts and osteoclasts [11]. Osteoclasts are derived from hematopoietic progenitors (i.e. monocyte/macrophage) in the bone marrow. Receptor activator of nuclear kappa B ligand (RANKL) produced by osteoblasts bound to RANK receptors located on the surface of hematopoietic cells promotes differentiation into osteoclasts [11]. Activated osteoclasts attach to the bone surface and release proteolytic enzymes that digest connective tissue proteins and solubilize bone mineral. Production of enzymes such as tartrate-resistant acid of the phosphatase (TRAP) and collagen degradation products such as deoxypyridinoline (DPD) and C-terminal telopeptide of type I collagen (CTX) during osteoclastogenesis provides useful surrogate clinical markers of bone resorption. To counterbalance bone resorption, osteoblasts also produce osteoprotegerin (OPG) that inhibit osteoclastogenesis by binding to RANKL and blocking interaction with the RANK receptor [12]. Osteoblasts fill the cavity produced by osteoclast-mediated resorption by synthesizing and mineralizing new bone [11]. Hence, skeletal integrity requires a balance between bone-forming osteoblast activity and bone-resorbing osteoclast activity. Imbalances where bone resorption exceeds formation result in bone loss [12].

Osteoporosis is the result of increased osteoclast activity and/or decreased osteoblast activity during remodeling. Osteoblasts are õderived from pluripotent mesenchymal stem cells (MSCs) in the bone marrow. MSCs differentiate into either osteoblasts, adipocytes or chondrocytes depending on the activation of specific transcription factors [11]. Expression of the transcription factor, peroxisome proliferator activated receptor gamma (PPARγ), is the main determinant of MSC differentiation into adipocytes [13]. Several transcription factors are required for MSC differentiation into osteoblasts. Runt-related transcription factor 2 (Runx2) is considered the master regulator of osteoblast differentiation [14] and Osterix downstream of Runx2 is also essential [15]. MSCs committed to the osteoblast lineage form osteoprogenitors. Entering a proliferation phase, osteoprogenitors undergo morphological changes into pre-osteoblasts that are capable of synthesizing bone matrix and alkaline phosphatase (ALP) [11]. Pre-osteoblasts mature into osteoblasts that regulate bone matrix mineralization and produce osteocalcin [11]. Circulating ALP and osteocalcin provide useful surrogate clinical markers of bone formation. Osteoblast differentiation ends with the formation of osteocytes that regulate bone responses to mechanical stimuli and bone mineralization [16] (Fig. 1B).

The activity of transcription factors can be influenced by various local and systemic factors that include bone morphogenetic proteins [17], insulin-like growth factor (IGF) [18], the canonical wingless (Wnt)/β-catenin signaling pathway [19], mechanical forces [20], estrogen and other hormones [21]. The natural food component RES has both structural and functional similarities to estrogen [22]. Furthermore, dietary RES activates Sirtuin1 (Sirt1) known as the longevity gene [23]. Bäckesjö et al. [24] reported that Sirt1 activation decreases MSC differentiation into adipocytes while promoting differentiation into osteoblasts. Much of the knowledge about molecular mechanisms underlying RES as a dietary treatment for osteoporosis has been derived from *in vitro* studies.

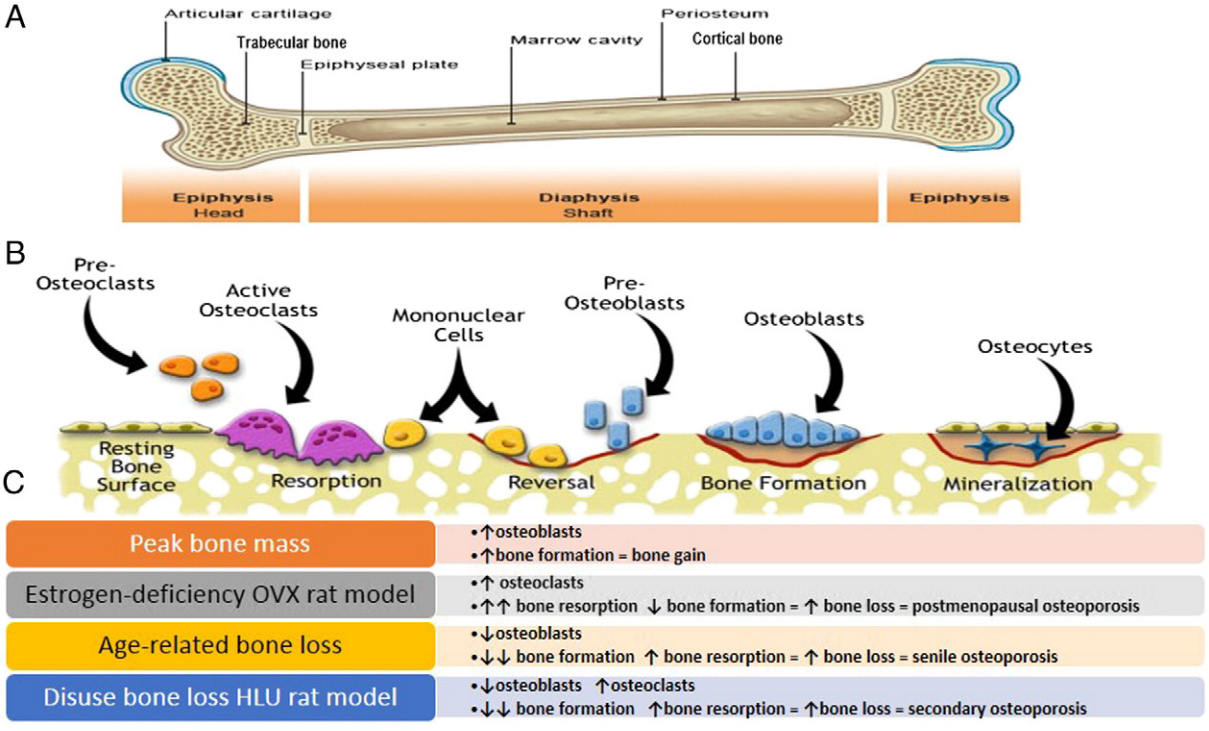

Fig. 1. Summary of steps in normal bone remodeling and the results of imbalances in bone turnover. A) femur anatomical sites, B) cell lineages involved in the process of bone remodeling, C) bone loss and acquisition due to alterations in bone formation and bone resorption. Symbol ↓ decrease, ↑ increase, ↑↑ predominant.
Adapted from the University of Michigan bone remodeling http://www.umich.edu/news/Releases/2005/Feb05/bone.html and Openstax College bone structure http://cnx.org/content/m46281/latest/.

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