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Nutraceuticals for better management of osteoporosis: An overview

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ABSTRACT

Osteoporosis is a common bone disorder observed particularly in aging population and post-menopausal women. It results from an imbalance in the natural process of bone remodeling, a continuous cycle for bone formation and bone resorption. Though various drugs acting on different therapeutic targets of osteoporosis are available, focus is now shifting towards the natural alternatives to avoid side effects associated with the drug therapy. This review encompasses the spectrum of nutraceuticals such as minerals, herbs, phytochemicals and dairy products which can be included in the regime for osteoporotic patients to support bone health. Although scientific studies provide evidences of therapeutic efficacy of nutraceuticals, in-depth clinical investigation is need of the hour for its safe consumption by osteoporotic population. Furthermore, global regulatory requirements can be recommended for rational and safe use of nutraceuticals considering the tremendous growth of nutraceutical market in the near future.

1. Introduction

Bones play a crucial role in well organized and lifelong working of many important skeletal functions. It not only supports and provides site for attachment of muscles, but also protects essential organs like the brain and the bone marrow. It also functions as a metabolic organ which stores calcium and phosphate. They are living tissues that rebuild constantly throughout the life. Bone is a reservoir of calcium ions and stores 99% of calcium (Appleton & Lockwood, 2006). Bone consists of organic phase comprising of collagen and mucopolysaccharides which provides flexibility whereas inorganic mineral phase comprising of hydroxyapatite (crystalline calcium phosphate) which provides bone rigidity and numerous cells which help in bone development and maintenance. Bone modeling begins from fetal stage and reaches maximum during puberty. After modeling, remodeling occurs which helps to maintain body mineral levels. Osteoclasts and osteoblasts are bone cells that play major role in remodeling. Osteoclasts promote the release of minerals from bone tissue whereas osteoblasts replace the bone minerals which are then mineralised. Thus, bone is a dynamic tissue which keeps on remodeling to meet the requirements of the body. However, a deregulation in this dynamic process gives rise to different kinds of bone problems (Heaney, 2006; Wiggins, 2016).

Osteoporosis is a debilitating medical condition which is marked by reduction in the bone density and degeneration of bone structure which results in bone weakness and increases the risk of fracture. Reduced bone mineral mass is the major contributing element to osteoporotic fractures (Fig. 1). The various factors that influence low bone mass are broadly classified into factors which cannot be altered and those factors which can be altered. Factors such as gender, age, body size, race and genetics cannot be altered whereas factors like hormonal status, lifestyle factors which includes diet, smoking and alcohol consumption patterns, physical activity levels can be changed. Osteoporosis is categorised into primary osteoporosis and secondary osteoporosis. Primary osteoporosis is further branched into subtypes: Type I and Type II. Type I osteoporosis, also known as postmenopausal osteoporosis, is a typical bone disorder observed in postmenopausal female that occurs due to estrogen deficiency following menopause. Type II osteoporosis, also referred as senile osteoporosis or age-related osteoporosis, is linked mainly with aging in men and women. Secondary osteoporosis occurs due to some underlying medical condition or medications that interfere in the process of normal bone formation (Feng & McDonald, 2011). It is estimated that osteoporosis affects approximately 200 million women worldwide in which 1/10th of population aged 60, 1/5th of those aged 70 and 2/5th of those aged 80 (Kanis, 2007). Currently there are various classes of drugs available for treatment of osteoporosis as given in Table 1. Unfortunately, these drugs are accompanied by severe adverse effects like atrial fibrillation, atypical subtrochanteric fracture, delayed fracture healing, hypersensitivity reactions, hot flashes, leg cramps, gastrointestinal effects like nausea, vomiting, constipation etc (Musette et al., 2010; Orwoll et al., 2003; Paggiosi at al., 2014; Rizzoli et al., 2011). Therefore this review focused at presenting different classes of nutraceuticals useful in overall bone health and for better management of osteoporosis.

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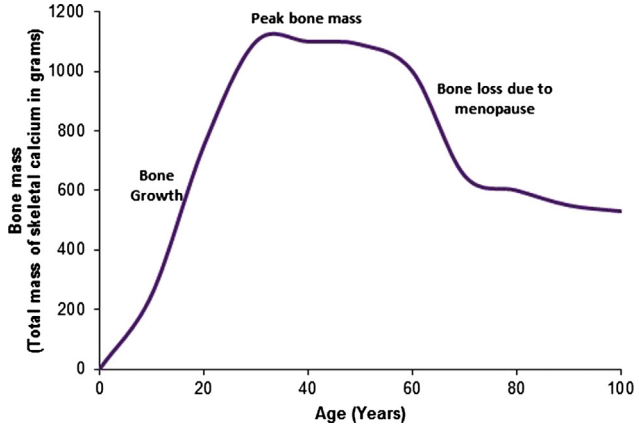

Fig. 1. Bone mass throughout life for females.

2. Physiology of bone formation and remodeling

Physiologically, osteoclasts originate from hematopoietic precursor cells responsible for bone resorption, while osteoblasts are derived from mesenchymal cells serve for bone formation. These two cells are dependent and connected to each other in the process of bone remodeling. Osteocytes are terminally differentiated osteoblasts which are present in mineralised bone and help to control the timing and site of bone remodeling (Kini & Nandeesh, 2012; Raisz, 1999).

2.1. Phases of bone remodeling

Activation phase: It involves stimulation of bone remodeling signal which can either be a mechanical strain on the bone or influence of some hormone (e.g. estrogen or parathyroid hormone). Osteocytes are able to sense mechanical strain caused by physical activities and converts it into biological signals that trigger bone remodeling (Bonewald, 2007). Similarly, parathyroid hormone (PTH) which is essential for maintaining calcium homeostasis can signal remodeling. PTH when binds to its receptors present on osteoblasts, leads to a series of events like- activation of protein kinase A, activation of protein kinase C, activation of intracellular calcium signalling pathway which in turn leads to enhanced osteoclast differentiation and activity and causes bone resorption (Juppner et al., 1991; Robinson et al., 2006).

Resorption phase: During this phase there is enrolment of osteoclast at bone remodeling site. In addition, osteoblast in response to PTH expresses master osteoclastogenesis cytokines, receptor activator of nuclear factor-{kappa}B ligand, colony-stimulating factor-1 and osteoprotegerin. Matrix metalloproteinases (MMPs) are also released from osteoblasts that causes degradation of osteoid which is unmineralised and forms sites for attachment for osteoclasts. The accumulation of hydrogen ions causes dissolution of mineralised bones and further organic matrix is degraded by various collagenolytic enzymes especially cathepsin K (Ma et al., 2001; Saftig et al., 1998; Yang et al., 2004).

Reversal Phase: In this phase, after osteoclast mediated bone resorption is complete, the surface of the bone gets ready for osteoblast mediated formation of the bone by removal of collagen remnants by mononuclear cells (Van Tran, Vignery, & Baron, 1982).

Formation Phase: Osteoblast progenitor cells differentiate and secrete molecules which help in bone formation. Various non-collagenous proteins like proteoglycans, glycosylated proteins like small integrin-binding ligand (SIBLING) proteins, alkaline phosphatase, lipids and Gly-containing proteins form the organic material along with collagen type I, called osteoids (Robey & Boskey, 2008). Finally, hydroxyapatite is incorporated in this newly formed osteoid to complete the process of bone formation (Murshed, Harmey, Millán, McKee, & Karsenty, 2005).

Termination phase: Remodeling concludes when equal quantity of resorbed bone is replaced with newly formed bone. After bone mineralization, osteoblasts undergo apoptosis and bone surface environment is again established to begin a new cycle of remodeling (Raggatt & Partridge, 2010). Osteoclasts generally need few weeks for bone resorption whereas osteoblasts take longer time, generally few months, to build new bone. Hence, any process which causes an increase in the rate of bone remodeling will result in overall loss of bone density over a period of time. The distinctive feature of osteoporosis is an overall decline in bone mass associated with an imbalance between bone resorption and the genesis of bone (Teitelbaum, 2000).

The bone remodeling cycle is illustrated in Fig. 2.

3. Factors leading to osteoporosis

3.1. Age

One of the most typical causes of age related loss of bone is build-up of bone marrow fat in place of osteoblastogenesis. Mesenchymal stem cells undergo differentiation to form adipocytes instead of osteoblasts. For mesenchymal stem cells to differentiate into osteoblast, it requires sufficient quantity of growth factors, initiation of lineage-specific transcription factors and adequate blood and oxygen supply within the bone marrow. Aging alters these favorable conditions for differentiation of mesenchymal stem cell into osteoblasts and facilitates its differentiation into adipocytes. Intermediate filament proteins called lamins found in lamina of the nucleus and matrix are important in regulation of mesenchymal stem cell differentiation. Also, there is significant reduction in lamin functioning in normal osteoblasts as a result of aging (Demontiero, Vidal, & Duque, 2012).

3.2. Genetic factors

Genetic studies could successfully identify various polymorphisms that are associated with Bone mineral density (BMD) and osteoporosis in which vitamin D receptor gene was evaluated for its effect on BMD in individuals. Genes like collagen type I alpha (COLIA 1) gene which encodes for type I collagen alpha1 chain is one of the significant candidate for pathogenesis of osteoporosis being a principal protein of the bones. Estrogen receptor alpha is another gene which is transcribed by gene ESR1, is also important for bone mass regulation. The ATP6i subunit of the osteoclast-specific pump is encoded by the TCIRG1 gene.

Table 1
Commonly used therapeutic drugs for treatment of osteoporosis.

Class	Drugs	Mechanism of action	Side effects
Bisphosphonates	Alendronate, Riserdronate, Ibandronate, Zoledronate	Binds to bony surfaces which undergo active resorption and blocks release of protons which are required for bone resorption.	Irritation of lining of esophagus and stomach, osteonecrosis of the jaw
Selective estrogen receptor modulator	Raloxifene	Mimics positive effects of estrogen on bone	Hot flushes, leg cramps, risk of blood clots and stroke
Parathyroid Hormone Treatment	Teriparatide	Similar in activity as human parathyroid hormone for bone development and homeostasis of calcium	Raises risk of certain type of bone cancer