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Clinical aspects and importance of nutrition in homeostasis of the bone tissue

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ABSTRACT

Substantial changes have occurred in the nutritional management of many diseases in the last twenty years. Introduction of standards, clinical review and implementation of evidence based practice led to re-evaluation of some established dietary interventions. The most common form of osteoporosis is the primary osteoporosis, which is the result of the bone loss and deterioration of bone structure, as people age. Bone loss and osteoporosis can be prevented through adequate nutrition, physical activity, and, if necessary, appropriate treatment. This review will focus on nutritional and clinical aspects of bone tissue homeostasis, with references to physiological and pathophysiological processes.

Keywords: Bone tissue; homeostasis; osteoporosis; clinical aspect

INTRODUCTION

Substantial changes have occurred in the nutritional management of many diseases in the last twenty years. The changes were accompanied with the increase of awareness of their significance and have also occurred in the nutritional management of bone tissue diseases. Many changes in clinical nutrition have been associated with the introduction of standards, clinical review and implementation of practice based on evidence, which led to re-evaluation of some established dietary interventions using the hierarchy of evidence approach. It is necessary to ensure the efficacy of nutritional interventions without undesirable side effects, and to systematically evaluate clinical practice, as well as to modify the practice in light of current research (1).

Osteoporosis is systemic skeletal disease and the most common metabolic disease of bones, characterized by reduced bone tissue mass and impaired microarchitecture. Consequently, the risk of fractures is increased, which results in increased morbidity and mortality, especially in the older population. Given that osteoporosis is a disease related to age, it is also related to low bone mineral density (BMD), microarchitectural bone deterioration, bone tissue fragility, and increased risk of fracture (2).

Osteoporosis is one of major public health problems in developed countries, with tendency to increase in relation to aging of population. Osteoporosis is more common in women, affecting 22 million women age >50 years in Europe, or 22% of the female population. At the age of 50 years, the lifetime probability of hip fracture is 7-25%, and it accounts for almost 50% of major fractures among

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European women (3). Between 2000 and 2050, the share of world population aged >60 years is foreseen to double, from 11% to 22%. The absolute number of people aged ≥60 years is expected to increase from 605 million to 2 billion by 2050, while the number of people aged ≥80 years will quadruple to 395 million by 2050 (4).

The risk of osteoporotic fracture increases significantly during the seventh decade of life, and the prevalence of sarcopenia increases significantly with age, which also contributes to the risk of fracture. Therefore, preventive therapy and adequate nutrition are extremely important for a person with increased risk of fractures (5).

BONE TISSUE HOMEOSTASIS

Bone tissue is the major supporting tissue in human body. Bone mass is formed in childhood and youth, and the process is active until thirty years of age when it reaches its maximum. Then it decreases with age, significantly more in women than in men, and it is determined largely by genetic factors (6). Low BMD may be the result of reduced bone building in childhood or puberty, or increased bone loss in later life. During a lifetime, the bone is constantly remodeled. It degrades when it is old, or bone structure is less viable, or when damaged by micro-fractures, and it is replaced by new and more resistant bone structure, which is especially important at the point of increased stress (7). Depending on the part of the skeleton, hereditary factors determine 50-85% of differences in bone mass. Among the set of genes that affect peak bone mass (PBM), it seems that the genes for collagen type 1 and vitamin D receptor have the major role (6). The other factors that cause low PBM include insufficient intake of calcium in childhood, low body weight, poor nutrition, delayed puberty, and insufficient physical activity (8,9).

Optimal treatment of fractures or bone defects requires the knowledge of complex cellular interactions involved in healing and remodeling of bone tissue. In addition, osteoclasts are important in this process because they play a key role in normal bone turnover and facilitate bone regeneration (10). Osteogenesis or ossification is a process in which bone tissue is formed. In the formation of bone tissue, osteogenic cells differentiate and develop into osteoblasts. According to osteoinduction principle, osteoblasts and formed bone tissue require corresponding base, a porous structure that enables three-dimensional penetration of bone tissue into the depth (11).

In general, osteogenesis involves two processes: a) the process of building bone tissue (osteoproduction) and b) degradation of bone tissue (osteo-reabsorption) (12). Building and degradation of bone tissue occur simultaneously. Synergistically and physiologically they are balanced processes, since both affect the formation and maintenance of the tissue homeostasis of skeletal system in accordance with functional requirements (Wolff's Law on Bone Transformation). During a lifespan, the skeletal system is subjected to continuous transformation in order to maintain its optimal function as the main supporting system in an adult organism. The balance between the processes of formation and degradation of bone tissue is variable and manifested in physiological and pathological processes. The disruption of physiological balance between these two processes is manifested in pathological osteogenesis where homeostasis of bone tissue is interrupted, regardless of the cause (osteoarthritis or osteoporosis). During embryonic development and growth of skeletal system, osteoproduction dominates and bone tissue mass is increased. Anatomical norm, i.e. the form and size of bones, is achieved in the formation phase during which the intensity of osteoproduction declines. Significant regeneration power of bone tissue appears in the healing process of bone fracture (13).

During embryonic development, the bones are developed from embryonic connective tissue. The organization and morphology of skeleton during the development are determined by a series of programmed and induced processes. The bones achieve normal anatomical size and form around the age of twenty. At that time, the proliferation of chondrocytes stops in the epiphyseal cartilage area which is closer to epiphysis, and the ossification on the diaphyseal side continues until disappearance of the epiphyseal cartilage. This results in synostosis between epiphysis and diaphysis and it marks cessation of bone growth in length. After the end of bone formation, life-long remodeling begins. Remodeling

is the response of bone tissue to biomechanical and metabolic demands of organism in order to maintain the homeostasis of skeletal system. The physiological remodeling takes place during the healing of microscopic damage sites of bone tissue. These damage sites (about 500 μm in diameter) occur during normal physical activity and they are considered as a physiological phenomenon (13).

When the biomechanical conditions are altered, as in the case of the change of direction of transmission of bone forces, their form and size may change, and they are specific for each bone. The formation of bones, in physiological conditions, is limited to the periods of embryonic development and postnatal life, and it ends in the third decade of life. During the remodeling, the quantity of bone tissue is not changed, instead, the existing bone mass is rearranged. About 25% of cancellous bone tissue and 3% of compact bone tissue remodel per year (14). The purpose of bone remodeling is the adaptation of skeletal system to biomechanical circumstances throughout life, with the minimal quantity of bone material. If the strength of skeletal system depended on the increase of bone mass, the massive skeletal system would represent a burden to the organism. It is established that the fragility of neck of the femur in elderly women is not a consequence of bone mass loss but of inadequate remodeling of the existing bone mass (15).

MicroRNAs (miRNA) are a class of small, endogenous, non-coding, single stranded RNAs. miRNAs are included in several developmental events during the embryogenesis and tissue homeostasis in adults. Epigenetically, miRNAs control gene expression through post-transcriptional regulation. Because the homeostasis of bone tissue is maintained through dynamic balance between osteoclast bone resorption and osteoblast bone formation, miRNAs are also important regulators of these processes. miRNAs may regulate osteogenesis and osteoclastogenesis positively or negatively, that is, miRNAs, target genes, intracellular effectors, and transcription factors affect homeostatic processes in bones (16).

NUTRITIONAL ASPECTS

Regarding the nutritional management of bone tissue diseases, existing evidence indicate the importance of nutrition quality and regular physical activity in order to ensure sufficient intake of proteins, calcium and vitamin D, which affect the pathogenesis of these diseases (17,18). At each stage of life, the dietary intake of the main bone nutrients, including calcium, vitamin D, and proteins contributes to the muscle and bone health, thereby decreasing the risk of falls, osteoporosis, and fractures later in life (19).

There is evidence that proteins from food directly influence key regulators of proteins and growth factors included in muscle and bone growth, such as rapamycin in mammals (mTOR) and insulin-like growth factor-I (IGF-I). Branched chain amino acids lead to the activation of mTOR and aromatic amino acids (which are especially represented in milk proteins) and this further leads to increased IGF-I and results in greater muscle mass and strength (20,21). Daily protein intake is advised, and the quantities are similar for all adults, regardless of age; about 0,8 g of proteins per kilogram of body mass each day (g/kg BW/d) (or 46-52 g/d) (22,23). The protein intake that represents 17-21% of total daily calories is recommended among adults of all ages (24).

Distribution of protein intake during the day may be important, and 20-25 g of dietary proteins per serving is proposed to allow proper stimulation of muscle protein synthesis after meal, during the 24-hour period. The daily intake of proteins indirectly increases the level of circulating IGF-I, by improving renal production of 1,25(OH)2D3, which stimulates intestinal absorption of calcium and inorganic phosphate, and increases tubular reabsorption of inorganic phosphate. This indirectly affects bone mineralization. Dietary proteins influence muscle anabolism through amino acids and IGF-I and indirectly affect muscle mass and strength. It was found that protein energy supplementation reduces the functional decline in weak elderly people and improves their physical activity (25,26).

CLINICAL ASPECTS

Elderly people who have osteoporotic hip fracture are often malnourished, especially in terms of protein intake, and insufficient protein intake may contribute to the occurrence of hip fracture. In a study on elderly people with a recent osteoporotic hip

fracture, protein supplementation was associated with increased serum IGF-I, decrease of bone loss of the proximal part of the femur, and shorter stay in rehabilitation hospitals (27). In a systematic review and meta-analysis, a positive association was found between protein intake and BMD, mineral composition of bones, and reduction of bone resorption markers (28). There is evidence that diets rich in proteins and dairy products may help to reduce the loss of bone mass during weight loss. Proteins may help to preserve bone mass during weight loss by stimulating IGF-I and increasing intestinal calcium absorption (29).

Dietary protein intake is important for bones and muscles, and protein intake is in a positive correlation with muscle mass and BMD in elderly people. The favorable effect of dietary proteins seems to be enhanced by simultaneous intake of foods that are metabolized to alkaline residues, such as fruits and vegetables (30).

A positive link between intake of dairy proteins and appendicular bone mineralization and muscle mass was found in elderly women (aged 80-92 years) (31). Dairy products including milk, yogurt, and cheese may represent an excellent food source of bone nutrients, since they provide a rich supply of calcium, phosphorus, and high-quality proteins, with a relatively low cost (32,33).

Dairy products provide a package of essential nutrients and it is difficult to get those in low-dairy or dairy-free diets. For many people, it is impossible to achieve the recommended daily intake of calcium with dairy-free diets. The recommended consumption is 3 servings of dairy products daily (for example, 1 glass of milk, 1 serving of cheese, 1 yogurt), and this amount meets the recommended daily intake of calcium for general population. As for bone health, there is growing evidence that the effects of age-related or postmenopausal bone loss on the risk of fracture depend on the amount of bone mass achieved during childhood and adolescence. It has been shown that adequate dietary intake of calcium and proteins is required to achieve optimal bone mass during skeletal growth and to prevent the loss of bone mass in elderly people. Current European Guide on Osteoporosis contains nutritive recommendations for bone health, including at least 1000 mg/d of calcium and 800 IU/d of vitamin D. Available data show a positive association between dairy food intake and markers for bone health (i.e., bone mineral density and markers of bone remodeling) (34).

In spite of well-grounded benefits of dairy products for bone health, some people avoid these products in their diets due to the belief that dairy products may be harmful for health, especially in people having a problem with weight, indigestion, arthritis, or in people trying to prevent cancer. Bioavailability of calcium from milk is high. In some people, digestion of milk causes gastrointestinal symptoms due to relative lack of lactase enzyme and undigested lactose is fermented by the intestinal bacteria. Self-diagnosis of lactose intolerance is common and often incorrect. In fact, the degree of lactose tolerance varies, and drastic restrictions are usually not necessary. Yogurts containing dissolved lactose and hard cheese that does not contain lactose are second-best sources of dietary calcium. In addition, some meta-analyses led to the conclusion that the restriction of dairy product intake is not reliable to help with a weight loss program. The data suggest that the consumption of dairy products reduces body fat and preserves decreased body mass. Furthermore, recent data suggest that consumption of dairy products protects from the risk of overweight and obesity. Studies on dairy products and arthritis are rare, nevertheless, previous research showed that no psychopathological reason exist for the patients with osteoarthritis or rheumatoid arthritis to avoid consumption of dairy products. In relation to all of the above-mentioned indications, we may say that dairy product intake, in the recommended dose of 3 servings a day, is safe, practical, and approachable as part of balanced diet. Proven benefits of dairy products for bone health significantly outweigh the possible, but unproven undesirable consequences (35).

In young women, consuming milk proteins after resistance exercises improves their anabolism. In addition, consuming milk proteins after resistance exercises has a positive effect on body composition by promoting fat loss, gain or maintenance of lean mass, and bone preservation. Nevertheless, an increase of BMD measured by densitometry, also called dual-energy x-ray absorptiometry (DEXA), may appear as artifacts of the measurement method (36,37).

Cooper et al. conducted research on 900 pregnant women with a serum plasma 25-hydroxyvitamin D [25(OH)D] levels from 25-100 nmol/l at 12 weeks gestation. The pregnant women with similar base line levels of 25(OH)D were randomly assigned to group receiving 1000 international units (IU) cholecalciferol/d or group receiving placebo until delivery. 25(OH)D was measured at 14 and 34 weeks of gestation. At 34 weeks gestation, the women in the treated group had a higher mean value of 25(OH)D. The newborns were subjected to DEXA assessment of bone mass within 14 days from birth. The authors concluded that the prenatal supplement of 1000 IU/d of cholecalciferol reduces the prevalence of vitamin D insufficiency, and prevents gestational reduction of 25(OH)D in women who deliver in winter or spring (38).

Diet and exercise are important in preventing the reduction of muscles and bones. Vitamin D insufficiency is associated with reduced muscle performance and increased risks of fall, as well as increased rates of bone mass loss and fractures. Vitamin D plays a key role in the metabolism of calcium and phosphate and bone health. In the previous decade vitamin D was in focus of research, and besides its well-known role in calcium metabolism, the research revealed that the low levels of vitamin D are related to neurodegenerative disorders, cancer, altered glucose metabolism and cardiovascular diseases. The link between vitamin D and many non-skeletal disorders has directed the attention of researchers not only to elderly people, but also to younger population, which seems to show a low circulating levels of 25 (OH) D3 (39).

The supplementation caused an increase in myocyte cross-sectional area, through the activation of the vitamin D receptor in muscle tissue. In Europe, the recommended daily dose is 400 IU of vitamin D3 for people older than 65 years (40). Numerous epidemiological studies showed that vitamin D deficiency is present in over 50% of general population (41,42). A person can get smaller amount of vitamin D from low vitamin D food. However, for the most part, vitamin D is provided by synthesis from provitamin D (7-dehydrocholesterol) in the skin, under the influence of sunlight. With age, the content of 7-dehydrocholesterol in the skin is reduced, making elderly people dependent on regular vitamin D intake through supplements. This is required for the adequate intestinal absorption of calcium (from food or pills) and for the prevention of hypocalcemia and secondary hyperparathyroidism, which would inevitably lead to the loss of bone mass (3,6,13,16). In elderly people who have been regularly receiving vitamin D supplements, risk of fall and fracture is reduced, since vitamin D helps to maintain muscle strength and stability of walk (43).

CONCLUSION

Bone tissue is the major supporting tissue in human body, with a variety of dynamic functions, including movement, protection of internal organs, and hematopoiesis. During life, the skeletal system is a subject to continuous transformation in order to maintain the optimal function of the main supporting system in an adult organism. The balance between the processes of bone tissue formation and degradation is variable and is manifested in physiological and pathological processes. About 25% of cancellous bone substance and 3% of compact bone substance are remodeled per year. The purpose of bone remodeling is adjusting the morphology of skeletal system to biomechanical circumstances during a lifetime, with minimal quantity of bone material. A large number of studies indicate the importance of proper nutrition and regular physical activity, in order to ensure sufficient intake of proteins, calcium and vitamin D, aiming at the prevention of bone diseases. At each stage of life, adequate dietary intake of main bone nutrients contributes to muscle and bone health, thereby reducing the risk of falls, osteoporosis, and bone fracture.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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