REVIEW ARTICLE

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The influence of homocysteine on osteoporosis

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Abstract: *Osteoporosis is a major health problem, and the economic costs are expected to rise due to an increase in life expectancy throughout the world. Its major consequence is fractures, and especially hip fractures are associated with institutionalization and increased mortality. Homocysteine is an amino acid intermediate formed during the metabolism of methionine. Homocysteinuria is a rare autosomal recessive biochemical abnormality which causes elevated plasma concentrations of homocysteine and severe occlusive vascular disease. In patients with homocysteinuria, there is an increased prevalence of skeletal deformities, including osteoporosis, which is a primary risk factor for hip fracture. The high prevalence of osteoporosis among patients with homocysteinuria suggests that high levels of plasmatic homocysteine may also increase the risk of fractures. Nutritional factors such as vitamins B12, B6, and folate are cofactors in homocysteine metabolism, and vitamin intakes may inversely affect plasma homocysteine levels.*

Keywords: *osteoporosis, homocysteine, hip fracture*

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INTRODUCTION

Osteoporosis is a major health problem, and the economic burden is expected to rise due to an increase in life expectancy throughout the world. Its major consequence is fractures, and especially hip fractures are associated with institutionalization and increased mortality. The prevalence of osteoporosis increases with age due to an imbalance in the rate at which bone is removed and replaced during the bone remodeling cycle, which is an important physiological process that is essential for maintenance of a healthy skeleton.

Pharmacological interventions may prevent 30-60% of fractures in patients with osteoporosis. Common sites for osteoporotic fracture are the spine, hip, distal forearm and proximal humerus. The remaining lifetime probability in women at the menopause of a fracture at any one of these sites exceeds that of breast cancer (approximately 12%), and the likelihood of a fracture at any of these sites is 40% or more in developed countries [1].

The level of bone mass can be assessed with adequate precision by measuring bone mineral density using dual X-ray absorptiometry. It has

been suggested that bone strength may be reflected, independently of bone mineral density level, by ultrasonic measurements of bone and by measuring bone turnover using specific serum and urinary markers of bone formation and resorption.

Physical activity as a way to prevent osteoporosis is based on evidence that it can regulate bone maintenance and stimulate bone formation including the accumulation of mineral, in addition to strengthening muscles, improving balance, and thus reducing the overall risk of falls and fractures. It is well known the important influence of hormones as well as dietary and specific nutrient abundance on bone, growth and health is emphasized and premature bone loss associated with dietary restriction and estradiol withdrawal in exercise-induced amenorrhoea [2].

OSTEOPOROSIS

It is becoming increasingly clear that there is a relationship between growth and development in early childhood and bone health in old age. In fact, suboptimal bone development leads to a reduction in peak bone mass, and a higher risk of osteoporotic fracture later in life. Osteoporosis is a skeletal disorder characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility. Preventative strategies against osteoporosis can be aimed at either optimizing the peak bone mass obtained, or reducing the rate of bone loss.

One of the largest risk factors for fractures is a reduction in bone mineral density. Risk factors for fracture can be purely skeletal-related affecting bone mass, bone geometry, bone micro-architecture and bone turnover, or solely fall-related such as neuromuscular dysfunction, poor balance, cognitive impairment, cardiovascular instability, reduced visual acuity and sedative medications. Others risks are both skeletal and fall related such as age, genotype, and family history of fracture, weight, weight change and mobility [3]. Falls history is a further independent risk factor for fracture, in particular in men [4]. About 50% of white women and 20% of men will have an osteoporosis-related fracture in their lifetimes. Fractures of the hip and spine may be disabling and are associated with mortality rates that are about 20% greater than that of an age-matched population. The goal of any treatment for osteoporosis is to improve bone strength, thereby decreasing fracture risk.

Bone remodeling is the result of two opposite activities, the production of new bone matrix by osteoblasts and the destruction of old bone by osteoclasts. The rates of bone production and destruction can be evaluated either by measuring predominantly osteoblastic or osteoclastic enzyme activities or by assaying bone matrix components released in the bloodstream and excreted in the urine [5].

Factors which influence negatively the osteogenetic potential are age, nutrition diseases and endocrinopathy, ionized radiations treatments and different toxic factors. It has been scientifically proved the fact that elder patients have decreased general biological potential. Regarding the bone system, there occur structural changes which weaken the resistance, to which we can add a diminishing of the response potential towards harmful factors. These lacks are considered to belong to multiple causes: a diminishing of the vitamin D action and of calcitonin, hyperactivity of the parathyroid hormones with osteoblast inhibition, etc. [6] As a result, osteolysis-osteo-synthesis dynamics is reversed, resorbing processes become dominant: osteodystrophy, osteoporosis, senile osteopenia, metabolic and endocrine osteopathy, which, affecting the very bone structure, are the main causes of diminish in the osteogenic potential in elderly patients. Nutrition diseases and endocrinopathies seem to have the most harmful effects on osteogenesis and the repairing processes of the bone tissue.

The evaluation of biochemical markers of bone turnover has been useful in clinical research. However, the predictive factor of these

measurements is not defined clearly, and these findings should not be used as a replacement for bone density testing [7]. There is a high prevalence of calcium, protein and vitamin D insufficiency in the elderly. Calcium and vitamin D supplements decrease secondary hyperparathyroi-dism and reduce the risk of proximal femur fracture, particularly in the elderly living in nursing homes. Sufficient protein intakes are necessary to maintain the function of the musculoskeletal system, but they also decrease the complications that occur after an osteoporotic fracture.

HOMOCYSTEINE

Sulfur is the seventh most abundant element measurable in the human body and is supplied mainly by the intake of methionine, an indispensable amino acid found in plant and animal proteins. Inhibition of cystathionine-β-synthase activity causes the upstream sequestration of homocysteine and the downstream drop in cysteine and glutathione [8]. Homocysteine is an aminoacid which contains a thiol group formed by methionine intracellular demethylation (alpha amino gama methylthio butyric). In plasma, homocysteine is found free in oxidized or disulphidic form, linked to proteins. Homocysteine has two ways to be metabolised, a metabolic path is represented by transsulfuration to cysteine through cystatin synthetasis, enzymes which need vitamin B6 as co-factor (proving the need of vitamin B6 administration during the treatment). Synthesis of cysteine as a product of the transsulfuration pathway can be viewed as part of methionine or homocysteine degradation, with cysteine being the vehicle for sulfur conversion to end products (sulfate, taurine) that can be excreted in the urine. Transsulfuration of homocysteine to cysteine is catalyzed by two pyridoxal 5′-phosphate-dependent enzymes, cystathionine β-synthase and cystathionine γ-lyase. The transsulfuration pathway is responsible for catabolism of the carbon chain of methionine, release of the amino nitrogen in a form that can be funneled into pathways of nitrogen excretion, and transfer of Met sulfur to serine to synthesize cysteine [9].

Another metabolic path is remethylation to methionine in the presence of methylentetra-hydrofolate reductase (MTHFR) and methionine synthesis in the presence of folic acid as an under layer for vitamin B12 as co-enzyme (proving the need of folic acid and vitamin B12 administration during the treatment). There are studies which proved that the level of homocysteine in blood is inversely proportional with folate levels, vitamin B12, vitamin B6 and oxygen intake induced by these vitamins [10].

Homocysteinuria is a rare autosomal recessive biochemical abnormality which causes elevated plasma concentrations of homocysteine and severe occlusive vascular disease. In patients with homocysteinuria, there is an increased prevalence of skeletal deformities, including osteoporosis, which is a primary risk factor for hip fracture. Blood levels of total homocysteine increase throughout life in men and women. Prior to puberty, both sexes enjoy optimally healthy levels (6 µmol/L). During puberty, levels rise, more in males than women, reaching, on average, almost 10 µmol/L in men and more than 8 µmol/L in women. As we age, mean values of homocysteine continue to rise and the concentrations usually remain lower in women than in men. Adults without homocysteinuria who have high homocysteine levels are also at risk for fractures. Thus, elevated plasma homocysteine concentrations (>14 µmol/L) are associated with osteoporosis and may increase the risk of hip fracture, in both men and women. These can lead to substantial disability, high medical costs, and death [11]. Elevated plasma homocysteine concentrations are associated with reduced physical performance and muscle strength in older women [12].

Hyperhomocysteinemia may contribute to the development of osteoporosis. High hyper-homocysteine and low vitamin B12 concentrations were significantly associated with low bone turnover markers, high markers of bone turnover, and increased fracture risk [13]. Folate and vitamins B12 and B6 are major determinants of homocysteine concentrations in older persons [14]. The B vitamins folate, B12, and B6 are important cofactors in homocysteine metabolism, and low status of these

nutrients is the primary determinant of elevated plasma homocysteine concentrations in elders. Patients with pernicious anemia have decreased bone mineral density at the lumbar spine, and in comparison with the general population they have almost double the risk of hip fracture. Gene polymorphisms related to homocysteine metabolism also may result in high homocysteine levels. Thus, nutritional factors such as B12/folate deficiency and genetic factors may affect homocysteine levels and contribute to fracture risk.

Hyperhomocysteinemia is regarded as a risk factor for ischemic stroke and for hip fractures in Parkinson's disease patients receiving levodopa [15]. The high prevalence of osteoporosis among patients with homocysteinuria suggests that hyperhomocysteine may also increase the risk of fractures [16]. Higher plasma levels of total homocysteine and folate were independent predictors of coronary heart disease [17]. In the Framingham study authors had shown that plasma total homocysteine concentration is inversely related to the intake and plasma levels of folate and vitamin B6 as well as vitamin B12 plasma levels. Almost two-thirds of the prevalence of high homocysteine is attributable to low vitamin status or intake. Elevated homocysteine concentrations in plasma are a risk factor for prevalence of extracranial carotid artery stenosis of at least 25% in both men and women [18]. Some researchers want to determine if there is a possibility that plasma total homocysteine may serve as an indicator of the status and perhaps the intake of a number of vitamins, including folic acid, vitamin B12, and vitamin B6. This possibility derived from the large number of studies that implied that methionine metabolism is tightly regulated and from other studies that showed that deficiencies in the above vitamins are often associated with hyper-homocysteinemia.

It was shown that premenopausal women have lower homocysteine levels than men and postmenopausal women. Higher plasma levels of total homocysteine concentrations in men than in women may be explained by differences in muscle mass, hormone and vitamin status [19]. Factors that influence total homocysteine plasma levels in the general population include diet, in particular folate intake, blood levels of folate, vitamin B12, and betaine, renal function, and the MTHFR 677C>T polymorphism [20]. There are studies to establish that increasing evidence that plasma total homocysteine is inversely associated with bone health. It has been speculated that moderately elevated total homocysteine levels could contribute to osteoporotic changes, based on the fact that osteoporosis is a common phenomenon in homocysteinuria. High total homocysteine and low vitamin B12 concentrations are significantly associated with high levels of markers of bone turnover, and relations have been reported between total homocysteine and markers of bone resorption [13].

Elevated plasma total homocysteine, deficiencies of folate and vitamin B12 are associated with risk of osteoporosis and fracture. In some studies, there were examined whether plasma levels of elevated plasma total homocysteine, folate, and vitamin B12 predicted hip fracture [21]. They found that elevated plasma total homocysteine is a predictor for hip fracture among elderly men and women.

CONCLUSION

In patients with homocysteinuria, there is an increased prevalence of skeletal deformities, including osteoporosis, which is a primary risk factor for hip fracture. The high prevalence of osteoporosis among patients with homocysteinuria suggests that hyperhomocysteine may also increase the risk of fractures. Nutritional factors such as vitamins B12, B6, and folate are cofactors in homocysteine metabolism, and vitamin intakes may inversely affect plasma homocysteine levels.

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