Research Progress on the Influence of Mediterranean Diet Pattern on Osteoporosis in the Elderly

Linjue Yan *

Faculty of Chinese Medicine, Macau University of Science and Technology, Macau, 999078, China

* Corresponding Author Email: 1220011278@student.must.edu.mo

Abstract. The Mediterranean diet (MD) refers to the dietary habits of southern European countries located on the Mediterranean coast. It is rich in various nutrients necessary for the human body and is a healthy dietary model. The research determined that the prevalence of osteoporosis (OP) among Mediterranean coastal nations is notably low, underscoring the significance of investigating the underlying principles and impact of this dietary pattern on skeletal health. Nowadays, a multitude of investigations are being conducted to assess the impact of individual nutrient components on OP, but the research of comprehensively coordinating various nutrient elements and considering the actual situation in different regions is still insufficient. In this paper, the factors that are easy to induce OP are paired with various rich nutrient elements in MD one by one to provide a new way for the prevention and treatment of OP. Applying the research results of MD to other countries and regions to prevent OP is an effective way to reduce the incidence of this disease in the future.

Keywords: Mediterranean diet; osteoporosis; nutrient; fracture.

1. Introduction

Osteoporosis (OP) is a common systemic metabolic bone disease, which is mainly characterized by decreased bone mass, bone microstructure damage, bone strength decline, resulting in increased bone fragility and prone to fracture [1]. A meta-analysis showed that the prevalence of OP among the elderly aged 60 years and older in China was as high as 37.7%, and increased with age, making it a major global public health problem. Understanding the risk factors of OP is essential for prevention and treatment.

The etiology of OP in the elderly is very complex. Recent studies believe that the emergence and progression of OP are intricately linked to gender, age, genetics, race, region, national culture and additional contributing factors, but it is difficult to intervene in these uncontrollable factors. The controllable factors such as diet, nutrition, exercise and living habits can be intervened artificially. Although OP cannot be cured, active and effective prevention can delay the occurrence and development of OP. Especially in dietary nutrition, a healthy dietary pattern is particularly important for the prevention of OP. Research has demonstrated that nations characterized by a predominant Mediterranean diet (MD) exhibit a reduced prevalence of OP. MD is a dietary style that focuses on eating a large number of fruits, vegetables, beans, extra virgin olive oil, whole grains and fish [2]. This dietary pattern is characterized by high protein and high unsaturated fatty acids, and also contains a series of complex nutritional elements and bioactive phytochemicals with anti-inflammatory, antioxidant and alkalinization properties [3].

In the past, there were many literatures on the effect of individual nutrient elements on OP, but few literatures on the synergy of various foods. This article reviews the prevention principle and clinical research progress of MD on OP in the elderly, and provides new ideas for the prevention and treatment of OP.

2. Positive Effects of Nutritional Elements in MD on Bone Mass

Bone mass is one of the important criteria to measure bone strength, and the reduction of bone mass is the most direct factor to induce OP. Based on the diverse nutritional elements in the MD, this

paper mainly discusses the positive effects of high protein, phenolic compounds, rich vitamins and ω -3 polyunsaturated fatty acids (omega-3PUFAs) on bone mass.

2.1. High Protein in MD Can Provide Osteogenic Raw Materials and Reduce Bone Resorption

The protein in MD mainly comes from the animal protein of fish and seafood and the plant protein of beans and whole grains. Eating a large number of beans and whole grains is the main characteristic of MD [4]. Protein accounts for half of bone volume. Collagen and various non collagens constitute the organic matter of bone. Therefore, appropriate dietary protein intake is essential to maintain and increase adult bone mass. Investigations have revealed a correlation between protein consumption and bone resorption indicators: a minimal intake of dietary protein correlates with elevated urinary excretion of deoxypyridinoline, conversely, an ample protein intake is linked to diminished excretion levels of urinary N-terminal peptide. Protein can not only provide necessary amino acid precursor raw materials for the synthesis and maintenance of bone structure, but also increase the secretion of insulin-like growth factor (IGF-I) to stimulate bone formation [5]. IGF-I is generally considered as an osteotrophic factor, which is involved in the synthesis of calcitriol, inhibits parathyroid hormone, increases the renal reabsorption rate of phosphate, reduces bone resorption and increases intestinal calcium absorption [6]. The protein component of olive oil within the MD fosters osteogenesis, as it enhances the differentiation of osteoblasts from mesenchymal stem cells in bone marrow and concurrently curbs the proliferation of adipocytes. Moreover, the rich vegetables and fruits in MD contain more potassium and organic anions, which can form an alkaline environment, thus reducing the acid load brought by dietary high protein to reduce bone turnover [5]. Based on the above research, it is speculated that MD can not only provide a large number of raw materials for bone formation, but also slow down bone loss and stimulate osteoblast proliferation and differentiation through the synergistic effect of various nutrient elements, so as to achieve the purpose of preventing OP.

2.2. Phenolic Compounds in MD Can Regulate Bone Turnover

Olive oil, beans and various vegetables and fruits in MD contain a rich variety of phenolic compounds. Phenolic compounds can regulate the proliferation ability and maturity of osteoblasts by increasing alkaline phosphatase activity and the deposition of calcium ions in the extracellular matrix [6]. The mechanism also includes inhibiting bone resorption, stimulating the signal pathway of osteocyte growth and differentiation, regulating the expression of bone formation transcription factors (TFs), and reducing oxidative stress and inflammation [7]. Phenolic compounds are compounds formed by many substances, including simple phenolic substances, such as hydroxytyrosol, tyrosol, etc; Compounds like luteolin and apigenin, classified as flavonoids, along with more intricate substances, including those derived from oleuropein and flavonoid glycosides, etc., are noteworthy in this context.

2.2.1. Hydroxytyrosol olive

The MD is predominantly characterized by the use of oil, with olive oil constituting a significant portion of the dietary fat intake, ranging from one-third to two-thirds in the region's residents. It is a food source of a variety of phenolic compounds, among which hydroxytyrosol is one of the most effective anti-oxidants in olive oil. Hagiwara et al showed that 10-100 mmol/l hydroxytyrosol stimulated calcium deposition, and 50-100 mmol/l hydroxytyrosol inhibited the formation of multinucleated osteoclasts. Hydroxytyrosol can effectively reduce the level of hydrogen peroxide in mouse embryonic osteoblast precursor cells, while hydrogen peroxide can inhibit differentiation markers (such as alkaline phosphatase activity), type I collagen gene expression and osteoblast mineralization [8]. Based on the above research, it is speculated that hydroxytyrosol in MD can regulate the proliferation ability and maturity of osteoblasts, regulate the signaling pathways related to bone metabolism, and help slow down the progression of OP.

2.2.2. Flavonoids

In MD, soybeans and bean products (45%), tea and coffee (25%), nuts (10%), rice and cereals (5%) are the main dietary sources of isoflavones in the flavonoid subclass, in which soybeans contain about 0.2-1.6 mg of isoflavones per gram of dry weight [9]. Some studies have found that soy isoflavones exhibit weak estrogen effect by binding to estrogen receptors. Akhlaghi et al. [10] believed that soybean and soybean isoflavones were protective compounds against estrogen deficiency. Luteolin, a flavonoid present in Mediterranean extra virgin olive oil, has the capacity to prevent the differentiation of bone marrow monocytes and RAW264.7 macrophages into osteoclasts, as well as to suppress the bone resorptive activity of these osteoclasts. This research suggests that the consumption of flavonoids within the MD is intricately linked to an increase in bone mineral density and a decrease in the risk of OP.

2.2.3. Other polyphenols

The formation process of osteoblasts includes proliferation, extracellular matrix synthesis, maturation and mineralization. Each stage is regulated by the coordinated expression of major TFs, the most important of which are Runx2 Osterix, β-catenin, Activating TF 4 and activator protein 1 [10]. Oleuropein, a dietary component in MD, is a schizophylene ether polyphenol that can increase Runx2 Osterix. The expression of type I collagen, osteocalcin and alkaline phosphatase shows that oleuropein can promote the formation of osteoblasts at the early and late stages of differentiation, which is conducive to bone protection and repair [6], and further shows that it is beneficial in the prevention and treatment of OP.

2.3. The Rich Vitamins in MD Can Mediate Calcium Transport and Reduce Oxidative Stress

Moderate consumption of fish is also a feature of MD. The consumption of fish constitutes 87% of the overall vitamin D intake from food sources in the diet of Spain. Soybean in MD is similar to natto in Japan, which contains a large amount of vitamin K, while other vegetables, fruits and cereals are the main sources of vitamin C, vitamin B, vitamin A, etc. in the diet. Casado, et al. believed that oxidative stress would promote the differentiation of mesenchymal stem cells into adipocytes and inhibit the formation of osteoblasts [11]. Antioxidant vitamins can reduce oxidative stress by scavenging free radicals to prevent OP and its complications. It is axiomatic that vitamin D plays a crucial role in skeletal health. Upon binding to the vitamin D receptor gene, its action is mediated through both genomic and non-genomic mechanisms. Vitamin D is first converted into 25 hydroxyvitamin D (25-OHD), and then into vitamin 1, 25 dihydroxyvitamin D3 [1, 25- (OH) 2D3]. 1, 25- (OH) 2D3 serves as the principal stimulant for enhancing calcium absorption within the small intestine. This process induces alterations in the architecture and functionality of the small intestinal epithelium, thereby facilitating the translocation of bioavailable calcium across the intestinal lining and augmenting the uptake of dietary calcium. Areco, et al. believed that 1, 25- (OH) 2D3 could significantly increase the mRNA levels of Claudin-2 and claudin-12 in Caco-2 cells [12]. Jennings, et, al. conducted a one-year intervention of the MD and vitamin D 3 supplement (10 μ g/d) on subjects through a randomized controlled trial, which significantly reduced the bone loss of femoral neck in OP patients [13]. Studies have shown that vitamin K is a substance dependent on osteocalcin, matrix Gla protein, and protein-S. It can inhibit the NF-κB receptor activator (RANK)-NF-κB receptor activator ligand (RANKL) pathway, thereby inhibiting osteoclast activity and differentiation regulation to reduce bone resorption [14]. Vitamin K is a γ - carboxylase cofactor that can convert uncarboxylated osteocalcin to carboxylated osteocalcin. Osteocalcin is a calcium binding protein in bone in the γ - carboxylated state, which can effectively combine calcium with bone hydroxyapatite crystals [14]. These studies showed that the abundant vitamins in MD were beneficial to prevent OP and fracture complications.

2.4. Positive Effects of Omega-3 Polyunsaturated Fatty Acids in MD on Bone Metabolism

The Mediterranean region is one of the regions with the highest average consumption of fish and seafood in Europe. Fish is the main source of Omega-3 Polyunsaturated Fatty Acids (ω-3PUFAs), eicosapntemacnioc acid and docosahexaenoic acid. The content of the above substances in marine fish is higher than that in freshwater fish [15]. Over the past few decades, an extensive body of research has demonstrated that ω-3PUFAs exert a beneficial influence on bone metabolism and contribute to the mitigation of hip fracture risk. These fatty acids are capable of suppressing the proliferation and activation of osteoclasts. Intakes of dietary ω-3PUFAs can diminish the expression levels of inflammatory cytokines, such as interleukin-1, interleukin-6, and tumor necrosis factor, which in turn lessens the synthesis of prostaglandin E2. This reduction consequently leads to a decrease in the production of insulin-like growth factors that are known to promote osteoclast differentiation. Secondly, ω-3PUFAs can regulate calcium balance by increasing calcium absorption and reducing urinary calcium excretion, andω-3PUFAs promote osteoblast differentiation by enhancing the expression of key TFs [16]. Dietary omega-3pufas can promote the differentiation of preosteoblasts into mature osteoblasts by up regulating the expression of IGF-I, IGF binding protein and TGF-b1, and reducing the expression of peroxisome proliferator activated receptor γ. Based on the above research, it is speculated that ω-3PUFAs can work with other nutrients in MD to reduce the cellular inflammatory response, promote the absorption of raw materials required for bone formation and enhance the expression of osteogenic TFs with the aim of augmenting bone mass and diminishing the likelihood of OP.

3. Positive Effect of MD on Bone Mineral Density

The correlation between a substantial dietary intake of green and dark yellow vegetables, mushrooms, fish, shellfish, and fruits and bone mineral density is positive, with the daily ingestion of vegetables alone contributing to a 1% enhancement in bone mineral density.

Perez Rey, et al evaluated bone mineral density in 422 Spanish premenopausal women and showed that total bone mineral density, trabecular bone mineral density and cortical bone mineral density were positively correlated with more stringent MD [17]. Lavado Garcia, et al. showed in a Spanish study that dietary intake of omega-3pufas was positively correlated with hip and lumbar spine bone mineral density in healthy and OP women [15]. The whole-body bone mineral density of women with high seafood intake (>250 g/ week) was significantly higher than that of women with low seafood intake (<250 g/ week). Fujita, et al. found that in 1662 older Japanese men, increased intake of soy products was significantly associated with increased bone mineral density in the hip and femoral neck [18]. Data from the South Korean National Health and Nutrition Examination Survey indicates that a dietary pattern akin to the MD, characterized by the consumption of "dairy products and fruits," is associated with a 53% reduction in the risk of lumbar OP. Hardcastle, et al. found in a study of Scottish perimenopausal women that flavonoid intake was positively correlated with spine and femoral neck bone mineral density, and negatively correlated with bone resorption markers [19]. A Korean survey showed that among men, adherence to the dietary pattern of "fruit, milk and whole grains" reduced the risk of OP by 64%. Investigations have demonstrated that a daily intake of 250 mg of polyphenol-rich Mediterranean olive oil over a 12-month period in patients with osteoporosis (OP) can markedly enhance serum osteocalcin levels and maintain the bone mineral density of the lumbar spine. Based on the above research, it is presumed that the dietary pattern of MD can reduce the risk of OP to a certain extent.

4. The Influence of MD on Fracture of OP Complications

The common complications of OP are lumbosacral pain, shortened length, kyphosis, and fragility fractures. Osteoporotic fragility fractures represent the predominant and severe consequence of the

disease, predominantly manifesting as forearm fractures and vertebral compressions, with hip fractures being recognized as the gravest among them.

A comprehensive study conducted by showed that the risk of hip and total fractures increased by 2.6 times and 1.6 times respectively for each standard deviation reduction in bone mineral density [20]. Benetou, et al. found that strict adherence to MD could reduce the incidence of hip fracture by 7%, especially for male participants older than 60 years old, through an adult cohort study of 188795 participants from eight European countries [21]. A prospective study of 144580 postmenopausal women found that high protein intake was associated with a lower risk of hip fracture and forearm fracture [22]. Langsetmo, et al. carried out a study on osteoporotic fractures in men [23]. In a study encompassing 5875 male participants with an average age of 73.6 years, they assessed the "impact of protein on fragility fractures" and yielded comparable outcomes. The research indicated that the annual incidence rate of hip fractures among individuals in the group with the highest protein consumption was 2.91 cases per 1000 individuals, whereas for those in the group with the lowest protein consumption, the rate was 5.27 per 1000 individuals. It was observed that an elevated total protein intake corresponded to greater total bone mineral density at the hip and a reduced risk of fractures. The women's Health Initiative of the National Institutes of health released in 2016 found that the Mediterranean diet reduced the risk of hip fracture in women by 20%, but not all fragile fractures [24]. A large longitudinal prospective cohort study of the European Prospective Investigation into Cancer investigated 25450 subjects and found that strict adherence to MD could reduce the total incidence of hip fracture by at least 20% [25].

Most studies have shown that the nutritional elements in MD have a preventive effect on preventing some fractures caused by OP, especially hip fractures. However, due to the regional differences in these experimental studies, and only a certain nutrient element was studied separately, the intake of other nutrient elements in daily diet was not strictly controlled during the period, and most of them were horizontal studies, lacking a return visit, so it is difficult to get the results, and further experiments are needed to prove this result.

5. Conclusion

OP impacts not merely the daily activities and life quality of the aged population, but also exacerbates the economic strain on the nation, requiring extensive and expensive medical care, and diet to prevent OP will become a simpler method. In contemporary times, MD is increasingly recognized not just as a prevalent dietary pattern but also as a holistic lifestyle approach, because it focuses on the overall type of diet rather than the intake of a single nutrient element. The MD can not only produce synergy between the various nutrient elements, but also reduce the risk of excessive intake of other nutrient elements. According to the effects of various nutrient elements in MD on osteogenesis, bone resorption, related signaling pathways and gene expression, and based on the analysis of various experimental data, it is presumed that MD may prevent the occurrence of OP and its complications.

However, the nationality, region and age span of the research objects in these test data are large, the research on nutrient elements is not concentrated, the joint action mechanism of them is not clear, and the differences of food sources for obtaining the same nutrient elements in different regions are not taken into account. In order to allow residents of more countries to share the fruits of the Mediterranean diet, we must improve it on the basis of MD and in combination with the national conditions of various countries, and find substitutes for some regional specialty foods. Therefore, it is also necessary to further study the differential application of MD in different regions, and find out various new dietary patterns based on MD suitable for different nationalities and regions, so as to realize the maximum value of MD for the prevention and treatment of OP.

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