Nutrición Hospitalaria

Nutr Hosp. 2014;29(5):989-996
ISSN 0212-1611 • CODEN NUHOEQ
S.V.R. 318

Revisión

Adherence to Mediterranean diet and bone health

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Abstract

Introduction: **Several studies have concluded that incidences of osteoporosis and osteoporosis-related fractures vary across the European Union, the lowest incidence being reported in the Mediterranean area. The beneficial effect is mainly attributed to a specific eating pattern. The Mediterranean diet contain a complex array of naturally occurring bioactive molecules with antioxidant, anti-inflammatory and alkalinising properties that may contribute to the bone-sparing effect of the Mediterranean diet.**

Objective: **The purpose of this review is to examine the evidence to date on the effects of Mediterranean diet on bone health.**

Methods: **The search for articles came from extensive research in the following databases: PubMed, Scopus and Web of Science. We used the search terms "Mediterranean diet", "adherence", "fruit and vegetable", "olive oil", "fish" "legume", "cereal" "alcohol", "bone", "osteoporosis", "fracture", and combinations, such as "Mediterranean diet and bone" or "Mediterranean diet and fracture".**

Results: **A limited number of studies have examined the relationship between Mediterranean Diet and bone health, and they have reported conflicting results. On the one hand, adherence to a traditional MeDi has been associated with higher bone mineral density and lower fracture risk. The results of these studies could be attributed to the combined beneficial effects of individual components of the Mediterranean diet. On the contrary, several studies failed to show any association between adherence to the MeDi and indices of bone mass.**

Conclusions: **Further large-scale studies are required to clarify the effect of Mediterranean diet on bone health, in order to establish the role of this diet in the prevention of osteoporosis.**

(*Nutr Hosp.* 2014;29:989-996)

DOI:10.3305/nh.2014.29.5.7332

Key words: *Mediterranean diet. Osteoporosis. Bone.*

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Recibido: 7-II-2014.
1.ª Revisión: 11-II-2014.
Aceptado: 12-III-2014.

ADHERENCIA A LA DIETA MEDITERRÁNEA Y SALUD ÓSEA

Resumen

Introducción: **Se han encontrado diferencias en los valores de incidencia de osteoporosis y fracturas relacionadas entre los países de la Unión Europea, siendo menor en los países de la zona mediterránea. Este hecho se atribuye principalmente a un patrón de alimentación específica común. La dieta mediterránea contiene un complejo conjunto de componentes bioactivos con propiedades antioxidantes, anti-inflamatorias y alcalinizantes que pueden contribuir al efecto de esta dieta en la salud ósea.**

Objetivo: **El propósito de esta revisión es examinar la evidencia hasta la fecha sobre los efectos de la dieta mediterránea sobre la salud ósea.**

Métodos: **Se realizó una búsqueda en la literatura científica utilizando las siguientes base de datos: PubMed, Scopus and Web of Science. Utilizamos los términos de búsqueda "Dieta Mediterránea", "adhesión", "frutas y verduras", "aceite de oliva", "pescado" "legumbres", "cereal", "alcohol", "hueso", "osteoporosis","fractura", y combinaciones, como "Dieta Mediterránea y el hueso" o "Dieta mediterránea y fracturas".**

Resultados: **Existe un número limitado de estudios que analicen la relación entre el seguimiento de la Dieta Mediterránea y la salud ósea, mostrando resultados contradictorios. Diversos trabajos han mostrado que la adherencia a una dieta mediterránea tradicional se asociado con una mayor densidad mineral ósea y un menor riesgo de fractura en población adulta. Los resultados de estos estudios podrían atribuirse a un efecto beneficioso combinado de los componentes individuales de la dieta mediterránea. Por el contrario, en otros trabajos no se ha encontrado ninguna asociación entre la adherencia a la dieta mediterránea y los índices de masa ósea.**

Conclusiones: **Se requieren más estudios a gran escala para aclarar el efecto de la dieta mediterránea sobre la salud ósea, con el fin de establecer el papel de la dieta en la prevención de la osteoporosis.**

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Palabras clave: *Dieta mediterránea. Osteoporosis. Hueso.*

Introduction

Osteoporosis (OP) is an important worldwide public health concern[1] that affects many millions of people around the world and that will take on increasing significance as people live longer and the world s population continues to increase in number[2]. In addition, osteoporosis related fractures are one of the leading causes of significant morbidity and disability in elderly patients and increases the economic burden on the health care system.The mechanisms involved in osteoporosis pathogenesis are not fully understood[3]. A reduction in bone density in earlier life is likely to increase the risk of OP and its sequelae in adulthood. It is therefore important to raise awareness among the general population on the need to form and maintain good bone health from childhood through the adoption of healthy habits. OP development is influenced by multiple factors. Bone modelling and remodelling processes are governed not only by heritable traits but also by nutritional, mechanical and hormonal factors[4]. Besides the aging process, an inadequate diet and sedentary lifestyle can reduce mineralization.

Although nutrition is only one of the many factors that influence bone mass and fragility fractures, it is of particular importance to bone health because it is modifiable. Diet can be modified for the maintenance and development of bone mass. Proper nutrient intake has a crucial role in both prevention and treatment of osteoporosis[5]. The most relevant nutrients to bone health are calcium and phosphorus because they compose roughly 80% to 90% of the mineral content of bone hydroxyapatite; protein is essential because it is incorporated into the organic matrix of bone for collagen structure upon which mineralization occurs; trace elements, and vitamins (e.g., vitamins D and K) are also crucial in carrying out metabolic processes and reactions in bone[6,7]. Other benefits on bone metabolism derives from bioactive components found basically in vegetables but also some herbs and fruit. Phytochemicals, antioxidants, and other bioactive compounds influence bone metabolism through a variety of mechanisms mainly in reducing oxidative stress and inflammation[8].

To date, the most consistently followed approach to examine the potential relation between dietary factors and skeletal health was based on particular nutrients such as calcium and vitamin D[3]. However, people do not eat isolated nutrients but meals consisting of a variety of foods with complex combinations of nutrients and bioactive components. The traditional analysis considering the effect of a few isolated nutrients on bone health misses a lot of information regarding complex or cumulative correlations and interactions between these compounds contained in food. For this reason, there is an increasing interest in the study of dietary patterns that could answer some questions and promote the development of appropriate recommendations for overall dietary habits[9] .

Several studies have concluded that incidences of osteoporosis and osteoporosis-related fractures vary across the European Union. Conspicuous differences are encountered in the severity of osteoporosis, the lowest incidence being reported in the Mediterranean area[10]. The beneficial effect is mainly attributed to a specific eating pattern. The Mediterranean diet (MeDi) key characteristics are high intake of vegetables, legumes, fruits and cereals; moderate to high intake of fish; low intake of saturated lipids and high intake of unsaturated lipids, particulary olive oil; low to moderate intake of dairy products, low intake of meat; and modest intake of ethanol, mostly in the form of wine[11,12]. The Mediterranean diet was introduced to the scientific community by the classic Seven Countries study. Since then data on the association between this diet and cardiovascular disease[13,14], cancer and other chronic diseases have been accumulating[15,16]. However, a limited number of cross-sectional studies have examined the relationship between Mediterranean diet adherence and bone health, and they have reported conflicting results. Therefore, the purpose of this review is to examine the evidence to date on the effects of Mediterranean diet on bone health.

Methods

The search for articles came from extensive research in the following databases: PubMed, Scopus and Web of Science. We used the search terms “Mediterranean diet”, “adherence”, “fruit and vegetable“, “olive oil“, “fish” “legume”, “cereal” “alcohol”, “bone”, “osteoporosis”, “fracture”, and combinations, such as “Mediterranean diet and bone” or “Mediterranean diet and fracture”. The titles and abstracts of the located documents were initially reviewed and the reference lists of selected papers were searched to identify additional articles. We narrowed the search to studies published in English. Additional publications were identified from references provided in original papers.

Results and discussion

Adherence to Mediterranean diet and bone health

The Mediterranean diet is characterized by a high intake of olive oil, plant products, fish and seafood; a low intake of dairies, meat and meat products; and a moderate ethanol intake[15]. These food items contain a complex array of naturally occurring bioactive molecules with antioxidant, anti-inflammatory and alkalinising properties that may contribute to the bone-sparing effect of the Mediterranean diet[10].

Adherence to a dietary pattern close to the Mediterranean diet, have shown to prevent bone disease. Eating habits based on fruit, vegetables, milk, and cereals –that is, similar to those of the Mediterranean

diet– were proven by the Framingham study to be significantly associated with greater bone mass[17]. Nakashima and Takayanagi[18] studied associations between dietary patterns and bone mineral density in Japanese farmwomen and showed that a "healthy" pattern, described by high intakes of green and dark yellow vegetables, mushrooms, fish and shellfish, and fruit, was positively related to bone mineral density. Furthermore, the effect of vegetarian dietary patterns on skeletal health has been studied; lacto-ovo vegetarians appear to have normal bone mass when compared with omnivores. However, a more recent study reported that the scientific findings support the hypothesis that vegans do have lower bone mineral density than their nonvegan counterparts[19].

There are few studies that have assessed the effect of the Mediterranean diet on bone health. Besides, the impact of MeDi adherence on bone health remains unclear. In table I are summarized the characteristics of these studies included in relation to where the work was conducted, the number of participants in each study, the methods used to evaluate Mediterranean diet adherence, and the main results. Kontogianni et al.[20] described that adherence to a Mediterranean diet evaluated through a Mediterranean Diet Score was not associated with bone mass rates in a sample of adult Greek women, whereas adherence to a dietary pattern close to the Mediterranean diet, i.e., high consumption of fish and olive oil and low red meat intakes, was positively related to bone mass, suggesting the potential bone-preserving properties of this pattern through adult life. An interventional study conducted in Spain[21], concluded that a Mediterranean dietary pattern enriched with mixed nuts, does not seem to have any significant effect on bone metabolism in elderly subjects. However the authors pointed out that the sample selection criteria could limit the extrapolation of the findings, as the endpoint of the study was cardiovascular mortality, so the study focused on subjects with a high risk of cardiovascular disease and had already been eating a reasonably good Mediterranean diet pattern for a long time before randomization into the trial[21]. Recently, Rivas and coworkers[22] hypothesized that adherence to the Mediterranean diet measured as a Mediterranean diet score (MDS) has a beneficial effect on bone mineral density in the calcaneus measured by a dual energy X-ray absorptiometry. For the purposes of this study, a sample of healthy women from Southern Spain was chosen. Subjects were grouped into two major groups: a first group consisted of women of reproductive age, and a second group consisted of postmenopausal women. Significant linear trends between the MDS and bone mineral density were observed in all subjects studied. The authors concluded that a varied diet based on Mediterranean diet patterns may be beneficial in the prevention of osteoporosis. Fernandez-Real et al.[23] compared the effects of a virgin olive oil enriched Mediterranean diet, a walnut-enriched Mediterranean diet, and a low-fat diet for two years on osteocalcin and bone formation markers in the blood of men at high risk of cardiovascular disease. The virgin olive oil enriched Mediterranean diet alone was associated with increased serum levels of osteocalcin and the bone remodelling marker procollagen amino-terminal propeptide, suggesting a protective role for this diet in bone health.

The potential protective effect of the MeDi against the risk of hip fractures has been evaluated in several studies. Recently, in a large cohort of adults from eight European countries, Benetou et al[11] reported an inverse association between adherence to a Mediterranean-type diet and the risk of hip fracture in European older persons. Indeed, in this large cohort of adults enrolled in the EPIC study (N = 188,795 participants, 802 incident hip fractures), higher adherence to the MeDi was associated with a 7% decrease in hip fracture incidence, notably among participants aged 60 years or older and among men in the model adjusted only. On the contrary Feart and coworkers[24] showed that greater MeDi adherence was not associated with a decreased risk of fractures in French older persons.

There is evidence that specific components of Mediterranean diet may prevent the prevention of osteoporosis and/or hip fracture occurrence. In this context, a summary of the studies that demonstrate this association is shown below.

Olive oil and bone

Scarce epidemiological literature is available about the association between fat intake and the bone health. Saturated fat (SFA) intake has been reported to be associated with a higher risk of bone loss and osteoporotic fractures[25]. On the contrary, monounsaturated fat (MUFA) has been reported to have a beneficial effect on bone health[25,26]. Various epidemiological studies have associated the intake of the monounsaturated fatty acids of olive oil with bone health. A study of male and female adults in Greece[26] reported a positive association between the intake of monounsaturated fats and mineral bone density; the authors highlighted the substantially lower incidence of fractures in Greece, where there is high olive oil consumption, than in the USA or North European countries. Rivas et al.[4] described in female adults in Spain a significant correlation between the consumption of monounsaturated fatty acids and the mineral density of the heel bone (calcaneus).

Besides triglycerides, olive oil contains a wide variety of so-called minor compounds that are of major importance from a chemical and organoleptic standpoint. These include phenolic compounds, which constitute a highly complex fraction formed by numerous substances, some of which are yet to be identified. The known substances include simple phenols, e.g., hydroxytyrosol, tyrosol, caffeic acid, vanillic acid, *p*-coumaric acid, ferulic acid, and vanillin; flavonoids,

Tabla I

Description of the studies that have assessed the effect of the Mediterranean diet on bone health

Reference	*Country*	*Subjects*	*Method for measuring bone mass/fracture risk*	*Method used to evaluate MeDi adherence*	*Results*	*Conclusions*
Kontogani *et al*. (2010)[20]	Greece.	Adult women (N=300)	Lumbar spine and total BMD by DEXA.	Mediterranean Diet Score (Trichopoulou et al., 2003)[22].	Adherence to MedDi was not associated with indices of bone mass. Consumption of fish, olive oil and low intake of red meat was associated with lumbar spine BMD (p = 0.017) and total body BMD (p = 0.048)	Adherence to a MedDi was not associated with indices of bone mass.
Bullo *et al*. (2009)[21]	Spain.	Adult aged 60 to 80 at high risk for CVdisease (N=230).	Bone formation and resorption markers Bone mass by ultrasound scanning.	Three interventional groups: low-fat diet, a MedDi supplemented with VOO, or MedDi supplemented with nuts.	Subjects in MedDi with nuts group had nonsignificantly higher urine free deoxypyridoxine:creatinine ratio (p=0.14).	A Mediterranean dietary pattern does not seem to have a much greater effect on bone metabolism biomarker.
Fernández-real *et al*. (2012)[23]	Spain.	Adult aged 60 to 80 years at high risk for CVdisease (N=230).	Total circulating osteocalcin Bone markers N-terminal propeptide (P1NP).	Three interventional groups: low-fat diet, a MedDi supplemented with VOO, or MedDi supplemented with nuts.	Total osteocalcin increased in the MedDiet+VOO group (p=0.007) in parallel to increased P1NP levels (p=0.01) but not in subjects on the MedDiet+nuts (p=0.32).	Consumption of a Mediterranean diet enriched with virgin olive oil for 2 years is associated with increased serum osteocalcin and P1NP concentrations, suggesting protective effects on bone.
Rivas *et al*. (2013)[22]	Spain.	Adult women aged 18-65 years (N=200).	Calcaneous BMD by DEXA.	Mediterranean Diet Score (Trichopoulou et al., 2003)[22].	Significant linear trends between MeDi adherence and BMD were observed (p= 0.001).	MedDi pattern is associated with higher BMD.
Benetou et al. (2013)[11]	European countries participants in the EPIC study.	Adults aged 35-70 years (N= 188,795).	Incident hip fracture was reported by hip and radius fracture registries for a median of 9 years.	Mediterranean Diet Score (Trichopoulou et al., 2003)[22].	Adherence to MeDi was associated with a 7% decrease in hip fracture incidence. Association was more evident among men and older individuals.	Increased adherence to MeDi appears to protect against hip fracture occurrence, particularly among men.
Feart et al. (2013)[24]	France	Adult aged 67 years or older (N=1,482).	Incidence of hip, vertebral and wrist fractures were self-reported every 2 years over 8 years.	Mediterranean Diet Score (Trichopoulou et al., 2003)[22].	Higher MeDi adherence was associated with a non-significant increased risk of fractures at any site.	Greater MeDi adherence was not associated with a decreased risk of fractures in French older persons.

MeDi: Mediterranean diet. BMD: bone mineral density. DEXA: Dual-energy X-ray absorptiometry. CV: cardiovascular. VOO: Virgin olive oil.

e.g., luteolin and apigenin; and other more complex compounds such as those derived from oleuropein, ligstroside, ligustaloside[27]. Numerous potential health benefits of the phenolic compounds of olive oil have been reported, but their role in the prevention of bone diseases (e.g., osteoporosis) has been less well studied. Researchers have shown the phenolic compounds in different vegetables species can modulate the functions of osteoblastic cells, including their proliferative capacity and maturation, by increasing alkaline phosphatase activity and the deposit of calcium ions in the extracellular matrix[28-30]. Oleuropein, the main phenolic compound in olive-tree leaves, together with virgin olive oil and olives, was proved to be effective in a rat model of senile osteoporosis with a dosage of 150 mg/kg diet. In addition oleuropein shifts the differentiation of mesenchymal stromal cells in favour of osteoblastogenesis suggesting that oleuropein intake might have preventive effects against the bone loss associated with osteoporosis and aging[31]. The main phenolic compounds in virgin olive oil are tyrosol and hydroxytyrosol. Their administration in the diet at doses of 0.017% prevented the inflammation-induced bone mass loss in ovariectomized rats in a model of senile osteoporosis and increased their osteoblast activity, as evidenced by their elevated plasma osteocalcin levels[32,33]. Finally, luteolin, a flavonoid present in VOO, lessens bone mass loss in postmenopausal osteoporosis by reducing osteoclast differentiation and function[34].

Intake of fruits and vegetables: implications for bone health

Fruit and vegetable consumption is a common feature of the Mediterranean diet. Recent studies have focused on the effects of fruit and vegetable intakes on bone health[35,36]. Fruit and vegetable intake has been associated with increased bone mineral density or reduced fracture risk[37]. Larger bone size in early pubertal children and adolescents[38-40], and better bone mass in adult men and women have been associated with fruit and vegetable consumption[41,42]. In addition, it has been demonstrated that a dietary intervention based on low fat and increased fruit, vegetable, and grain intake reduced moderately the risk of multiple falls and slightly lower hip BMD[43].

The mechanism whereby fruit and vegetables may affect bone is not clear and may be multifactorial[44]. Fruits and vegetables might affect bone health via the effects of several components in these foods, such as minerals (e.g., calcium, potassium, and magnesium), vitamins (e.g., vitamin K and C), phytochemicals (e.g., phytoestrogens), and oligosaccharides (especially inulin-type fructans), either through their effect on calcium absorption or their involvement in the bone remodeling sequence, could mediate this association[11,45]. In addition, fruits and vegetables contain many different antioxidant components. Several lines of evidence suggest a tight association between oxidative stress and the pathogenesis of osteoporosis in humans. It has been shown that osteoporotic women have lower serum antioxidants levels as compared with controls[12,46]. Recently, Rivas et al.[3] demonstrated that the overall dietary antioxidant intake was significantly associated with bone mineral density in adult women.

It should be taken into account that a higher dietary acid load is believed to result in bone mineral dissolution and greater bone resorption, and a diet rich in fruit and vegetables may result in a more alkaline environment, which has been proven to reduce urinary calcium excretion[43]. The low grade metabolic acidosis induced by the modern diet is exacerbated during ageing when renal function begins to decline requiring the body's skeletal reserves to be called upon to relinquish bicarbonate to produce alkaline buffers needed to continuously balance the acid load.Typical diets are acidic because predominantly acid (hydrogen ions) rather than base (bicarbonate) is created during the metabolism of the daily food intake. Acid forming grains and high protein food derived from animal origin (meat, fish, and eggs) contain sulphur-based amino acids, methionine, and cysteine which create acid when metabolized. Alkaline forming foods contain potassium salts which can be broken down to make alkaline buffers[47]. Fruit/vegetables influence on acid-base balance is crucial, being the unique dietary source of alkaline precursor constituents, so it is important reason to increase consumption to avoid bone loss during ageing[8,48,49]. Vegetables and fruit are considered alkaline because of their high mineral content in the form of salts of organic acids. The salts, predominantly potassium based but also calcium and magnesium, generate bicarbonate to balance the acid produced from the rest of the diet[20].

Consumption of legumes and cereal and bone health

Legume and cereal consumption is high in Mediterranean areas. These foods are highly rich in vitamin B, calcium, phytoestrogens and other phytochemicals. Thus, an adequate intake of these foods has been associated with higher bone mineral density, decreased bone loss with ageing, or reduced risk of fracture[22]. There are data showing that legumes and grains may protect bone metabolism in humans[50]. It has been showed that the consumption of legumes decreased bone turnover in ovariectomized rats. In a recent study, Park et al.[51] showed that a diet containing legumes significantly increased the bone mineral density of the femur and spine, and bone volume of the femur in ovariectomized rats. On the contrary, Rivas and coworkers[22] did not find any significant association between legume and cereal intake and bone mineral density in a sample of healthy women from Southern Spain. One explanation could be that the consumption

of this food group was similar in all the subjects studied, so it may be difficult to find any significant differences. In addition non-refined cereals and legumes are acid-producing foods, which may alter the acid-base balance that is associated with negative impact on bone health[20].

Alcohol effects on bone

Alcohol and more specifically wine, is an essential component of the Mediterranean diet. There is inconsistent evidence regarding the association between alcohol consumption and bone mineral density (BMD). Tucker et al.[52] showed that moderate consumption of alcohol may be beneficial to bone in men and postmenopausal women. However, in men, high liquor intakes (> 2 drinks/d) were associated with significantly lower BMD. The authors concluded that the tendency toward stronger associations between BMD and beer or wine, relative to liquor, suggests that constituents other than ethanol may contribute to bone health. Ying et al.[53] describe the associations between total and beverage-specific alcohol intake and bone loss in older men and women. Their data showed that alcohol intake especially red wine might prevent bone loss in older men. However, women consuming excessive alcohol amount, were found to be at higher risk for hip fracture incidence compared to those consuming moderate amounts. This finding is in agreement with results from other relevant investigations in which moderate intake of alcohol was found to increase bone mineral density[54]. Nevertheless, over and beyond bone mineral density, one cannot oversee the effect of high alcohol consumption on the risk of falling, as well as its association with low body mass index, which is a risk factor for hip fractures.

Fish bone health benefits

A moderate consumption of fish is recommended for a healthy diet and is also a feature of the Mediterranean diet. Fish is a source of high quality protein; omega-3 fatty acids; vitamins, such as A and D; and minerals, such as selenium, calcium, iodine and zinc[55]. Many of these nutrients have positive effects on bone health. The positive effects of calcium and vitamin D, which are the most important nutrients for bone health, have long been established. In Spain, fish consumption accounts for 87% of total dietary vitamin D intake. Several studies have shown a potentially beneficial effect of fish intake[56,57] against osteoporosis and fracture occurrence. Recently, omega-3 fatty acids, especially eicosapentaenoic acid and docosahexaenoic acid, have been shown to have a beneficial effect on bone health. Several mechanisms have been proposed (affecting bone formation, bone resorption, serum calcium and vitamin D, oxidative stress, and inflammatory mediators). However, neither the exact benefit nor the exact mechanism of action of fatty acids has been determined yet. Therefore, although there are some clinical evidences linking bone metabolism and dietary lipids, more clinical trials are necessary to prove whether dietary changes or omega-3 supplementation play a major role in bone health and turnover[8].

Conclusion

In conclusion, a limited number of studies have examined the relationship between Mediterranean Diet and bone health, and they have reported conflicting results. On the one hand, adherence to a traditional MeDi has been associated with higher bone mineral density and lower fracture risk. The results of these studies could be attributed to the combined beneficial effects of individual components of the Mediterranean diet. On the contrary, several studies failed to show any association between adherence to the MeDi and indices of bone mass. There is evidence that specific components of this diet may play a role in the prevention of osteoporosis and/or hip fracture occurrence. In this context, an association has been showed between individual key characteristics of MeDi, such as high consumption of fruits, vegetables, and olive oil, as well as moderate to high consumption of fish, and moderate intake of alcohol with reduced incidence of osteoporosis, or reduced fracture occurrence. Further large-scale studies are required to clarify the effect of Mediterranean diet on bone health, in order to establish the role of this diet in the prevention of osteoporosis.

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