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## Osteoporosis, Nutrition and Adolescence

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### 1. Introduction

Osteoporosis is a worldwide health problem characterized by low bone mineral density and structural deterioration of bone tissue, leading to bone fragility and an increased susceptibility to fractures. Skeletal bone is maintained by the continuous process of bone remodeling by osteoclasts, cells that break down bone, and osteoblasts, cells that rebuild bone. An imbalance between bone resorption and accrual derives to overall bone loss, which in time leads to osteoporosis (Schettler & Gustafson, 2004). After the third decade of life, the bone mass naturally declines approximately 1-2% per year in women, and 0.3-1% per year in men, leading to losses of 30-50% of their initial bone mass in women and 20-30% in men during their lifetime (Riggs & Melton, 1986). As a consequence, both men and women may develop osteoporosis, maybe the most common chronic disability of postmenopausal women. However, osteoporosis should not be considered solely as adult disease, since bone health must be a lifelong concern, with special focus on the adolescent years (Schettler & Gustafson, 2004). In this sense, Kreipe (1992) suggested that "senile osteoporosis is a pediatric disease".

Osteoporosis in adolescence may be a primary or secondary consequence of diseases or disorders genetic but, in addition, it may be induced by erroneous lifestyle habits, including poor dietary habits, insufficient exposure to sunlight and low physical activities (Campos et al., 2003). The primary forms of osteoporosis in adolescents are relatively rare, and some of them are familiar or genetically determined. In this group may be included the osteogenesis imperfecta, a form of osteoporosis because of bone fragility which is characterized by weak bones that fracture easily, and the idiopathic juvenile osteoporosis, a rare disease associated with a negative calcium balance and characterized by repeated fractures (Bianchi, 2007). The secondary forms of osteoporosis result as a consequence of diseases associated with low bone mass and increased risk of fractures, such as neuromuscular disorders, chronic or endocrine diseases, and inborn errors of metabolism. Moreover, the treatment of some of these diseases may be associated to osteoporosis since several medications such as glucocorticoids, anticoagulants or anticonvulsant drugs can be negatively related to bone metabolism (Bianchi, 2007; Campos et al., 2003). On the other hand, conditions that result in pubertal retardation in adolescents such as anorexia nervosa or amenorrhea induced by exercise, can also be highlighted as causes of osteoporosis in this stage of life.

Although osteoporosis is not common among adolescents, adolescence is a key factor on the development of this disease in the adult age. It has been reported that, probably, the most important factor in the primary prevention of osteoporosis is the attainment of an optimal

peak bone mass during adolescence (Ott, 1990) and, therefore, any factor adversely impacting on bone acquisition during childhood or adolescence can potentially have long-standing detrimental effects on bone health predisposing to osteoporosis (Saggese et al., 2001). Several interconnected factors influence bone mass accumulation during growth, including genetic, hormonal, nutritional and lifestyle factors. Hereditary factors are responsible for around 80% of final peak bone mass, although there are clear suggestions that exogenous factors influence the acquisition of up to 20-25% of bone mass, so that the attainment of 100% of peak bone mass potential may be achieved only by their modulation. According to Ferrari et al. (2000), nutritional and genetic factors may interact to influence bone modeling, affecting bone mineral density (BMD), bone size and architecture, and mineral homeostasis during the years of peak bone mass acquisition. Therefore, together with another lifestyle factors, nutrition during adolescence has an important role in prevention of osteoporosis, and diets consumed during this stage of life should be balanced and equilibrated in order to meet the adolescent's requirements, especially those related to bone health.

## 2. Bone physiology during adolescence

Adolescence is characterized by an accelerated growth rate associated with rapid muscular, skeletal, and sexual development. During this period 15-25% of the adult size is acquired, approximately 45-50% of total adult skeletal mass is completed and up to 95% of total bone development is completed prior to the age of 18 (Bailey et al., 2000; Henry et al., 2004). Bones are growing in length and width, cortical thickness is increasing, and there is a dramatic increase in bone mass as well as a significant increase in bone density. Bone mineral content during adolescence is more a function of pubertal stage than a function of chronological age (Rico et al., 1993). Before puberty, no substantial gender difference has been reported in bone mass when adjusted for age, nutrition and physical activity. This absence of sex differences in bone mass is maintained until the onset of pubertal maturation, since the gender difference in bone mass is expressed during this period. Bone mineral content accretion accelerates in girls, reflecting the earlier onset of puberty in them, whereas boys have a greater increase in bone mineral content during puberty, resulting in greater values of skeletal maturity (Faulkner et al., 1996). Then, by the age of 10 the mean height-gain velocity is 6 cm/year in girls and increases to an average peak of 9 cm/year by the age of 12. Peak height-gain velocity for boys starts at the age of 12 years (5 cm/year) and reaches a maximum by the age of 14 years (10 cm/year). Mean height gain velocity is close to zero at age 15 in girls, and at age 17 in boys (Matkovic et al., 2004).

Bone is composed by cells (osteoblasts and osteoclasts), minerals (mainly calcium and phosphorus) and organic matrix (collagen and other proteins). Osteoblasts synthesize and mineralize the matrix proteins with hydroxyapatite crystals, whereas osteoclasts promote bone resorption, thus maintaining constant tissue remodeling (Van der sluis & Muinck Keizer-Schrama, 2001). During adolescence two phenomena are produced simultaneously, the synthesis of new bone from growth cartilage due to the process of endochondral ossification, and the modelling-remodelling of previously synthesized bone. The process of bone formation and resorption in the body is continuous, but in adolescents the rate of formation predominates over that of resorption. During puberty, several physiological and endocrine factors have a main role in the accumulation of bone mass. Some of these factors have an important influence on calcium absorption and retention; calcium is the most

important constituent of bone and, therefore, promoting calcium metabolism is a positive factor to enhance bone mineralization. The hormonal changes associated with puberty begin 2–3 years before this period, when an acceleration of growth is observed. The maturation of the hypothalamo-pituitary gonadal axis includes the gonadotropin-releasing hormone (GnRH). At a preprogrammed time in a child's life, there is an increase in the amplitude of GnRH pulses which triggers a cascade of events including increases in the amplitude of follicle-stimulating hormone (FSH) and luteinizing hormone (LH) pulses, followed by a marked elevation in gonadal sex steroidal output, which in turn increases the production of growth hormone (GH) in the hypophysis and of insulin-like growth factor-1 (IGF-1) in different tissues (Mauras et al., 1996). Moreover, sex steroids can act centrally by regulating GH secretion and peripherally modulating GH responsiveness (Figure 1). Higher levels of GH and of sexual steroids during the prepubertal period have a positive influence on bone mineral density and the accumulation of calcium in the skeleton (Krabbe et al., 1979). The effects of GH on bone turnover may be partly mediated by locally produced IGF-1, which is a beneficial factor on skeletal development and bone formation. IGF-1 serum levels increase and reach a maximum during puberty, at 14.5 years in girls and 15.5 years in boys (Juul et al., 1994). This factor seems to be a major regulator of bone growth during childhood and adolescence.

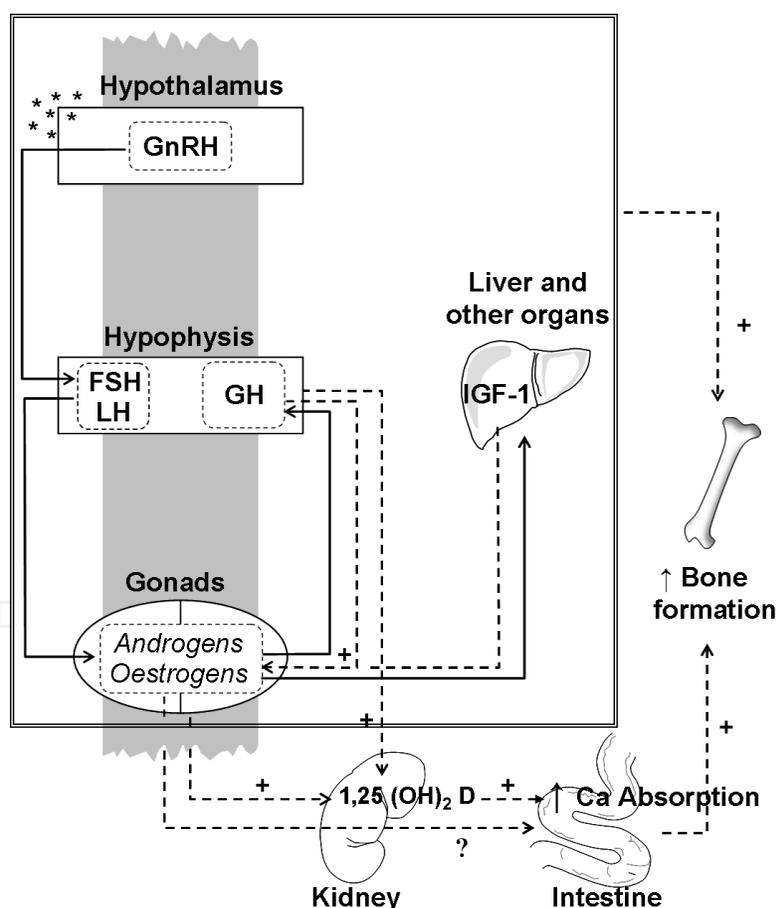


Fig. 1. Hormonal changes during adolescence which are determinants of calcium absorption and bone formation. GnRH: Gonadotropin-releasing hormone. FSH: Folliclestimulating hormone. LH: Luteinizing hormone. GH: Growth hormone. IGF-1: insulin-like growth factor-1. \*\*\* : Pulses. — : Hormonal changes. - - - : Effects on calcium absorption and bone formation. Modified from Mesias et al. (2011).

Many of these hormones have an influence on calcium absorption: GH enhances intestinal calcium absorption, increasing 1,25-dihydroxyvitamin D production by stimulating renal 1- $\alpha$ -hydroxylase and supports phosphate retention by increasing the renal threshold for phosphate excretion (Bouillon, 1991). The final effect of these actions is the increase of the calcium-phosphate product in the extracellular fluids, which represents a main mechanism for bone matrix mineralization. It is known that GH deficiency may decrease bone turnover, and the balance between bone formation and bone resorption might be uncontrolled. In this sense, it has been demonstrated that children with GH deficiency have reduced bone turnover and bone mass accumulation (Saggese et al., 1995). Several studies have showed that adequate doses and duration of GH replacement therapy are able to increase bone turnover and to achieve bone mineral density values within the normal range (Saggese et al., 1996), suggesting that GH has a fundamental role in the acquisition of peak of bone mass. Moreover, GH, together with IGF-1 stimulates sex steroids secretion (Bouillon, 1991). Both estrogens and androgens influence phospho-calcium metabolism regulating calcium fluxes and bone calcium deposition, increasing calcium absorption and retention (Mauras, 1999). The route by which many of these hormones augment during puberty favoring calcium absorption and bone mass accumulation is across 1,25-dihydroxyvitamin D, the principal enhancer of this mineral absorption at any stage of life but especially in the pediatric period. Nevertheless, although vitamin D is necessary for calcium absorption, on the contrary to the situation found with adults, no relation seems to exist between serum levels of 25-hydroxyvitamin D and calcium absorption in adolescents who are not deficient in this vitamin. This may be because they can adapt to low levels of this vitamin, by increasing calcium absorption independently of the vitamin or, as diverse authors indicate, because during puberty the efficacy of conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D increases to meet the needs for skeletal growth (Abrams et al., 2005). With the secretion of sex hormones during puberty, bone growth accelerates and bone mass accumulation increases. In females, the accretion rate increases about 4-fold before menarche, although bone mass changes little or even decreases thereafter. In males, bone mass accretion increases approximately 6-fold during puberty with a slower but still marked accretion at many skeletal sites thereafter. In addition, there are gender differences in the porosity of bone between adolescent boys and girls that may reflect greater bone remodelling in boys at this time. As a result of these differences, males have a larger bone size and greater thickness after puberty than females, but there is little difference in volumetric density (Prentice et al., 2006). Estrogens are an important determinant of bone mineral density in girls during puberty; this is confirmed by diverse studies in which girls with an early or regular menarche had higher bone mineral density, while a late menarche or amenorrhea in ballet ballerinas or in patients with anorexia nervosa were related to a limited density and even to fractures (Bachrach et al., 1991; Young et al., 1994). Estrogens can decrease the rate of bone turnover, and inhibit the osteoclastic resorption of bone by affecting bone cell differentiation and function. They also affect the parathyroid hormone (PTH) and, as mentioned previously, vitamin D metabolism. Androgens may also be important determinants of bone density, although studies carried out with animals have shown that estrogens play a more important role than androgens in skeletal mineralization (Frank, 1995). Another factor related to mineral density is serum calcitriol (1,25-dihydroxyvitaminD). It is demonstrated (Ilich et al., 1997) that calcitriol levels can be positively associated with changes in total bone mineral density during pubertal growth,

presumably in response to the high requirements for calcium during this critical phase of skeletal development.

### 3. Nutritional factors affecting bone development

During adolescence several nutritional factors play a major role in the bone mass gain process and, therefore, some of the nutrients and food components consumed as part of the diet can potentially impact bone accrual during this stage of life. In addition, several nutritional disorders may be associated with osteoporosis.

Dietary factors that may affect bone metabolism include minerals such as calcium, phosphorus and magnesium and a variety of nutrients cofactors such as vitamins D, C and K, and other minerals such as copper, zinc and manganese. In addition, a positive energy balance from macronutrients is important during growth for synthesis of bone. On the other hand, protein comprises most of the nonmineral composition of bone, and an adequate protein intake is essential for bone matrix synthesis (Saggese et al., 2001). Therefore, diet must contribute sufficient and appropriate nutrients to allow, together with healthy lifestyle habits, achieve the maximum genetic potential for bone mass development.

#### 3.1 Calcium

Calcium is the most abundant mineral in the organism and contributes approximately 1-2% to the adult human body weight. About 99% of body calcium is deposited in bone and teeth and, hence, its main function is structural, being essential for optimal growth and development. A dynamic balance exists between calcium in the extracellular medium and that found in bone, and about 500 mg of this mineral enter and depart daily from the bones (Pérez Llamas et al., 2010). The bone acts as a reservoir of calcium to maintain extracellular homeostasis and transfers the mineral if its concentration in blood falls below normal values (9.0-10.2 mg/dl), especially in situations of chronic calcium deficiency resulting from continual inadequate intake or poor intestinal absorption. Therefore, mineral deficiency leads to inadequate mineralization of bone matrix, resulting in rickets in children and adolescents and, along with other risk factors, contributing to possible osteoporosis in adulthood (Mesías et al., 2011).

Calcium requirements vary throughout life; greater needs are shown during periods of intense growth such as childhood and adolescence, during pregnancy and lactation, and also later in life. Among adolescents, a calcium increase is needed as a result of the intensive bone and muscular development. Therefore, adequate calcium intake during growing is essential to reach the optimum peak bone mass, which, as it has been above mentioned, protects against osteoporosis in the adult age (Story & Stang, 2005). Although peak bone mass has a large genetic component, there is evidence that it can be enhanced by increasing calcium consumption. Several studies in children and adolescents have shown that bone mass and bone density increase with calcium dietary supplements, and therefore, providing adequate calcium intake during the formative years is one approach to optimizing peak bone mass (Cromer & Harel, 2000).

Given the high proportion of body calcium present in bone and the importance of this as the major calcium reservoir, the development and maintenance of bone are the major determinants of calcium needs. Therefore, adolescents must consume diets that are balanced and adjusted to their requirements in order to meet calcium recommendations and to obtain the energy and nutrients that promote mineral utilization. Several studies have

demonstrated the importance of considering both food groups and the overall diet in assessing their impact on bone health, which may partially explain the relationship between nutrient intake and bone mineral acquisition in children and adolescents (Heaney, 2004; Seiquer et al., 2008). Milk and dairy products contribute around 70% of total dietary calcium and thus, they are by far the main source of calcium in Western diets (Guéguen & Pointillart, 2000). Addition of these products to the adolescent's diet is the best strategy to meet calcium recommendations and to achieve optimal bone mineralization (Cadogan et al., 1997). Dairy products contribute from 42% of the total calcium consumed by British adolescents (Moynihan et al., 1996) to 70% by Australian (Department of Community Services, 1989), Spanish (Seiquer et al., 2006), or American adolescents (Fiorito et al., 2006). Dietary calcium supplements improves bone mineral accretion by 1-5% among adolescents consuming less than 1000 mg Ca/day, and by up to 10% when supplemental calcium is provided by dairy products (Kerstetter & Insogna, 1995). In this sense, Lyriris et al. (1997) found a correlation between the consumption of dairy products by young adult humans and bone density. Moreover, low milk intake during childhood and adolescence is associated with a greater incidence of fracture among older women (Kalkwarf et al., 2003). Cereals may also constitute an important calcium source, whereas meat, eggs, fish and legumes are minority calcium sources in the diet of adolescents (Seiquer et al., 2008). In addition, drinking water, including mineral water, may provide 6-7% of daily calcium intake (Guéguen & Pointillart, 2000). On the other hand, nutrients found in abundance in fruit and vegetables may be protective for bone health (Jones et al., 2001), as discussed below.

To achieve the maximum peak bone mass during adolescence, it is mandatory a positive calcium balance, i.e., the calcium body retention calculated as intake minus losses (Anderson & Garner, 1996). Usually the calcium balance increase in parallel to the intake, which suggests that the intake of this mineral may limit growth. Dietary calcium during this stage has a direct relationship with bone mineralization and low intake during puberty may limit it (Cadogan et al., 1997; Matkovic et al., 2004). Thus, if calcium intake is below 500 mg/day in childhood, more than 50% of ingested calcium must be retained in order to obtain adequate mineral accretion (Mølgaard et al., 1999). Balance studies carried out in adolescents support that calcium retention is associated with calcium intake, but at intakes up to 1300 mg/day a plateau is reached (Jackman et al., 1997). Therefore, calcium is a threshold nutrient, i.e., at suboptimal intake the body's ability to store calcium as bone tissue is limited by the intake of the mineral, but increasing calcium intake above the body's requirements does not result in further increases of stores (Mesías et al. 2011). At calcium intakes producing optimal bone mass, increasing calcium intake will not result in more bone (Flynn, 2003).

Intestinal calcium absorption varies with age and adapts to different physiological situations, so that when needs are high, mineral absorption becomes more efficient. Puberty is associated with a high rate of dietary calcium absorption, not only in absolute values but in fractional absorption rates or digestibility, in order to satisfy the increased calcium requirements for the intensive adolescent growth (Abrams & Stuff, 1994). To enable an increase in mineral absorption, adolescents have a low rate of calcium fecal excretion. Besides the amount of calcium in the diet, food ingredients are also a critical factor in determining the available calcium for bone development and maintenance. There is therefore a need to identify food components and/or functional food ingredients that optimize calcium absorption and bioavailability. Some components of the diet have been suggested as enhancers or inhibitors of calcium absorption. Thus, phytates found in bran

and most cereals and seeds, oxalates in spinach or walnuts, and tannins in tea, can form insoluble complexes with calcium, thereby reducing its absorption. However, Guéguen and Pointillart (2000) show that these factors only seem to significantly affect calcium balance if the overall diet is unbalanced. Milk and dairy products are considered good sources of this mineral due to their high calcium content and bioavailability (proportion of calcium retained from intake). Around 40% of the calcium from these products may be absorbed due to the particular physico-chemical form of the element and the presence of absorption promoters such as lactose and caseinphosphopeptides. The latter, moreover, can limit the inhibitory effect of other compounds (Guéguen and Pointillart, 2000). Milk nutrients may promote bone mineralization because, in addition of being a major source of calcium, milk provides phosphates, magnesium, proteins, and as yet unidentified nutrients likely to favor bone health (Esterle et al., 2009). Vitamin D is also an essential factor for intestinal calcium absorption and plays a central role in maintaining calcium homeostasis and skeletal integrity. Adequate levels of this vitamin are obtained by suitable intake and sufficient exposure to sunlight, which is the major source of vitamin D in the organism (Bener et al., 2008). On the other hand, certain lipids may favor calcium bioavailability; it has been shown that a high ratio of unsaturated to saturated fatty acids has beneficial effects on calcium absorption (Haag et al., 2003). Fish may be a good source of calcium because on the one hand its protein is as positive as casein in promoting calcium absorption (García-Arias et al., 1994), and on the other hand because omega-3 fatty acid might promote calcium transport (Haag et al., 2003). It should be noted that the positive effect of fish fat in calcium utilization is promoted when it is consumed together with olive oil (Pérez-Granados et al., 2000), as it occurs when fried fish are consumed. Olive oil may be another contributor to enhanced calcium utilization, assays have shown that oleuropein, an olive oil phenolic compound, reduces bone loss (Puel et al., 2004). Studies in humans (Van den Heuvel et al., 1999) and experiments in rats (López et al., 2000) have revealed a positive effect on apparent calcium absorption after consumption of oligofructose. This compound may also diminish the negative effects of phytic acids. A diet rich in cereals, fruits, and vegetables can increase the presence of these prebiotic products in the digestive system, helping to improve calcium absorption in this physiological stage when demands for the mineral are high.

Dietary calcium intake and urinary excretion of calcium seem to be also important determinants of mineral retention in the body. Although in adults urinary calcium may reflect the intake, in adolescents levels of calcium in urine represent obligatory renal losses that are independent of the consumption. Therefore, it can be supposed that only an unavoidable amount of calcium is lost because its use at this stage of life is a matter of priority for the organism. During childhood, urinary calcium excretion doubles, from ~40 mg/day in young children to ~80 mg/day just before puberty. However, during the peak of maximum growth, this value decreases, especially among males. Calcium excretion rises to reach the values of adulthood (100-250 mg/day) by the end of adolescence (Manz et al., 1999; Peacock, 1991). This increase in urinary calcium excretion in late adolescence probably reflects the decreasing needs of the skeleton for calcium (Peacock, 1991). In addition to the physiological status, certain dietary components may affect urinary losses of calcium. Some dietary factors affecting urine losses have a major influence on calcium balance and may even become more important than those influencing the intestinal availability of calcium. Thus, excessive protein intake, particularly animal protein, generally leads to an increase of the calcium lost in urine (Ginty, 2003), although it seems unclear whether protein intake has a negative effect on calcium balance and bone mineralization in children and adolescents.

Independent factors can be related to urinary mineral excretion, but total urinary excretion is determined by the metabolic effect of the overall diet. Nutritional intervention studies have shown that a high intake of fruits and vegetables decreases urinary calcium in adults and adolescents (Tylavsky et al., 2004). In turn, fruits and vegetables provide organic salts of potassium and magnesium that have a buffering effect and consequently decrease urinary calcium. This effect has been demonstrated in adults (Whiting et al., 1997) and in adolescents (Jones et al., 2001). On the contrary, low phosphorus and high sodium and caffeine intake are associated with increased urinary calcium (Kiel et al., 1990; Brunette et al., 1992; Weisinger & Bellorin-Font, 1998). With an adequate diet, calcium bioavailability is favored, reaching values around 36.5% for boys and 29.6% for girls, or even higher when diets provide suitable amounts of the mineral (Bailey et al., 2000; Seiquer et al., 2008). Thus, as mentioned above, the dietary habits of adolescents are an important factor to meet calcium requirements and, consequently, needs for pubertal growth.

### 3.2 Phosphorus

Together with calcium, phosphorus is essential during adolescence to support the rapid rate of bone accretion that takes place in the adolescent growth spurt. Almost 85% of the body's phosphorus is located in bone as calcium phosphate salt in the form of hydroxyapatite, with a Ca:P molar ratio approximating 1.7:1 and, therefore, this mineral must be present in adequate amounts in the diet to mineralize and maintain the skeleton. Adequate supplies of both minerals are crucial to maximize bone mineral accrual during growth, considered the best strategy to prevent age-related osteoporotic fractures later in life (Weaver, 2000). However, in spite of dietary phosphorus has an important and positive role to play in the development of peak bone mass, it has been suggested that both high and low phosphorus intakes may seriously alter calcium metabolism. On the one hand, excessive amounts of this element may be harmful to bone health and it should be taken into account the low calcium to phosphorus ratio. There is some evidence that increased phosphorus intake depresses ionised calcium leading to an increase in PHT and, hence, a rise in the rate of bone resorption (Calvo et al., 1988). On the other hand, it has been reported that low phosphorus intake is associated with increased urinary calcium (Weisinger & Bellorin-Font, 1998). Other studies have failed to show a deleterious long-term effect of different phosphorus intakes on calcium balance (Heaney & Recker, 1982).

### 3.3 Magnesium

Total body magnesium content is approximately 25 g, 60-65% of which is found in bone. Part of this magnesium is in equilibrium in an exchangeable way with the extracellular magnesium, and may serve as a reservoir for maintaining a normal extracellular magnesium concentration; so that at reduced plasma concentration, magnesium can be rapidly released from the bone surface and at increased plasma concentrations magnesium remains bound to the surface of bone (Elin, 1994). However, experimental evidences that dietary magnesium influences the development of peak bone mass are scarce.

Magnesium plays a major role in bone and mineral homeostasis and can also directly affect bone cell function as well as influence hydroxyapatite crystal formation and growth. This element is required for matrix and mineral metabolism in the bone through its indispensable role in metabolism of ATP and as a cofactor for over 300 enzymes (Sojka, 1995). Although the requirement for magnesium retention during childhood and adolescence is uncertain, it

is likely to be 5-10 mg/day (Andon et al., 1996) and may increase during the pubertal growth spurt in order to support the more rapid rate of bone formation during this period (Abrams et al., 1997).

The bioavailability of magnesium may be affected by several dietary factors such as phosphorus, calcium, sodium or protein. It is known that high phosphate diets can decrease intestinal magnesium absorption due to the ability of phosphate to bind magnesium (Reinhold et al., 1991), whereas high sodium and calcium intake may result in increased renal magnesium excretion (Kesteloot & Joossens, 1990). In addition, dietary protein may also influence magnesium utilization; magnesium balance is negative when protein intake is less than 30 g/day, due to a high mineral excretion in urine and feces (Hunt & Schofield, 1969) whereas higher protein intakes, around 94 g/day, also may increase renal magnesium excretion (Mahalko et al., 1983), since the acid load increases urinary magnesium excretion (Wong et al., 1986).

### 3.4 Protein

In addition to calcium, dietary protein represents a nutrient essential for the synthesis of bone matrix. Protein is a major constituent of bone, so adequate protein intake is critical to maintaining bone health. Several studies have demonstrated that a selective deficiency in dietary proteins, without any associated insufficiency in other macronutrients such as total energy, calcium and vitamin D, causes a rapid and marked alteration in bone mass, microarchitecture and strength (Bonjour, 2005). It is known that proteins can stimulate intestinal calcium absorption and enhance IGF-I. Preclinical studies in adult animals have documented that an isocaloric low protein diet reduces IGF-1, induces negative bone balance with both decreased formation and increased resorption, thereby leading to a decline in bone strength (Ammann et al., 2000; Bourrin et al., 2000).

However, the effects of dietary protein intake on bone health are controversial, since it also has been documented that higher protein diets increase urinary calcium, being therefore a risk factor for osteoporosis. Protein intake increases acid production and renal acid excretion due to the releasing of protons during the oxidation of sulfur-containing amino acids such as methionine, cysteine, and cystine. This metabolic acid load might cause the dissolution of bone mineral, which would originate an increased calciuria, resulting in an accelerated loss of bone mineral mass and, thereby, increasing the risk of osteoporotic fracture at long term. The higher content of sulfur-containing amino acids in animal proteins compared with vegetable proteins would lead to increased urinary excretion of calcium and, therefore, to exacerbation of age-related bone loss. Therefore, vegetal proteins might be bone protective whereas animal proteins would be harmful for the acquisition and the maintenance of the bone mineral mass (Sellmeyer et al., 2001). However, the harmful effect of excessive animal protein in skeleton formation seems to be only significant when calcium intake is inadequate (Heaney, 1998).

## 4. Dietary habits of adolescents related to bone health

### 4.1 Intake of bone-forming nutrients

Although adequate calcium intake during childhood and adolescence is mandatory, a high percentage of American and European adolescents fail to meet the recommendations of this mineral (Table 1).

	Recommendations	Intakes	
	DRI <sup>1-2</sup>	Europeans <sup>2-3</sup>	Americans <sup>4-5</sup>
Calcium	1300 mg/day	596-1400 mg/day	793-1081 mg/day
Phosphorus	1250 mg/day	949-1848 mg/day	1093-1533 mg/day
Magnesium	240-410 mg/day	185-360 mg/day	216-284 mg/day
Protein	34-52 g/day	53-127 g/day	78 g/day

References: <sup>1</sup>Institute of Medicine (1997); <sup>2</sup>Institute of Medicine (2005); <sup>3</sup>Lambert et al. (2004); <sup>4</sup>Elmadfa et al. (2005); <sup>5</sup>Rockett et al. (2001); <sup>6</sup>Ervin et al. (2004).

Table 1. Recommendations and intakes of calcium, phosphorus, magnesium and protein among adolescents.

According to Grunbaum et al. (2004), only 11% of female and 23% of male American adolescents drink three or more glasses of milk daily, and only 19% of girls and 52% of boys meet calcium recommendations (Damore et al., 2007). Among Spanish population, 13–14% of boys and 29–40% of girls have inadequate calcium intakes (Serra Majem et al., 2006). In conclusion, calcium content in the adolescents diet frequently fails to meet the body's needs during the growth spurt (Rockett et al., 2001; Lambert et al., 2004; Elmadfa et al., 2005), which, as it has been mentioned before, might have a deleterious effect on the acquisition of the peak bone mass and, therefore, an important repercussion on osteoporosis in adult age. In recent years the contribution of milk to total beverage intake has significantly decreased among boys and girls because milk has been replaced by carbonated beverages (Vatanparast et al., 2006). Since 1965, milk consumption has decreased by 74%, and consumption of non-citrus juices and carbonated beverages has increased by 118% (Schettler & Gustafson, 2004). Therefore, soft drinks negatively affect bone mineralization because they are associated with lower milk consumption. But, moreover, a further negative effect concerns their phosphorus and caffeine content; the phosphoric acid content of soft drinks may limit calcium absorption and contribute to bone loss increasing bone resorption and fracture risk (Wyshak & Frisch, 1994; Wyshak, 2000), whereas caffeine has been associated with reduced bone mineral density and increased fracture risk (Kiel et al., 1990). Both effects have been demonstrated in children who frequently consume cola drinks (Heaney et al., 2000). However, several studies have reported that the negative impact of soft drink on bone mass is observed in adolescent girls but not in boys (Whiting et al., 2001; McGartland et al., 2003), which implies that bone accrual mechanisms in adolescent girls have more vulnerable conditions.

As it can be observed in Table 1, a certain proportion of American and European adolescents also fail to meet phosphorus recommendations. However, the overall phosphorus intake has increased during the last years as a consequence of the changing dietary habits of adolescents, on the one hand, the greater carbonated beverages consumption and, on the other hand, the increased intake of processed and fast foods, very frequently consumed among this age group. Manufactured and fast foods have a high content of phosphorus-containing additives, used to preserve moisture or color, to emulsify ingredients, enhance flavor, and to stabilize foods. According to Coates et al. (2005), these additives are the most rapidly growing source of dietary phosphorus over the last two decades and may contribute to one-third of overall phosphorus intake in the general population. The high phosphorus

intake, therefore, should be taken into account due to its negative association with calcium metabolism and, in addition, with intestinal magnesium absorption.

Regarding magnesium intake, many adolescents usually do not reach mineral recommendations (Table 1), but, moreover, dietary factors can affect metabolism and excretion of this mineral, as mentioned. Abrams et al. (1997) reported that among boys and girls aged 9-14 years consuming RDA magnesium intakes, a significant number of them were in negative magnesium balance. This negative balance appeared to be related primarily to urinary excretion of magnesium, probably affected by dietary factors, which might affect to mineral homeostasis and bone formation.

On the other hand, as it is usual among population of Western countries, the protein intake among adolescents is above the recommendations, with special contribution of animal proteins (García-Closas et al., 2006). High protein intake may be related to increased urinary calcium and magnesium excretion but, moreover, the low consumption of fruits and vegetables among adolescents decreases the buffering effect above-mentioned, increasing the negative effects of protein on mineral utilization and, therefore, on bone health. Several authors have shown the link between fruits and vegetables and peak bone mass acquisition in boys and girls (Tylavsky et al., 2004). Whiting et al. (2004) confirm that girls consuming adequate amounts of this food group show a greater bone mineral trajectory than those consuming fewer than 5 servings/day. In the same way, subjects with an intake of 10 servings per day of fruits and vegetables presented a higher total body bone mineral content than did those consuming 1 serving/day (Vatanparast et al., 2005). Moreover, fruit and vegetables provide vitamin K, which is an essential cofactor for osteoblastic activity (Feskanich et al., 1999) and natural antioxidants like phytoestrogens, which seem to play a role in bone metabolism. Phytoestrogens, like estrogens, stimulate human osteoblasts and modulate osteoclast activity, thus preventing bone resorption (Chiechi & Micheli, 2005). Therefore, a diminution of fruits and vegetable consumption, frequently observed in adolescents, avoid the protector effect of these types of foods on bone.

It is well known that the dietary habits of adolescents have changed in recent decades and that there is a tendency to a higher consumption of soft drinks, snacks, bakery products, and fast foods, which, particularly, has increased from 2% of total energy in the late 1970s to 10% of total energy in the mid-1990s (Guthrie et al., 2002; Libuda et al., 2008). As it has been mentioned, the consumption of these kinds of foods may be associated to lower intake of fruits and dairy products and greater intake of phosphorus due to high phosphorus-containing additives, which implies negative effects on calcium utilization. Together with phosphate salts, processed foods are also rich in sodium salts-containing additives (He et al., 2008) which, certainly, increases sodium intake. It is known that average sodium intakes in children and adolescents well exceed nutritional needs, overcoming even 3.5 g/day (Falkner & Michel, 1997). Since the elevated consumption of sodium also damages bone by increasing the urinary calcium excretion and decreasing calcium absorption (Brunette et al., 1992), reducing sodium intake should be seriously considered among adolescents.

#### **4.2 Intake of Maillard reaction products**

The Maillard reaction, also termed nonenzymatic browning reaction, is usually developed in processed and fast foods, since it commonly occurs during the thermal processing of foods rich in proteins and sugars or fats, producing colored compounds that contribute to the aroma, color, and flavor of cooked foods. Controlled browning is therefore pursued through

many food technologic and domestic processes such as roasting, baking, frying and even re-heating, aimed at promoting consumer acceptance (Ames, 1998). Thus, the Maillard reaction products (MRP) are widely consumed as a part of the human diet, especially among adolescents, according to their dietary habits and the high content of snacks and fast foods in their diets (Delgado-Andrade et al., 2007). In addition to their sensory properties, MRP is associated with certain positive biological effects, such as antioxidant activity (Seiquer et al., 2008), but at the same time with negative actions, including degradation of nutritional protein quality (Alkanhal et al., 2001) and modifications in vitamins (O'Brien and Morrissey, 1989) or mineral availability (Navarro, 2003).

Our research group has realized several studies with the objective of comparing the effects of diets with different MRP contents on the utilization of dietary protein and on mineral availability in adolescents. In a 2-period crossover trial, a group of healthy male adolescents aged 11-14 years consumed two types of diets, both balanced and varied and with the same nutrient composition, but with different content in MRP. The first one was a MRP-poor diet, free, as far as possible, of foods in which the Maillard reaction develops during cooking practices or foods that naturally contain these products whereas the second one was a MRP-rich diet, high, as far as possible, in processed foods with an evident development of browning. The utilization of the different nutrients by the subjects under consumption of the different diets was measured. The effects of the high consumption of MRP on nutrient concerning bone formation are summarized in Table 2.

Factor	Absorption	Retention	Digestibility	Bioavailability	References
Calcium	=	=	=	=	Mesías et al., 2009
Phosphorus	↓↓	↓	↓↓	↓	Delgado-Andrade et al., 2011
Protein	↓↓	↓	↓↓	↓	Seiquer et al., 2006

Table 2. Effects of a MRP-rich diet on protein and mineral availability compared with a MRP-poor diet in adolescents. =: non effect; ↓↓: effect statistically significant; ↓: effect non significant statistically.

Absorption and digestibility of nitrogen were significantly lower when subjects consumed the MRP-rich diet than the MRP-poor diet, whereas negative effects on the protein balance did not reach statistical significance. It was deduced that the consumption of a diet rich in browning products negatively affects protein digestibility (Seiquer et al., 2006). Regarding minerals, it is known that MRP may behave as anionic polymers that chelate metal cations, affecting mineral solubility at intestinal conditions and mineral availability (Navarro, 2003). In our assays we observed that high MRP intake has no apparent effects on dietary calcium bioavailability in adolescent, although possible metabolic changes cannot be discounted, as a lower deoxyypyridinoline urinary excretion was observed with MRP-rich diet consumption, which may be related to decreased bone turnover at this age (Mesías et al., 2009). On the contrary, this diet had clear negative effects on dietary phosphorus absorption, tending to decrease the phosphorus balance (Delgado-Andrade et al., 2011). In a similar way, MRP-rich diet did not affect zinc but negatively affected copper bioavailability (unpublished data). It should be borne in mind that the food habits of adolescents are changing toward monotonous and unbalanced diets with a considerable MRP content, and

an increasing proportion of total energy intake is obtained from fast food and snacks, as mentioned. In these conditions, the effects observed in our studies could be aggravated. In view of the current dietary habits of adolescents, and the well-established relationship between protein and mineral deficiency with bone formation during the growth spurt, and, consequently, with osteoporosis in the adult period, it seems of special interest to take into account the possible long-term effects of dietary MRP on bone health.

#### 4.3 The Mediterranean diet

The Mediterranean diet has been proposed as one of the healthiest dietary models and its health benefits have been demonstrated in a large number of studies. Moreover, the Mediterranean diet incorporates practically all the factors that may positively influence bone health. However, current dietary patterns are considerably far from the characteristics of the Mediterranean diet, particularly among adolescents due to the increased habit of eating away from home and the higher consumption of snacks and fast foods.

This diet is characterized by moderate levels of animal protein, abundant fresh fruits and vegetables, cereals and fish, and little saturated fat. Olive oil is used as the main dietary fat.

Our research group has also studied the effects of a varied diet based on Mediterranean patterns on the utilization and availability of nutrients essential for bone formation, such as protein and minerals, among adolescents. A summary of the results obtained in our studies, comparing with those obtained when the subjects are under their own diets, is shown in Table 3.

Factor	Absorption	Retention	Digestibility	Bioavailability	References
Calcium	↑↑	↑↑	↑	↑↑	Seiquer et al., 2008
Phosphorus	↑	↑↑	=	↑↑	unpublished data
Protein	=	↑↑	=	↑↑	unpublished data

Table 3. Effects of a varied diet based on Mediterranean patterns on protein and mineral availability in adolescents. =: non effect; ↑↑: effect statistically significant; ↑: effect non significant statistically.

It has been shown that dietary calcium utilization during adolescence may be greatly improved by a diet based on the Mediterranean patterns (Seiquer et al., 2008). Compared with the consumption of their habitual diets, adolescents significantly increased the absorption and retention of the dietary calcium, and, as a consequence, calcium utilization efficiency was significantly improved when subjects consumed the Mediterranean diet. In a similar way, after this same diet consumption, adolescents significantly increased phosphorus and protein retention and bioavailability (unpublished data). Therefore, a diet with sufficient calcium, phosphorus and protein and based on the Mediterranean diet patterns is advantageous for bone formation during periods of intense growth, such as the adolescence, when factors affecting bone health will be determinants for the development of osteoporosis later in life.

#### 4.4 Lifestyle: Physical activity and others

Together with eating behaviors, weight-bearing physical activity is a modifiable pattern that could be of potential importance in ensuring that the maximum genetic potential for bone

mass is achieved (Matkovic et al., 1990). This kind of activity could be defined as physical activity in which gravity exerts force on bones or any activity done standing up (e.g., walking or jumping), not including activities that involve only resistance or that are done sitting down (e.g., bicycling or swimming). In general, studies support the view that moderate weight-bearing activity has a more positive effect on bone mass than do non-weight-bearing activities, which impose minimal physical strain on bone (Cromer & Harel, 2000). Several studies have shown that both exercise and calcium interventions have an overall beneficial impact on bone acquisition during childhood and adolescence (Stear et al., 2003). According to Anderson (2001), physical activities during the critical growing years make important contributions to the accrual of bone mass, perhaps independently of calcium intake. In this way, Nickols-Richardson et al. (1999) reported that a relatively low calcium intake may be compensated by regular physical activities in the accrual of peak bone mass.

The current lifestyle habits of many adolescents, based mainly in inadequate dietary intake and insufficient physical activity, have resulted in an increased level of overweight and obesity particularly in Western countries. Overweight among children has been related with an increased incidence of fractures (Greer & Krebs, 2006), which is probably explained by the fact that calcium intake is negatively correlated with body fat percentage and body mass index during childhood (Carruth and Skinner, 2001; Skinner et al., 2003). The inverse relationship between calcium intake and fatty tissue gain has been recently confirmed by Lederer et al. (2009) in male adolescents. It has been shown that overweight children have a lower bone mass and bone area relative to their body weight than do children with a healthy body weight, which may predispose them to fractures (Goulding et al., 2000). Trends in diet and exercise coupled with an increasingly aging population indicate that the incidence of osteoporosis will triple by the year of 2040 (Schettler & Gustafson, 2004), with the result that both diet and physical activity are considered to be important and complementary factors to prevent this disease.

Other fact that should be taken into account among adolescents in order to prevent osteoporosis is tobacco and alcohol consumption. It has been reported that the prevalence of concurrent alcohol and tobacco use among European and American adolescents comes to 20-25% (Anthony and Echeagaray-Wagner, 2000; Schmid et al., 2007). Clinical findings indicate that there is an inverse relationship between bone mineral density and smoking, due to its negative effect on calcium absorption and estrogen metabolism (Bailey et al., 2000; Valimaki et al., 1994). Moreover, heavy alcohol consumption hinders calcium absorption and damages bone cells (Bennet, 1995). On the other hand anorexia nervosa, a dangerous disease in adolescent girls at the time of the initial peak bone mass formation, is known to be associated with low bone mass content, even in short duration cases, effects that may persist even after recovery (Misra et al., 2004; Winston et al., 2008). It has been reported that adult women with anorexia nervosa initiated during adolescence have lower bone mass than those with adult onset anorexia nervosa (Biller et al., 1989). This disease includes alterations of the GH-IGF-1 axis and, moreover, both hypogonadism and the cortisol excess associated to it may contribute to the development of osteopenia and osteoporosis (Misra et al., 2005a; 2005b).

## 5. Conclusion

Prevention of osteoporosis in adulthood begins in childhood. Therefore, in the fight against osteoporosis, modifiable factors such as dietary and lifestyle patterns should be taken into account from the beginning of life. Adolescence is a phase of particular interest for the

prevention of osteoporosis due, on the one hand, to the special dietary habits of adolescents, and on the other hand, to the great development and acquisition of the skeletal mass during this stage of life. Not only meeting adequate intakes of minerals and protein is required during adolescence, but, moreover, the composition of the whole diet will be determinant for consecution of the maximum genetic potential for growth and bone development. Diet, therefore, must contribute sufficient and appropriate nutrients to allow, together with healthy lifestyle habits including physical activity, the maximum bone mass development genetically programmed, which will be the best strategy in the prevention of osteoporosis. Due to the progressive incidence of osteoporosis in Western countries, intervention policies for this important and vulnerable sector of the population should be aimed to promote the consumption of adjusted and balanced diets among adolescents, since the adequate utilization of nutrients, together with exercise, will benefit their present and future health.

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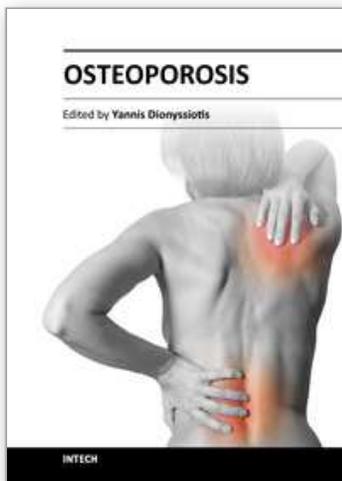
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## **Osteoporosis**

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Osteoporosis is a public health issue worldwide. During the last few years, progress has been made concerning the knowledge of the pathophysiological mechanism of the disease. Sophisticated technologies have added important information in bone mineral density measurements and, additionally, geometrical and mechanical properties of bone. New bone indices have been developed from biochemical and hormonal measurements in order to investigate bone metabolism. Although it is clear that drugs are an essential element of the therapy, beyond medication there are other interventions in the management of the disease. Prevention of osteoporosis starts in young ages and continues during aging in order to prevent fractures associated with impaired quality of life, physical decline, mortality, and high cost for the health system. A number of different specialties are holding the scientific knowledge in osteoporosis. For this reason, we have collected papers from scientific departments all over the world for this book. The book includes up-to-date information about basics of bones, epidemiological data, diagnosis and assessment of osteoporosis, secondary osteoporosis, pediatric issues, prevention and treatment strategies, and research papers from osteoporotic fields.

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