Bone fragility in young people: significant anamnestic elements

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ABSTRACT

Various factors are known to interfere with gain in bone density and structure during growth and development. Bone status in childhood has been shown to be a predictor of bone mass in young adulthood. This concise review aims to discuss the main factors that can influence peak bone mass during growth and development, and whether they may be predictors of future bone fragility risk, useful for physicians taking care of children and adolescents.

KEYWORDS

Children and adolescent bone health, peak bone mass, predictors of bone fragility, osteoporosis prevention.

Introduction

Bone tissue and bone turnover respond throughout life to a complex interplay of regulatory factors. Attempting to draw a complete picture of the anamnestic factors significant for an increased risk of bone fragility in young women and, less frequently, young men is therefore challenging.

We know that the bone structure and density of a thirty-year-old person is the result of various determinants acting during intrauterine life, infancy, and childhood. Pubertal maturation and adolescence are also crucial periods for skeletal growth, bone modeling, and bone mass accrual. Subsequently, bone density continues to increase up to the age of 25-30 years, depending on the site considered.

The importance of maximizing bone mineral accrual during the years of growth is now clearly recognized [1]. Knowledge about predictors of poor bone health may therefore be important to optimize later bone mass and strength. Given its impact on public health, it is important to identify anamnestic predictors of low bone mass in childhood and adolescence in order to identify individuals at risk and thus allow preventive interventions to be implemented by pediatricians and family physicians. This is the main goal of this paper in which, therefore, we briefly consider the multiple determinants of low bone mass in young people with the aim of outlining a targeted anamnestic tool.

Genetic causes

Family studies have shown that genetic background has a strong impact on bone mass in adult women. According to heritability studies, 50-85% of the variance in bone mineral density (BMD) is controlled by genetic factors which are mostly polygenic [2]. Genome-wide association studies have identified about 100 loci associated with BMD in premenopausal women; a few studies investigated genetic factors influencing pediatric bone accrual and strength, focusing mainly on different genes [3,4]. Studies in males are few, but disease-causing variants in genes involved in bone turnover have been demonstrated in about 20% of men with low bone mass disorders [5].

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Nutritional factors

Bone formation begins in the embryo in the sixth-seventh week of pregnancy and continues during gestation supported by maternal nutrients. The programming of bone mineral content (BMC) and therefore of bone dimensions occurs during intrauterine life and in the first period of postnatal life. Fetal growth restriction and low birthweight were found to be significantly correlated with BMC (more so than with BMD) in a cohort of 25-year-old women [6]. Maternal smoking has a negative effect. Breastfeeding is beneficially associated with multiple outcomes of bone health measured during infancy, adolescence, and at 25 years of age [7].

Dietary intake of calcium and protein during childhood is critical for bone growth and health [8]. According to reference intake levels of nutrients and energy for the Italian population (the LARN document), 1000 mg/day of calcium between 4 and 8 years and 1200 mg/day from 9 to 18 years are needed. In observational studies, consumption of dairy products, accounting, respectively, for 50-60% and 20-30% of daily calcium and protein intake, is associated with a lower risk of hip fracture in adults [9]. A vegan diet during childhood, without adequate use of nutritional supplements, can be a risk factor for impaired physiological bone accrual, as documented in a meta-analysis of

29 selected studies [10]. Maternal and child nutrition is important in terms of not only calcium intake, but also exposure to pollutants affecting bone health, such as perfluoroalkyl substances [11] and polycyclic aromatic hydrocarbons [12]. Nanoplastics are another pollutant widely present in our food chain with an impact on bone modeling [13]. Recent studies also suggest an impact, on bone health, of exposure to particulate matter, i.e., the mixture of particles suspended in the air and capable of crossing the respiratory membrane, entering the bloodstream, and reaching different tissues, including bone [14]. However, detecting exposure to pollutants through anamnesis is very complex.

Long-term consumption of both caffeinated and non-caffeinated soft drinks is negatively associated with variables of bone modeling and remodeling in adolescent girls. The mechanisms of this negative effect include the supplanting of milk and other proteins in children's diets, the low pH values of these beverages, and, in the case of cola drinks, the phosphoric acid and caffeine contents [15].

Physical activity

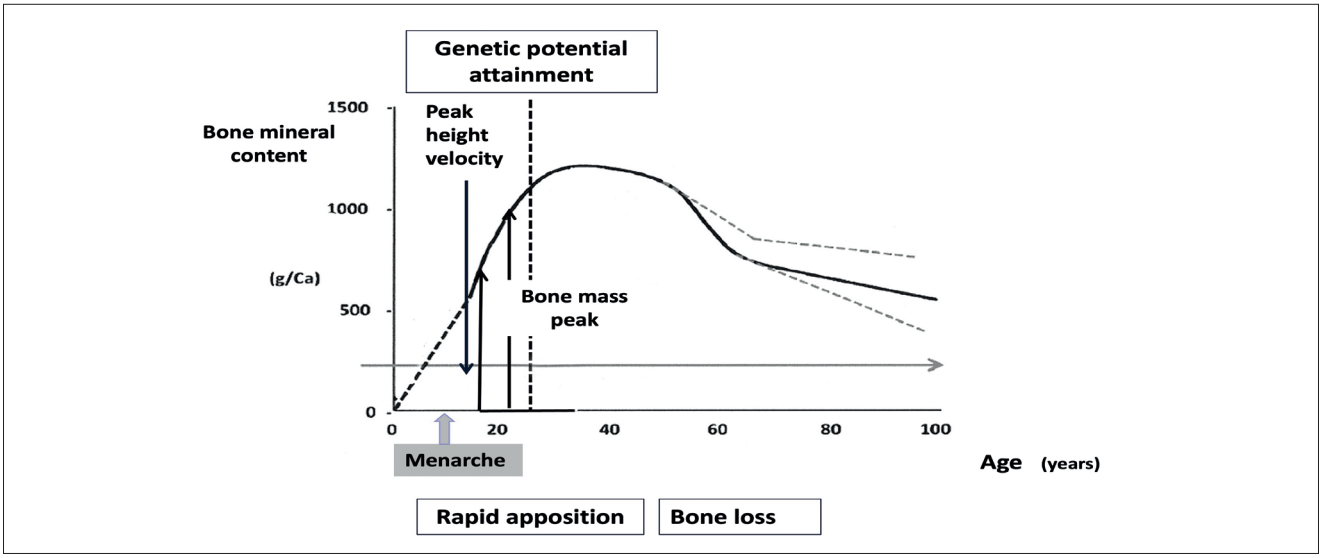
Physical activity during preadolescence and adolescence, maximizing skeletal exposure to mechanical loading, is an effective strategy for optimizing bone accrual, even if the effect is more marked in boys than in girls [16]. Evidence from randomized trials has some limitations, and does not allow the different effects of various types of training, or of exercise duration, to be established. A 10-year longitudinal study conducted from middle childhood to adolescence in more than 300 boys and girls confirmed that high participation in moderate-to-vigorous physical activity during childhood is necessary to improve bone strength in late puberty [17]. This is in agreement with the knowledge that growing bones are more sensitive than adult bones to mechanical and biochemical stimuli deriving from muscle. Another important difference is whether the activity is performed mainly indoors or outdoors, in the latter case involving significant sunlight exposure, which is the main source of vitamin D. Children and adolescents are more able than adults to produce vitamin D precursors in the skin. Dietary sources of vitamin D are few in number and, moreover, unpopular in the diets of young people. 25-hydroxyvitamin D serum levels in Italian children and adolescents reveal a high prevalence of deficiency [18], but there is still debate over the best method for measuring vitamin D status in this age group, Observational studies suggest that at least 10 µg/day vitamin D supplementation is needed to achieve optimal bone health in children and adolescents, but the results of randomized, controlled trials have been ambiguous.

Timing of puberty

Female pubertal maturation is characterized by an increase in linear growth and an acceleration in the deposition of calcium in the bone matrix, evident about 8 months after the growth spurt. In this period of life about 280 mg of calcium are added daily, accounting for about a quarter of the adult bone mass in two years of rapid growth. This phenomenon continues rapidly even in the first post-menarche years. In girls, maximum BMC (estimated at around 2,120 g) is reached on average within 7 years after the peak of growth velocity, at around 18 years of age. Furthermore, a different chronology of growth and mineralization in different sites has been demonstrated, in particular between areas with a prevalence of cortical bone and areas with a prevalence of trabecular bone, such as the spine [19]. Various longitudinal and cross-sectional studies have demonstrated that peak bone mass (PBM) i.e., the reaching of a plateau of volume and mineralization, occurs first for the long bones and then for the spine. In this district a small amount of bone mass probably continues to be added until the age of 25 years, or beyond (Fig.1).

Before puberty, males have been found to present higher BMD values than females in the mainly cortical bone sites (total body and femur), whereas in the sites with mainly cancellous bone, both sexes were equivalent until the age of 9 years. During puberty the gender difference in bone mass is expressed, with a

Figure 1 Trend of bone mass in females (modified from: Dei M, Bruni V "Paediatric and Adolescent Gynaecology" OEO, 2023).



delayed but probably more prolonged period of bone maturation in males than in females, and a larger increase in bone size and cortical thickness. Hormonal differences play a role, but the effect of a stronger lean mass is probably prevalent [20].

The timing of puberty varies widely between subjects as it is related to genetic factors but also to metabolic maturation and the occurrence of stressful events. Delayed pubertal development, even if constitutional, reduces BMD in subjects of both sexes under 18 years [21], and it is associated with impaired microstructural bone components and reduced mechanical resistance. The deficiency also persists into adult life. The underlying mechanism is not univocal: besides the delayed effect of bone-stimulating hormones (growth hormone, estrogens, androgens, etc.), common genetic regulators of pubertal timing and bone acquisition, and markers of epigenetic modulations are under study.

Endocrine and metabolic disorders

Bone turnover is physiologically affected by various endocrine stimuli, in addition to calcium-regulating hormones and growth hormones (GH and IGF-1). In girls, estrogens reduce trabecular bone resorption, promote the survival of osteocytes, increase the mesenchymal precursors of osteoblasts and osteoclasts, stimulate the differentiation of osteoblasts, and act on vitamin D absorption and metabolism. Even progesterone and androgens have an osteogenic effect [22]. Ovarian hormonal peptides, such as activin, inhibin, and Anti-Müllerian hormone (AMH), regulate bone mass. Estrogens are the dominant sex steroid regulating bone metabolism in boys, too. Testosterone plays a role during growth, and also later, indirectly, via aromatization to estrogens or via growth hormones.

Thyroid hormone levels affect the activity of chondrocytes and osteoblasts. Gut hormones (GIP, GLP1, GLP2 and PYY), both directly and modulated by microbiota, act on bone metabolism and induce a circadian rhythm with increased resorption during the night time compared with the day time [23]. Insulin is a critical element in osteoblast differentiation from bone marrow stromal cells, which leads to the enhanced production of osteocalcin that can, in turn, stimulate pancreatic β-cell proliferation [24]. Leptin, which is secreted by adipocytes and has specific receptors on bone marrow mesenchymal stromal cells and osteoblasts, has a similar stimulatory effect, as well as an indirect effect mediated by the ventromedial hypothalamus [25]. Endogenous glucocorticoids have anabolic effects on bone mass regulation, while excessive or exogenous glucocorticoids can have detrimental effects on bone. The study of endocrine regulation of bone growth and mass is open to further contributions.

Bone itself works as an endocrine organ and secretes several systemic humoral factors, including fibroblast growth factor 23, osteocalcin, sclerostin, and lipocalin 2, exerting profound effects on metabolic homeostasis.

Based on these premises, the occurrence of endocrine diseases affecting pubertal maturation, menstrual function, and metabolism in the peri-menarche years has significant repercussions on the attainment of peak bone mass. Subjects with hypogonadisms related to hypothalamic-pituitary diseases or to primary gonadal failure display bone mass deficiency. Turner syndrome deserves special consideration; this is a condition characterized by reduced bone mass derived from a combination of hormonal imbalance and intrinsic bone abnormalities associated with X-chromosome haploinsufficiency. Lower cortical porosity along with lower trabecular density and reduction in bone biomechanical strength have been described [26]. In all these clinical situations, Turner syndrome included, the importance of timely, appropriate, and tailored-dose estrogen therapy for osteoporosis prevention is well established. Reduced bone mass since adolescence has been described in subjects with Klinefelter syndrome, and it might be related to both reduced bone formation and higher bone resorption. Although low testosterone levels are clearly involved in the pathogenesis, this relationship is not always evident. Impaired muscle strength is a predictive factor [27].

In adolescent girls, bone turnover and the menstrual cycle are both highly vulnerable to energy deficiency and stress response activation. Functional hypothalamic amenorrhea is prevalent in the first gynecological years, when just over half of the skeleton is laid down. The pathogenesis of this disorder is complex and involves increases in CRF, ACTH, and cortisol production and dysregulation of autonomic nervous system functioning, low caloric intake inhibiting hypothalamic GnRH release, energy deficiency related to physical activity. Eating disorders associated with reduced nutrient intake and other weight control behaviors (smoking, anti-hunger supplements, vomiting, laxatives and abuse of diuretics) are present in about 16% of teenagers [28]. Besides hypoestrogenism and hypoandrogenism, due to suppression of ovarian function, other factors — reduction of anabolic hormones (IGF-1, Insulin, leptin), activation of stress response, low-grade inflammatory state, endothelial alterations, and immunological dysfunction — act synergically in reducing bone apposition and/or bone mineral density [29]. The International Olympic Committee underlined the importance of highlighting relative energy deficiency in sport (REDs) as a cause of stress fractures, tendon detachments, and poor health in athletes. In its last consensus statement, a clinical assessment tool to facilitate the detection of REDs was proposed [30]. Although the relationship is less evident in boys, in some elite gymnasts and in subjects with eating disorders an energy intake deficiency relative to energy expenditure is possible with repercussions on spermatogenesis and bone health.

Considering other metabolic alterations, not infrequent in childhood and adolescence, being overweight is another risk factor for impaired bone health, because the differentiation of mesenchymal stem cells in the bone marrow is driven toward adipocyte at the expense of osteoblast production. Furthermore, adipose tissue releases inflammatory molecules that upregulate the activation of osteoclasts, favoring bone fragility [31].

Moreover, insulin resistance modifies the effect of insulin on bone structure and of osteocalcin on pancreatic insulin secretion with negative effects on bone turnover. Overweight and insulin resistance are frequently associated with polycystic ovary syndrome. In subjects with this syndrome, the presence of dysmetabolism, together with chronic low-grade inflammation and vitamin D deficiency, may adversely affect bone health [32].

Bone health should be considered in subjects with gender dysphoria assigned male at birth. The treatment with GnRH agonists followed by long-term estrogen therapy is not always adequate to maintain physiological trabecular bone density. This is not the case for subjects assigned female at birth and receiving androgen-based gender-affirming therapy [33].

Chronic diseases

Almost all chronic diseases in childhood and adolescence (Table I) have an impact on bone accrual and mineralization. The pathogenesis is often multifactorial, consisting of:

- an inflammatory state and alterations of gut microbiota, further influencing the inflammatory environment through effects on T-cell production of immune mediators and cytokines that stimulate osteoclastogenesis;
- reduced absorption of nutrients, as in celiac disease, Crohn's disease, chronic hepatopathies;
- impairment of glucose homeostasis, as in poorly controlled type 1 diabetes;
- an impact on calcium metabolism, as in untreated hyperthyroidism;
- acidosis, as in chronic kidney disease;
- altered body composition, with reduced lean mass, as in cystic fibrosis;
- hypoxia and bone marrow hyperplasia, as in hemoglobinopathies;
- treatments as a possible concurrent cause, as in severe chronic asthma.

Medications

Table II summarizes the main drugs affecting bone mass. Their effects depend on dosage, timing of administration, and sometimes bone districts, for instance, with prolonged administration of glucocorticoids cortical bone is more affected than trabecular bone and long bones show increased fragility.

Table I Chronic diseases affecting peak bone mass

Celiac disease
Chronic kidney diseases
Chronic liver diseases (congenital biliary atresia, autoimmune liver disease, α-1-antitrypsin deficiency)
Cystic fibrosis
Congenital heart diseases
Crohn's disease
Hemoglobinopathies (sickle cell anemia, beta thalassemia)
HIV infection
Juvenile idiopathic arthritis
Severe asthma
Systemic lupus erythematosus
Type 1 diabetes (and MODY)

Debate on the possible repercussions of hormonal contraceptive use on the rapid acquisition of bone mass in the first years after menarche is still open. Various longitudinal studies, not all of comparable quality, have examined the effects of pills containing ethinyl estradiol and a progestin on BMD, with increase of BMD found to be lower in over half of pill users compared with controls. Well-conducted cross-sectional studies and a meta-analysis of selected trials [34] also show similar results. This reduction of BMD is not associated with an evident increase in fracture risk. Moreover, the effect does not seem to be dependent on estrogen dosages or type of progestin. We do not yet know whether the use of contraceptives containing natural estrogens (estradiol, estetrol) might be a valid option in order to avoid such repercussions. It is therefore important to pay particular attention to lifestyle factors with impacts on bone in young adolescents seeking hormonal contraception.

Table II Medications affecting peak bone mass.

Glucocorticoids
Antidepressants (SSRIs)
Antiepileptics
Chemotherapeutic agents
Immunosuppressants
Lithium
Pioglitazone
Warfarin

Table III Predictors of bone fragility at a young age emerging from a targeted clinical history

Genetics	Osteoporosis in relatives Spontaneous fractures in relatives Hip fractures in relatives
Nutrition	**Intrauterine** - Intrauterine growth restriction - Maternal smoking - Low birthweight **Infancy** - Breastfeeding **Childhood and adolescence** - Dairy product intake - Selective eating - Vegan diet - Soft drink use
Physical activity	Type of sport Hours per week dedicated Strenuous exercise Indoor/ outdoor
Menstrual function	Age at menarche Primary amenorrhea Menstrual disorders: functional hypothalamic amenorrhea Polycystic ovary syndrome
Metabolic dysfunction	Insulin resistance Overweight/obesity
Chronic diseases	Table I
Medications	Table II

Conclusions

Health care providers dealing with children and adolescents must be aware of multiple risk factors for bone health, because osteoporosis prevention begins at birth or perhaps even before. A targeted clinical history (Table III) is a valid tool for detecting indicators of risk, in order to promote strategies to optimize bone acquisition.

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