Review

Osteoporosis in children and adolescents

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Abstract

In recent years, the issue of low bone density in children and adolescents has attracted much attention. The classical definition of osteoporosis should be valid at any age, yet its practical applicability to children and adolescents remains a matter of debate and there is no consensus on a diagnosis based solely on the BMD value. The clinical relevance of uncomplicated low bone density in the young and its long-term consequences remain difficult to evaluate and there is only preliminary evidence that the BMD value is a predictor of fracture risk in growing subjects. Moreover, the interpretation of densitometric data in the young is difficult because the "normal" BMD values to be used for comparison are continuously changing with age, and in addition, depend on several variables, such as gender, body size, pubertal stage, skeletal maturation and ethnicity. Although Z-score values below −2 are generally considered a serious warning, most bone specialists make a diagnosis of osteoporosis in children and adolescents only in the presence of low BMD and at least one fragility fracture.

The scope of this review is limited to presenting a picture of the available knowledge. The literature on fractures will be presented in detail, since fractures are one of the key elements in the debate. There are countless papers on fractures in childhood and adolescence, but very few of them attempt to identify fragility fractures, and still fewer develop the concept of osteoporosis in the young in relation to fractures.

The different forms of primary and secondary osteoporosis, the more technical aspects of bone densitometry in pediatrics, and the delicate issue of treatment will be discussed only briefly.

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Contents

Introduction .................................................. 487
Understanding the growing skeleton ......................... 487
Measuring bone mineral density in growing subjects .... 488
Specific problems of DXA ................................... 488
Bone strength and muscle strength .......................... 488
Primary and secondary forms of osteoporosis in children and adolescents ................................ 488
Fractures ..................................................... 489
Epidemiology of fractures in children ....................... 489
Is low BMD a risk factor for fractures? ..................... 490
Children sustaining repeated fractures ..................... 490
Special risk factors for fractures in children .............. 490
The special case of vertebral fractures ..................... 491
Fractures in children affected by chronic diseases ........ 491
Long-term consequences of low bone density in childhood .................. 492

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Introduction

In recent years, the issue of low bone mass/low bone density in children and adolescents has attracted much attention. On the one hand, there is a growing awareness that the bone mineral mass acquired at the end of growth and development is a major determinant of the future risk of osteoporosis; on the other hand, the problem of osteoporosis is increasingly raised also in young patients.

Classically, osteoporosis is defined as low bone mineral density (BMD) with microarchitectural alterations of bone, increased bone fragility and a greater risk of fractures [1]. There is strong evidence that, in adults, the BMD value is a good predictor of the fracture risk, and it has been calculated that the fracture risk approximately doubles with each 1 SD decrease below the average value of sex-matched healthy young adults [2]. On this basis, a diagnosis of osteoporosis in adults is made if the BMD value falls more than 2.5 SD below the average value of healthy young adults ($T$-score $<-2.5$).

The definition of osteoporosis given above should be valid at any age, yet its practical applicability to children and adolescents remains a matter of debate and there is no consensus on a diagnosis based solely on the BMD value. The clinical relevance of uncomplicated low bone density in the young and its long-term consequences remain difficult to evaluate and there is only preliminary evidence that the BMD value is a predictor of fracture risk in growing subjects [3,4].

Moreover, the interpretation of densitometric data in the young is difficult because the “normal” BMD values to be used for comparison are continuously changing with age, and in addition, depend on several variables, such as gender, body size, pubertal stage, skeletal maturation and ethnicity. Usually, the reference population is one of ethnicity-, gender- and age-matched healthy controls and the index used is the difference between the observed BMD value and the reference (normal) BMD value, expressed in SD units. Such index is called $Z$-score, and is the only one to be used in the assessment of growing subjects. However, the uncorrected values of BMD and $Z$-score are not always satisfactory in the evaluation of a youngster since important variables, like body size and pubertal stage, must usually be taken into account. These problems will be further discussed below.

Although $Z$-score values below −2 are generally considered a serious warning, most bone specialists make a diagnosis of osteoporosis in children and adolescents only in the presence of low BMD and at least one fragility fracture [5], that is, only in the presence of what would be considered a complication of osteoporosis in adults.

This short introduction should suffice to understand the complexity behind a diagnosis of osteoporosis in children and adolescents. The scope of this review is limited to giving a picture of the available knowledge, keeping in mind that the times seem still not ripe for definitive conclusions. The literature on fractures will be presented in detail, since fractures are one of the key elements in the debate. The different forms of primary and secondary osteoporosis, the more technical aspects of bone densitometry in pediatrics, and also the delicate issue of treatment will be discussed only briefly, as they have been thoroughly dealt with elsewhere [5–9]. Sometimes, to avoid redundancy, the term “children” will be used in a wider sense than usual, to include young subjects up to about 20 years of age.

Understanding the growing skeleton

A short introduction to the process of skeletal growth and development is indicated at this point.

Throughout childhood and adolescence, the skeleton changes in both size and shape. 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. All these processes are influenced by genetic, hormonal and environmental factors. Up to 25% of peak bone mass (PBM) is acquired during the 2 years of peak height velocity. By age 18, at least 90% of PBM has been acquired, while the remaining 10% will be added later in the skeletal consolidation phase [10]. During puberty, the differences between genders become evident. Both the starting age of the pubertal spurt and the growth process are earlier in girls, but the duration of the growth spurt and the maximal peak of growth are greater in boys.

In the human skeleton, about 85% is cortical bone and 15% trabecular bone. Both the bone gain during growth and the bone loss in later age affect these two compartments differently [11,12]. Trabecular bone density is strongly influenced by the hormonal/metabolic factors associated with sexual maturation [13]. Consolidation of cortical bone is slower. Although the timing of peak values has not been precisely determined, the PBM is probably reached at the end of the second decade in the axial skeleton (predominantly trabecular bone), but only later in the appendicular skeleton (predominantly cortical bone) [14]. It must be borne in mind that these changes are not only continuous, but also subject to great individual variability, mostly related to the variability of pubertal development, and this is essential for the correct evaluation of BMD in young subjects.

Adequate calcium and vitamin D availability, together with regular physical activity, are among the most important environmental factors in the optimal accrual of bone mineral mass and density. Recent studies have pointed out the fundamental role of vitamin D in the development of strong bones. In a longitudinal study on 198 children, Javaid et al. [15] found that those born to
mothers with insufficient or deficient levels of 25(OH)-vitamin D during late pregnancy had low total-body and spine BMC at 9 years of age. In a 3-year longitudinal study on 171 healthy Finnish girls aged 9–15 years, Lehtonen-Veromaa et al. [16] found that pubertal girls with severe hypovitaminosis D may be at risk of not reaching optimal peak bone mass, particularly at lumbar spine.

Measuring bone mineral density in growing subjects

In the last decade, the measurement of bone mineral content (BMC) and bone mineral density in children and adolescents has become widely available and pediatric reference databases have been created. There are several methods for measuring BMD [7,8,17–21]. The most widely used is dual-energy X-ray absorptionometry (DXA), whose greatest advantages are low radiation dose, good precision and good reproducibility. The weaknesses of DXA are the impossibility to measure volumetric bone density and to distinguish between cortical and trabecular bone.

Central and peripheral quantitative computerized tomography (QCT and pQCT) produce three-dimensional images, but are less widely available and, in the case of central QCT, give a higher X-ray dose than DXA.

Quantitative ultrasound (QUS) techniques are radiation-free and less expensive, but only peripheral scans are available and different skeletal sites are measured by the different instruments, reducing the possibility of comparisons.

Magnetic resonance imaging is only used for special research purposes.

The correct use of the various densitometric techniques in children requires a deep understanding of their characteristics and limitations, and the problems posed by the growing skeleton must be considered.

Ideally, the “normal” BMD values to be used in the study of growing patients should be defined considering several variables (not only ethnicity, gender, and age, but also body size and pubertal stage), and for this reason, deciding what is a pathologically low BMD in children is a difficult task. Not only the choice of an appropriate control group is highly problematic, but also serial measurements in a single subject may be difficult to interpret.

Moreover, many cases of low BMD in the young are secondary to various pathological conditions, that cause a high variability, or even anomalies, in height, weight and pubertal development, and affect bone and bone development differently, or even affect some skeletal regions more than others (e.g. lower limbs more than trunk or vice versa). In these cases, specific corrections to the standard densitometric measures should be considered, as the usual comparison with ethnicity-, gender- and age-matched controls can give inaccurate results in terms of actual bone density and bone mass “loss”.

Specific problems of DXA

Since DXA is by far the most used method, some special remarks are indicated. The chief problem with DXA is that it does not measure the true bone mineral “density” (BMC/volume) but only an “areal” bone density (BMC/projection area). The areal BMD (g/cm²) is particularly deceptive when measured in growing patients, as it underestimates the true density value for smaller bones and overestimates it for larger bones. Thus, the influence of body size must always be considered, not only for the initial assessment, but also in the follow-up of growing patients; otherwise, for example, a subject might appear to have an increased BMD while this is only an artifact due to an increased bone size.

A widely used correction of the vertebral BMD value, trying to approximate the true “density”, is called bone mineral apparent density (BMAD, g/cm³), and is based on the assumption that the vertebral body is a cylinder: under this assumption, \( \text{BMAD} = \text{BMD} \times \frac{4}{3.14} \left( \frac{\text{vertebral body width}}{2} \right) \) [22]. Other correction methods are used for spine, hip and total body. Obviously, the same correction must be applied to both the studied subject(s) and the control population.

Bone strength and muscle strength

Considering that the clinical hallmark of osteoporosis is fragility fractures, the accent has recently been placed more on the concept of “compromised bone strength” rather than on low BMD, to underline that the risk of fractures is related to complex factors and not only to a simple quantitative measure. However, there is no objective measure for bone strength in vivo, so BMD remains the main diagnostic parameter [23].

A novel approach to the definition of osteoporosis in the young is based on the relationship between an individual’s BMC or BMD and muscle mass. Traditionally, BMC has been put in relation with body weight, and the influence of gravity has been considered its most important physical determinant. However, a deeper analysis led researchers to give more importance to the action of muscular work on bone, on the basis of the “mechanostat” model originally introduced by Frost to describe the muscle–bone interaction [24]. According to this model, the skeleton continuously adapts its strength to the strains that result from muscular action. The capacity of bone to increase its strength in response to mechanical forces is greatest during growth [18].

Some researchers deem it important, in evaluating the meaning of bone mass measurement, to put it in relation with the muscle mass. According to a simple algorithm proposed by Schoenau [25], if muscle mass is adequate for body height and BMC is adequate for muscle mass, the condition is considered “normal”. A diagnosis of osteoporosis should thus be considered only in the presence of an altered ratio between BMC and muscular mass, for example if there is a reduced BMC in the presence of a normal muscular mass, but not if there is a reduced BMC together with a reduced muscular mass [19,25,26]. However, the value of this model is to be confirmed by studies on larger samples and in different diseases affecting bone density.

Primary and secondary forms of osteoporosis in children and adolescents

There are some forms of primary and secondary osteoporosis typically observed in the young.

The primary forms (Table 1) are relatively rare, and some of them are familial or genetically determined. Multiple fractures are
frequent and may seriously affect a patient’s quality of life. Osteogenesis imperfecta (OI) is classified as a form of osteoporosis because of bone fragility, even if the primary defect is a genetically altered collagen structure. In the past decade, bisphosphonate treatment has radically altered its course in many cases. Idiopathic juvenile osteoporosis (IJO) is characterized by repeated fractures, including vertebral compression fractures. It is usually a self-limiting disease that spontaneously resolves after puberty, but in some cases it may result in severe deformities and functional impairment.

On the contrary, secondary forms of osteoporosis are increasingly observed in many chronic conditions (Table 2), particularly in those severe diseases in which a long survival is now the rule, thanks to aggressive treatment protocols. In these cases, low bone mass and an increased risk of fractures may be the consequence of the primary disease itself (because of reduced physical activity, intestinal malabsorption, malnutrition, hormonal or metabolic derangements, hypovitaminosis D, inflammation, cytokine increase, etc.) and/or of its treatment (e.g. corticosteroids, immunosuppressors). What to do in these cases, regarding both prevention and therapy, has become a serious problem, and most physicians will agree that these forms of osteoporosis are today’s great challenge in the pediatric bone field.

In general, osteoporosis should be suspected in young people in the presence of fractures for minimal trauma, chronic bone pain, or radiological evidence of rarefied bone. Bone densitometry is an important assessment tool, but a differential diagnosis is always required, particularly to exclude mineralization defects, such as those resulting from hypovitaminosis D. This is particularly important, considering the current reappearance of nutritional rickets [27]. In our opinion, appropriate skeletal and bone metabolism evaluations should be performed in all young patients affected by chronic diseases, particularly those characterized by chronic inflammation or requiring long-term corticosteroid therapy.

**Fractures**

Bone fragility (traumatic) fractures are the main complication of osteoporosis in adults, and the same would be expected at any age. However, there are objective difficulties in defining what constitutes the minimal trauma required to attribute a fracture to bone fragility, and a clear separation between traumatic and atraumatic fractures in young patients is difficult. There are countless papers on fractures in childhood and adolescence, but very few of them attempt to identify fragility fractures, and still fewer develop the concept of osteoporosis in the young in relation to fractures.

It must also be remembered that fractures, especially in infants, and especially if multiple or repeated, may be the consequence of violence and child abuse [28,29].

**Epidemiology of fractures in children**

Fractures are common events in children. Landin has estimated that 42% of boys and 27% of girls sustain a fracture between 0 and 16 years of age [30]. The peak of fracture rate during childhood/adolescence occurs between 10 and 15 years, at about 11 years in girls and 14 years in boys, together with the attainment of peak height velocity [31]. This can be explained by the higher frequency of risky physical activities at this age and by the relative undermineralization of bone resulting from the asynchrony between bone mineral accumulation and linear growth, since in both boys and girls, peak height velocity occurs...
0.5–0.7 years before peak bone mass acquisition velocity [10,32].

According to a large study in Malmo (Sweden), forearm is the most common fracture site in children aged 0–16, followed by hand phalanges and carpal–metacarpal bones [33]. In the last decades the incidence of fractures, particularly of distal forearm, in children and adolescents seems to be on the increase [33–36]. The reasons for this have not been clearly established. Lower physical activity, less time spent outdoor, unhealthy dietary habits, together with the longer survival in many chronic diseases and the wider use of corticosteroids, may all have some role.

Is low BMD a risk factor for fractures?

There is some evidence that children with lower-than-average BMD have a higher fracture rate. Some old and new reports suggest that forearm and wrist fractures are associated with low bone density in children [37–40]. Goulding [38] found that girls with forearm fractures have a lower BMD, a possible signal of a deficit in skeletal strength in otherwise healthy children. In an Australian study, the bone densities at the hip, spine and total body of 321 children (9–17 years) with upper limb fractures were compared with those of 321 class- and gender-matched controls without fractures. Both boys and girls with fractures had a slightly reduced BMD of spine and hip versus controls, and in both genders spine BMD and BMAD were consistently associated with all upper limb fractures, and spine and hip BMAD with wrist and forearm fractures [41]. Even if this was a retrospective study of fractures recorded in a regional fracture registry, a strong association between bone density and the 5-year fracture risk was observed: the risk increased markedly with a Z-score below −2.

There are also preliminary data from recent prospective studies showing an association between BMD and fracture risk in children. Goulding [3] calculated that girls have a twofold increase in the risk of new fractures for each reduction of 1 SD in total body BMD. In a British study, 6,213 children aged 9.9 years were studied with total body (TB) DXA and followed for 2 years. The risk of fracture was found to be increased of 89% for each SD decrease of BMC adjusted for height and weight [42]. A particularly interesting result of this prospective study was the predictive meaning of the TB areal BMD, which was found to be inversely related to the risk of fractures during the 2-year follow-up. Although bone size was not directly related to fracture risk, children with fractures tended to have a smaller skeleton for body size. In a Swiss prospective study (125 girls followed over 8.5 years) the cumulative incidence of fractures was 46.4%, mainly (48%) at forearm and wrist. Decreased bone mass gain in the axial and appendicular skeleton and reduced vertebral size were observed in girls who sustained fractures at the time of pubertal maturity. The authors’ conclusion is that fractures during childhood may be predictive of future low peak bone mass and bone fragility [43].

In a recent review and meta-analysis of studies on children up to 16 years of age, Clark et al. [44] conclude that there is some evidence of an association between low BMD and fractures; however, considering the nature (case-control) of the available studies and their possible biases, large prospective cohort studies are needed for definitive conclusions.

Children sustaining repeated fractures

A particularly interesting point is that many children, apparently healthy, suffer repeated fractures during growth. The Dunedin (New Zealand), study, following 601 subjects until 18 years of age, showed that 291 of them reported 498 fractures, with 172 sustaining a single fracture, and 119 more than one fracture [45]. Thus, 326 fractures (about 65% of all fractures) occurred in subjects with repeated fractures. In 83.2% of these cases, the first fracture occurred before 13 years of age. The risk of a second fracture after the first was 1.90-fold, and that of a third fracture after the second was 3.04-fold [46]. Another study focused on 313 children, aged up to 13 years, treated for a recent fracture [47]. In their lifetime, they had had a total of 468 fracture events: over half (54.7%) of these occurred in the 32.3% of children breaking bones more than once. Adverse reactions to milk (reported in 13.4% of the sample) were related to a younger age at first fracture. Moreover, children who had a first fracture before 4 years of age had a significantly higher rate of fractures (36.7 fractures per 100 years of exposure) than children sustaining their first fracture at an older age (e.g. 10.4 fractures per 100 years of exposure in the 10–13 age group).

Even if little information is available on this point, it seems reasonable to think that children with repeated fractures might have a particularly weak skeleton. This is confirmed by a study in which DXA measurements were done in 90 youngsters aged 5–19 years who had 2 or more forearm fractures: site-specific bone weakness (low BMC Z-score at the ultradistal radius) was found [48].

Special risk factors for fractures in children

Some studies have attempted to identify the risk factors for fractures, particularly for repeated fractures. For example, asthma and adverse reactions to cow milk were identified by Yeh et al. [47], and both should be seriously considered, given their frequency in the young. In another study, four risk factors were over-represented: early age of first fracture, adverse reactions to cow milk, low dietary calcium intake, and overweight [48]. In a population-based case-control study [49], the association between use of soft drinks, milk consumption, physical activity, bone mass and upper limb fractures was investigated in 206 children with fractures and 206 matched controls. A positive association between wrist and forearm fractures and cola drinks consumption was discovered, but the association was weak and apparently mediated by low physical activity and low BMD. Another recent article [50] observed that children with recurrent fractures had lower BMD for body size, lower milk intake and lower physical activity. Vice versa, they had a higher body mass index (BMI) and a higher consumption of carbonated beverages than children without fractures.

Even if conclusive evidences are still lacking, these data, taken together, suffice to state that apparently healthy children...
with recurrent fractures should be evaluated for low bone mass and the presence of possible risk factors, including underlying primary or secondary bone metabolic disease.

The special case of vertebral fractures

Special attention must be paid to the occurrence of vertebral fractures without severe trauma, an exceptionally rare event in the healthy young. The literature is quite lacking on this point, and the possibility that a vertebral fracture might be caused by a mild trauma, and that it could be a fragility fracture, is not always considered.

Vertebral fractures account for only 2–5% of all fractures in childhood, with an increased incidence in late adolescence [33,51,52]. According to studies conducted on the radiological archives of Malmö (Sweden), the annual incidence of vertebral fractures was 0.07% below 16 years of age, while it doubled to 0.14% in the 16–18 years group [53,54]. A similar incidence was observed in Edinburgh, 0.1% in adolescents aged 15–19 years [55], and in Great Britain, 0.13% in girls and 0.15% in boys aged 16–17 years [31].

Rarely, vertebral body collapse and back pain may be the only symptom present at the onset of childhood acute lymphatic leukemia, even with normal peripheral blood count [56].

Vertebral fractures occurring in very young subjects have a different clinical outcome from those occurring in older people. Karlsson et al. [53] made a clinical and radiological re-evaluation in 24 subjects (12 M, 12 F) who had suffered a vertebral fracture between 7 and 16 years of age, 27 to 47 years after the fracture. Subjective symptoms were scarce: only 3 patients had occasional back pain. Radiologically, a significant increase of the ratio of anterior height to posterior height of the fractured vertebral bodies was observed at follow-up, demonstrating the modeling capacity of the fractured vertebrae of very young patients. A decrease of the postrumoral kyphosis was observed in 8 (33%) subjects, all aged 13 or less at fracture. Moller et al. [54], who similarly studied 23 subjects (18 M, 5 F) with a vertebral fracture in late adolescence (16–18 years), also found that such fractures had a generally favorable outcome: only 5 subjects (21.7%) had occasional back pain, and in only one case the pain was serious enough to cause early retirement. However, in these patients, the ratio of anterior to posterior height of the fractured vertebral bodies was not changed at follow-up, indicating that the modeling capacity of fractured vertebrae is lost in late adolescence. Unfortunately, these studies do not report whether the subjects who have spine fractures in their youth have also an increased risk of fractures in later years, an important datum to consider in the evaluation of the long-term consequences of fragility fractures in the young.

Fractures in children affected by chronic diseases

Several reports seem to suggest that osteoporosis and fragility fractures are on the increase in patients affected by many chronic diseases, but even in these cases no systematically collected data on the incidence/prevalence of bone fragility fractures are available. With the exception of OI, only few data have been published. Moreover, the relatively small samples, the different characteristics of the control groups, and the different treatments of the same diseases do not allow strong conclusions.

Some studies did not find significant differences in the fracture rate between patients and controls. Persad et al. [57] made a questionnaire-based survey of fractures in children affected by inflammatory bowel diseases (IBD). One hundred thirty-two patients (age range 4–18 years) were compared to 131 healthy siblings (1–26 years): 29 (22%) of the patients had 41 fractures, while 44 (33.5%) of their siblings had 55 fractures, a difference that was not significant. However, the data were supplied by the patients' families in a mailed questionnaire, without any review of clinical or radiological records; only peripheral fractures were reported; and the age ranges of the patients and controls were different. A similar study, also based on a questionnaire, was conducted by Roven et al. on 186 subjects with mild-to-moderate cystic fibrosis (aged 6–25 years) and 427 healthy control subjects in the same age range [58]. Only peripheral fractures were reported. A fracture occurred in 2% of the subjects with cystic fibrosis and in 23% of the healthy controls, showing no differences in fracture risk. In a retrospective cohort study on the long-term fracture risk of 279 young subjects (<35 years of age) diagnosed with asthma in childhood, Melton et al. [59] found that 107 of them had 189 fractures, but that the overall fracture risk was not increased with respect to age- and gender-matched controls.

On the contrary, many studies found an increased fracture risk in children affected by various diseases. Van der Sluis et al. [60,61] found that children with acute lymphoblastic leukemia had a 6-fold higher fracture risk than controls and a significant decrease in total body BMD during chemotherapy, and for at least 6 months after its completion; however, on a 10-year follow-up, BMD was much improved and almost normal in some cases. In one of the few studies on a large group of children with a single disease (418 children with cerebral palsy) [62], 12% had fractures, and among them, 30% had multiple fractures. Older age and use of valproic acid were predictive of fractures. In a recent retrospective study over a 7-year period on 750 patients with epilepsy [63], the authors found that 39% of the patients had pathological fractures caused by low-intensity trauma and associated with reduced BMD, and that also in the youngest age group (under 20 years) pathological fractures were numerous, about 15% of all fractures. In a large retrospective cohort study on patients with childhood onset arthritis in the United Kingdom [64], Burnham et al. found that this condition is associated with a clinically significant risk of fractures in children and adolescents, and possibly also in adults. In a large population-based cohort study of 13,000 individuals affected by celiac disease, and 65,000 age- and gender-matched controls, contrary to earlier reports, Ludvigsson et al. [65] found that patients with celiac disease, including children, may be at increased risk of fractures, even in the long term. In particular, the hazard ratio of hip fractures in children was 2.6.

In a population-based, prospective 5-year follow-up study involving 196 Finnish children surviving organ transplantation [66], an elevated risk for fractures was observed. Seventy-five children (38% of the sample) had 166 fractures (102 vertebral) in total. The incidence of all fractures was 6-fold higher (92 vs.
impaired periosteal expansion during puberty [70]. Two cohort alterations (reduced total body bone mass, reduced lumbar spine that the late onset of puberty in males induces permanent skeletal delay of puberty, compared with 45 matched controls, concluded the year. Use of glucocorticoids and low BMD (Z-score)<−2), the fracture incidence were the main risk factors for multiple and recurrent fractures during the year of study [67].

Finally, in a 1-year multi-center study by 11 pediatric units in seven countries (Argentina, Czech Republic, Germany, Italy, Poland, The Netherlands, USA), the bone fragility fractures (i.e. fractures in the absence of major trauma) in youngsters with different chronic diseases potentially leading to reduced bone mass were evaluated. All new cases were recorded as soon as they occurred. The recorded “first fracture” events were 256, and 36 additional fractures after the first one were observed. Multiple sites were involved in 71 fracture events, so that the total number of recorded fractures was 362 (24 vertebral). In the six centers collecting the higher number of patients, the fracture incidence ranged from 2% to 25% of the total population followed during the year. Use of glucocorticoids and low BMD (Z-score<−2) were the main risk factors for multiple and recurrent fractures during the year of study [67].

Long-term consequences of low bone density in childhood

Considering that more than 90% of adult bone mass is gained during the first two decades of life, the possible long-term consequences of low bone density in the young deserve the greatest attention.

Some studies have evaluated the impact of bone-involving diseases during childhood on bone density and fracture risk in adult age. Zak et al. [68] evaluated bone metabolism in 65 men (mean age 32.2 years) with a history of juvenile chronic arthritis (JRA), and found a reduced BMD at spine and hip and an increased bone turnover with respect to a gender- and age-matched control group. These observations were confirmed by French et al. [69] in 32 adults (mean age 35 years), affected by JRA before 16 years of age. Many of them were osteopoenic, and among the factors associated with the reduced BMD at all sites (spine, hip, forearm, total body) there were reduced physical functioning, tobacco use, low calcium intake. Another study on 32 men (aged 21–33 years), with a history of constitutional delay of puberty, compared with 45 matched controls, concluded that the late onset of puberty in males induces permanent skeletal alterations (reduced total body bone mass, reduced lumbar spine bone width, reduced hip cross-sectional area), probably due to impaired periosteal expansion during puberty [70]. Two cohort studies on subjects with a history of anorexia nervosa documented an increased risk of fractures. In the first study [71], the fracture risk was greater in the 2,149 patients than in controls (incidence rate ratio: 1.98), and remained so more than 10 years after the diagnosis. In the second study [72], the fracture risk was increased in both women and men, compared with the expected numbers of fractures (standardized incidence ratio 2.9 for women and 3.4 for men). Other studies, evaluating survivors of childhood cancer, found a reduced BMD even 20 years after discontinuation of chemotherapy and recovery from the disease [73,74]. Such studies show how different diseases in childhood/adolescence can leave a permanent bone damage, even after their resolution, in terms of reduced BMD and increased fracture risk. This emphasizes that a low BMD in a young patient should be considered not only as a risk factor for the present, but also as a potential risk factor for the future, so that a strategy to minimize its impact should be sought.

Treatment

There is still no consensus on the treatment of osteoporosis in the young. With the exception of OI, controlled studies in children are lacking, and only a few have been done on sufficiently large samples. We can give only a rapid overview of this complex issue, and the reader is referred elsewhere for a fuller discussion [5,9].

A rational therapeutic approach to young patients affected by osteoporosis should first identify and then, whenever possible, reduce or eliminate all the known risk factors for low bone mass, before prescribing specific drugs. As a general rule, therapeutic interventions must be prudent, beginning with the simplest and safest ones, such as calcium and vitamin D supplementation. Physical activity is essential to increase BMD not only in health but also in different pathological conditions. Growth retardation, pubertal delay, or hypogonadism must be corrected with appropriate hormonal therapy. Effective control of the underlying disease is the best first-line approach to prevent secondary osteoporosis.

Regarding antiresorptive drugs, only bisphosphonates have been successfully used in children. They are now regularly used in children with severe OI or osteoporosis related to cerebral palsy, in which the repeated fractures dramatically affect the quality and expectancy of life [75,76]. On the contrary, there are still many doubts about using these drugs in children affected by mild primary diseases (e.g. OI with low fracture rate), spontaneously resolving diseases (e.g. most cases of IJO), or with low BMD but no fractures.

Bisphosphonates have been shown to increase BMD, relieve pain, increase mobility, and reduce fragility fractures in OI, corticosteroid-induced osteoporosis and other secondary osteoporosis (in connective tissue diseases, renal insufficiency, cerebral palsy, burns, etc.). Intravenous cyclical pamidronate or oral alendronate have been most often used [77–79].

Although the long-term safety of bisphosphonates in children is still under scrutiny, the original concerns have not been confirmed in over 10 years of pediatric use. Bisphos-
phosphonates did not alter the healing of fractures, the appearance of growth plates, the skeletal growth rate, the onset and course of puberty. Histological analysis did not reveal altered bone cellularity or structure, but only decreased bone resorption. Like in adults, adverse effects have been rare, and generally mild and reversible. Young women taking bisphosphonates must be advised to avoid pregnancy [5,9,79].

In conclusion, many consistent data demonstrate that, if correctly used, bisphosphonates are useful and effective agents in pediatric osteoporosis. In this writer’s opinion, they should be used in children only after all the alternative measures have been tried without success. Considering the difficulties in establishing the correct dose and the duration of therapy, and in monitoring the effects, their use should be reserved to specialized centers, with experience in pediatric bone diseases.

Conclusions

The meaning of the word osteoporosis in pediatrics remains somewhat ambiguous. On the one hand, it is commonly used to define, with a well-known term, a reduced bone mass and bone density, as if this automatically implied pathological bone fragility, which is precisely what we do not know yet. On the other hand, with a more careful approach, to speak of osteoporosis in children is considered inappropriate in the absence of fractures: but this unfortunately means that a diagnosis of osteoporosis in younger patients may be made too late.

The critical point is that there are no strong, consistent evidences that a certain degree of BMD reduction corresponds to a significantly higher risk of fractures also in pediatric patients, and there is not a threshold value of BMD with a clear prognostic meaning, allowing the separation of the subjects at high risk for fractures from those at low risk.

The weak, preliminary evidences that fractures are more frequent in subjects with a BMD Z-score below −2 may be considered a first approximation. This is more easily accepted in children affected by a chronic disease that is known to cause secondary osteoporosis, but the problem is present, and is even more complex, in children and adolescents who are apparently healthy, but have a low bone density. We are still confronted with the thorny question of how to interpret this finding and how much weight to give it. What are the short- and long-term risks of having a low bone density during the age of growth? Should we consider it a warning? Should we undertake preventive measures, and if yes, which ones? Should we wait and see how BMD behaves in time? When does “low bone density” become “osteoporosis”?

More research is needed to answer these questions, but three key points should be considered in an international research agenda:

- A consensus conference on the diagnostic criteria for osteoporosis in children and adolescents.
- Prospective, controlled, double-blind clinical trials, involving statistically significant samples, on the efficacy and safety of osteoporosis therapy in the young, including the use of calcium and vitamin D.
- Epidemiological studies on the fragility fractures in the young, also to evaluate their consequences and impact in later adult life.

References


