European **Rev**iew for **Med**ical and **Pharmacol**ogical **Sci**ences 2009; 13: 117-128

Bone health as a primary target in the pediatric age

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Abstract. – Bone tissue is constantly renewed during childhood and adolescence to assure skeleton growth both in size and mineral density: up to 90 percent of peak bone mass is acquired by age 18 in girls and age 20 in boys, which makes youth the best time to "invest" in bone health. The reduction in bone mineral density leading to compromised strength and microarchitecture of bone tissue can favour the occurrence of fragility fractures in the pediatric age. Assessing the normality of bone density measurements in childhood by current methods is hampered by the lack of normative control data. The understanding of factors useful for maximizing peak bone mass, as well as the knowledge of diagnostic tools and therapeutic strategies for managing a state of reduced bone mineral density are crucial to prevent fractures throughout lifetime.

Key Words:

Bone mineral density, Osteoporosis, Pediatrics.

Introduction

Bone is a living tissue which remains metabolically active throughout life: the skeleton provides support for muscles and locomotion, adapts its morphology to mechanical loading, acts as a store for minerals and offers a protective environment to bone marrow. At a histological level bone is a specialized form of connective tissue, composed of cells dispersed in an extracellular matrix rich of fibers and amorphous substances of proteic origin with the peculiarity of being mineralized, i.e. characterized by the *in situ* deposition of minerals[1]. Cells dispersed in the matrix are osteoblasts, osteocytes and osteoclasts. Figure 1 shows bone cells with their biochemical products used as "markers" of bone metabolism. Skeletal maturation can be considered complete at the acquisition of peak bone mass, the maximal amount of bone tissue accrued during growth and development, whilst subsequent consolidation continues in the early adulthood[2]. Bone mass construction is influenced by a variety of genetic factors (like gender, ethnicity and hormonal status) accounting for up to 75 percent and environmental factors (like nutrition, lifestyle behaviours, exercise habits, exposition to sunlight and eventual drug administration) accounting for the remaining 25 percent[3]. The precise age at which peak bone mass is acquired is still indefinable and may be site-dependent, though it is generally accepted that 16-18 years and 18-20 years correspond to the maximal bone density accumulated respectively in females and males, as emerged from studies deriving from densitometry techniques[4]. In the course of the following decades (beginning from 40 years) this quantity of bone tissue tends to decrease in a progressive trend. Since the risk of fractures is in inverse relation to bone mass, the achievement of a high peak bone mass at the end of adolescence represents the best modality to prevent the onset of fractures in adulthood[5].

Osteoporosis, Osteopenia, Rickets and Osteomalacia

The quantitative reduction of bone tissue is named "osteoporosis" and is associated with the risk of developing fragility fractures: this is the underlying cause of more than 1,5 million fractures annually (300,000 hip fractures and approximately 700,000 vertebral fractures) and affects 75 millions of individuals in the world and is characterized not only for a diminished bone mass, but also for a deteriorated quality of bone tissue. It is often a progressive and debilitating disease which leads to a huge social burden through an increased morbidity and high costs

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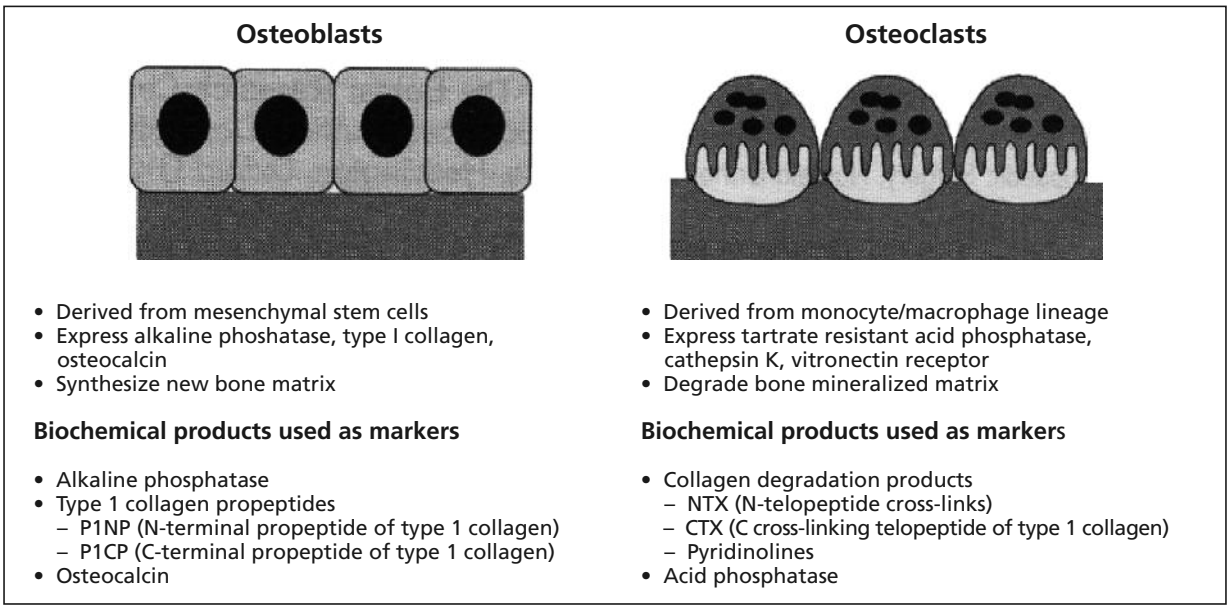

Figure 1. Osteoblasts and osteoclasts with their main features and biochemical products, which can be used to monitor bone metabolism.

associated with fractures. In 1973 Dent suggested that the origin of osteoporosis, traditionally considered a disease of the old age, had to be focused in the pediatric age[6]. The progressive reduction of bone mass in adulthood is associated with thinning and reduced number of trabeculae in the cancellous bone and thinning of the cortical bone[7]. All risk factors contributing to the pathogenesis of osteoporosis are listed in Table I. Sex female predisposition is depending on the overall inferior bone mass in comparison with males and on the control exerted by oestrogens in bone mass acquisition: in fact, a surgical menopause due to ovariectomy or a precocious menopause (beginning before 45 years) cause the reduction of bone mass with significant anticipation.

Classifications of osteoporosis are numerous, but the mostly used subdivision is in primitive and secondary forms (Table II). Primitive forms, causing more than 80% of cases, mostly referable to menopause and senility, are by definition unrelated to the possible known causes of osteoporosis. In the post-menopausal osteoporosis bone mass loss involves trabecular bone tissue, particularly in the vertebral column, while in the senile forms both trabecular and cortical bone tissue are involved[8]. Osteoporosis in males is usually considered to be involutional, though it can result secondary to corticosteroids, hypogonadism or alcohol abuse[9]. While the mineral component of the osteoporotic bone tissue is normal, though being quantitatively inferior, rickets and osteomalacia are characterized by a qualitative abnormality of bone tissue due to a mineralization defect in the proteic matrix, at the sites of bone growth or remodeling for rickets, leading to bone deformity and stunted growth rate in children. In particular, childhood rickets is characterized by reduced bone tissue formation and accumulation of non-mineralized "osteoid matrix"

Table I. Risk factors for the onset of osteoporosis.

- Ageing
- Female sex
- Precocious or post-surgical menopause (oestrogen deficiency)
- Chronic renal insufficiency
- Hyperthyroidism
- Long-term treatment with corticosteroids, anticonvulsivants or anticoagulants
- Nutritional disorders (with malabsorption)
- Incorrect nutritional habits (deficient calcium intake and hyperproteic diet)
- Low BMI (< 20)
- Insufficient physical activity
- Cigarette smoking
- Alcohol abuse
- Aeronautics activities
- Familiarity for osteoporosis

Table II. General classification of osteoporosis.

Primitive osteoporosis	Secondary osteoporosis
• Juvenile idiopathic osteoporosis • Idiopathic osteoporosis of adulthood • Postmenopausal osteoporosis (type I) • Age-related ("senile") osteoporosis (type II) • Heritable disorders of connective tissue (osteogenesis imperfecta, etc.)	• Endocrinopathies (Cushing's syndrome, hyperthyroidism, hyperparathyroidism) • Gastrointestinal diseases with malabsorption • Hematological diseases (leukemias, multiple myeloma) • Rheumatological diseases (rheumatoid arthritis, systemic lupus erythematosus) • Drug-induced osteoporosis (corticosteroids, antiepileptic drugs, anticoagulants) • Insufficient physical activity • Post-traumatic osteoporosis

caused by vitamin D, calcium and/or phosphate deficiency. Signs of rickets are related to the lacking calcium fixation in the skeleton with the following appearance of knock-knee, bow-leg, pectus carinatum, narrow chest, macrocrania, rachitic rosary and bracelet, while cramps in the limbs, muscle weakness and tetany are its most frequent symptoms. Very typical is the predisposition to late dentition, spontaneous multiple tooth decay and abscess formation[10]. Prophylaxis of nutritional rickets must begin in the neonatal period by vitamin D administraton (at a daily dose of 400 IU). Since the early 20th century, ultraviolet radiations or vitamin D ingestion have been recognized as a cure for rickets, with the exception of vitamin D-resistant familial hypophosphatemic rickets, in which treatment with high dose-vitamin D (1000-5000 IU/day) produced no improvement[11]. We can distinguish X-linked hypophosphatemic rickets (associated with *PHEX* mutations, causing renal phosphate wasting indirectly, through a humoral factor known as FGF 23 or "phosphatonin"), type 1-autosomal dominant (associated with reduced renal synthesis of 1,25-dihydroxyvitamin D, due to decreased mitochondrial alpha-1 hydroxylase activity) and type 2-autosomal dominant rickets (associated with reduced reply to 1,25-dihydroxyvitamin D). Diagnosis of hypophosphatemic rickets is currently based on detection of low serum phosphate, normal serum calcium, inappropriately normal serum 1,25-dihydroxyvitamin D, elevated serum alkaline phosphatase, normal to low serum parathyroid hormone, low tubular reabsorption rate of phosphate and radiological demonstration of rachitic bone deformities. Therapy requires 25,000-50,000 IU/day of vitamin D, calcium (0.5-5 g/day, although serum calcium concentrations must be periodically and carefully monitored to avoid hypercalciuria and nephrocalcinosis) and – in the X-linked form – oral phosphate (70-100 mg/kg/day)[12]. The defect of skeletal mineralization appearing in adulthood, when skeleton accretion has been already completed, is named "osteomalacia", characterized by a normal bone volume with reduced mineral content: its most frequent cause is lipid malabsorption with reduced levels of circulating vitamin D or vitamin D altered metabolism, calcium-poor diet (normally absorbed for about 40% of calcium ingested), poor exposition to sunlight (leading to an insufficient endogeneous vitamin D production), multiple pregnancies and breast-feeding[13].

Bone Mineral Density as a Parameter of Investigation

The amount of calcium in specific regions of the bones defines "bone mineral density" (BMD). Bone mass increases throughout childhood, with maximal bone mass accrual occurring in early to midpuberty and slowing in late puberty[14]. However, most published studies are cross-sectional and do not include individuals in sufficient numbers, encompassing the entire age span of interest, to determine the age at which peak bone mass is attained. Physical activity, particularly weight-bearing exercise, and exposition to sunlight are known to have a contributive role to the acquisition of a correct BMD, but after puberty other established elements are the maturity of secondary sexual characters in females and body weight in males[15]. BMD results are interpreted according to the World Health Organization criteria and are expressed in relation to specific skeletal sites through the comparison with values reported in referral populations[16]. The most used parameter to define BMD is T-score (patient's BMD – population peak BMD/SD of

population peak BMD), expressed in standard deviation (SD), which identifies BMD shifting from the average of a corresponding sex-matched population at the achievement of the maximal BMD (i.e. around 20 years). BMD is considered normal when the T-score is between –1 and +1 SD according to the 1994 World Health Organization statements (Table III). Osteoporosis is diagnosed if the T score is below –2.5 SD and osteopenia if the T score is included between –2.5 and –1 SD[17]. For most BMD tests, 1 SD difference in T-score equals a 10-15 percent decrease in bone density. Low BMD and fragility fractures are increasingly recognized in pediatrics and bone fragility should be suspected in all cases of fractures without substantial traumas[18]. Anyhow, the clinical relevance of uncomplicated low BMD in the child remains difficult to be evaluated as in adulthood, when fracture risk is exponentially related to BMD values[19]. The evaluation of bone densitometry is a matter of concern in pediatrics due to the physiologic continuous change of bone size and shape: thus, an apparent bone mass accrual might simply reflect an increase of bone volumetry[20]. In addition, reference values are referred to healthy subjects matched only for ethnicity, gender and age, but do not consider body weight and pubertal stage. The definition for adult osteoporosis cannot be applied to children and adolescents, who have not yet achieved their bone peak mass. Therefore, in the evolutive age it is preferable to use Z-score (patient's BMD – population age-related BMD/SD of age-related population BMD), expressed in SD, which identifies the comparison between child's BMD and the average BMD of a corresponding gender/age-matched pediatric population[21]. In the medical literature there is no unanimous agreement about the definition of threshold values in bone pathologic conditions of the pediatric age: the International Society for Clinical Densitometry disapproves the terms "osteoporosis" and "osteopenia" for the child, which should be totally substituted with the diction "low bone density for the chronological age" if the Z-score is below –2 DS[22]. In addition, the diagnosis of low BMD in children and adolescents should not be made on the basis of densitometric criteria alone, but in the presence of both clinically significant fracture history and low bone mass[23].

Causes of Reduced Bone Mineral Density in Pediatrics

Causes of bone fragility leading to reduced BMD in the pediatric age can be primary or secondary and are schematically listed in Table IV. Diseases primitively involving bone tissue are somewhat rare in the pediatric age. Idiopathic juvenile osteoporosis is a primary form of reduced BMD of unknown etiology and unexplained pathophysiology, rarely observed: its onset is before puberty and is characterized by pain in the back and feet, difficult deambulation, radiological evidence of osteoporosis and multiple fractures (typically in the metaphyses and vertebral bodies). This is a transient condition caused by hormonal imbalance related to the pubertal growth spurt, leading to osteoblast dysfunction and increased bone resorption: most of these children experience a complete recovery within 3-4 years and can be treated only with physical therapy; the diagnosis relies on the exclusion of other known causes of reduced BMD as congenital/acquired conditions and drug administration[24]. *Osteogenesis imperfecta* (or "brittle bone disease") deserves attention among causes of reduced BMD in pediatrics: this dominantly inherited disease is known in 9 forms of different severity, characterized by defects in the synthesis or structure of type I collagen, occurring as a result of a range of different mutations in type I collagen genes. Its peculiarity is proteic matrix reduction in bone tissue with following precocious multiple pathologic fractures and severe skeletal deformities[25]. The differential diagnosis between idiopathic juvenile osteoporosis and *osteogenesis imperfecta* has been specified in Table V. Other heritable disorders of connective tissue as Marfan syndrome, Ehlers-Danlos syndrome, homocystinuria and Bruck syndrome (with a clinical picture characterized by *osteogenesis imperfecta* combined with arthrogryposis multiplex) display a direct impact on bone tissue qual-

Table III. Definition of normal bone mineral density, osteopenia and osteoporosis in adults.

Normal bone mineral density	T-score > –1 DS
Osteopenia	T-score between –1 and –2.5 DS
Osteoporosis	T-score < –2.5 DS

Table IV. Primary and secondary causes of reduced bone mineral density in children.

Primary causes

- Juvenile idiopathic osteoporosis
- Heritable disorders of connective tissue (osteogenesis imperfecta, Marfan syndrome, Ehlers-Danlos syndrome, homocystinuria, Bruck syndrome)

Secondary causes

Genetic diseases
- Gaucher disease
- Mucopolysaccharidoses
- Turner syndrome
- Klinefelter syndrome
- Phenylketonuria
- Protein lysinuric intolerance
- Glycogen storage disorders
- Galactosemia
- Menkes disease

Diseases with reduced physical activity and insufficient mechanical loading of the skeleton
- Cerebral palsy
- Duchenne muscular dystrophy and dystrophinopathies
- Spinal neural tube defects (myelomeningocele)
- Progressive spinal amyotrophy
- Poliomyelitis
- Polytrauma with prolonged immobilization

Drugs with osteopenic effect
- Corticosteroids
- Antiepileptic drugs
- Anticoagulants (heparin and warfarin/acenocoumarol)
- Antiblastic chemotherapy (methotrexate, cyclosporine)
- Highly active antiretroviral therapy

Nutritional causes
- Malnutrition
- Diet without milk and derivates
- Carential rickets
- Total parenteral nutrition

Endocrine diseases
- Hypogonadotropic hypogonadism
- Delayed puberty
- Constitutional delay of puberty
- Functional hypothalamic amenorrhea
- Gonadal steroid insufficiency
- Oestrogen unresponsiveness (aromatase deficiency or oestrogen receptor defects)
- Growth hormone deficiency
- Hyperthyroidism
- Type 1 diabetes mellitus
- Cushing's syndrome/disease
- Primary hyperparathyroidism
- Acromegaly and hyperprolactinemia
- McCune-Albright's syndrome

Chronic diseases
- Cystic fibrosis
- Chronic kidney disease with renal failure
- Inflammatory bowel disease
- Celiac disease
- Anorexia nervosa and binge eating disorder
- Juvenile idiopathic arthritis
- Systemic lupus erythematosus
- Juvenile dermatomyositis
- Organ transplantation
- Congenital heart disease

Hematological diseases
- Thalassemia
- Sickle cell disease

Neoplasms invading the bone
- Lymphoblastic leukemia and lymphoma
- Neuroblastoma

Table V. Differential diagnosis between idiopathic juvenile osteoporosis and *osteogenesis imperfecta*. (Modified from Campos LM et al. J Pediatr (Rio J) 2003; 79: 481-8).

	Idiopathic juvenile osteoporosis	Osteogenesis imperfecta
Family history	Negative	Often positive
Age of onset	2-3 years before puberty	Birth or childhood
Duration of signs	1-4 years	Lifelong
Physical findings	Abnormal gait, metaphyseal fractures	Blue sclerae, short stature, thin gracile bones with multiple deformities, kyphoscoliosis, lax joints, dentinogenesis imperfecta, hernias, deafness
Biochemical abnormalities	–	Increased markers of bone resorption
Radiological abnormalities	Metaphysial fractures	Narrow long bones, diaphyseal and buckle fractures, presence of wormian bones in the skull
Molecular studies	Normal type I collagen	Abnormal type I collagen (>85% of cases)

ity. Patients with genetic diseases involving the skeleton, particularly lysosomal diseases deriving from genetic defects of lysosomal enzymes, which result in the accumulation of undegraded substrates in bone tissue, as mucopolysaccharidoses, are prone to the development of different levels of reduced bone mass, depending on various additional factors as nutritional deficiency, epilepsy and protracted immobilization[26].

Causes which secondarily reduce BMD are extremely heterogeneous and range from genetic, endocrine and hematological diseases to physical inactivity, various drugs and nutritional problems. Most children affected by chronic diseases fail to achieve an optimal peak bone mass. Among the numerous conditions involving the skeleton in a secondary fashion there is the prolonged immobilization: the defective use of limbs increases bone tissue resorption in the cancellous bone, where trabeculae become rarefied, thinner and more fragile. This can be typically observed in neuromuscular disorders as cerebral palsy, Duchenne muscular dystrophy and myelomeningocele[27]. Antiepileptic drugs as phenobarbital, phenytoin and carbamazepine have been shown to be associated with a lowering of BMD in childhood and adolescence by the induction of liver microsomial enzymes which accelerate vitamin D catabolism[28]. Anticoagulants influence bone tissue quality in different ways: heparin stimulates directly osteoclasts, warfarin and acenocoumarol reduce osteocalcin carboxylation by their role of vitamin K antagonists. Preventing bone demineralization induced by the longlasting administration of oral anticoagulants requires regular calcium and vitamin D consumption as well as carrying out a moderate physical activity[29]. In total parenteral nutrition there is an aluminium loading which reduces bone tissue formation and induce intense articular pain on the back and extremities: the only known treatment for this condition is the temporary or permanent interruption of total parenteral nutrition itself[30]. A state of renal osteodystrophy can begin in young patients with long-standing chronic renal insufficiency, owing to abnormal bone decalcification related to secondary hyperparathyroidism and disturbed vitamin D metabolism[31]. Multiple disorders resulting in deficient caloric and micronutrient intake, as calcium and vitamin D, may affect peak bone mass achievement during adolescence. Specific nutritional disorders associated with reduced BMD include cystic fibrosis, inflammatory bowel disease, celiac disease and anorexia nervosa[32]. The association of celiac disease with fractures is controversial in the medical literature, but follow-up studies of celiac patients on a gluten-free diet have demonstrated the normalization of BMD[33]. Women with anorexia nervosa who had onset of the disorder during adolescence have more severe osteopenia than those who developed the disorder during adulthood[34]. Patients with Cushing's syndrome (caused by prolonged exposure of body tissues to high levels of cortisol) and more often those with Cushing's disease (caused by a pituitary benign adenoma secreting large amounts of adrenocorticotropin) may have reduced bone mass due to the direct effect of hypercortisolemia on bone and the secondary hypogonadal state[35]. Glucocorticoids at high dosages administered for long periods in patients with inflammatory/autoimmune diseases or after organ transplantation can determine a secondary low BMD: metasteroidal consequences on bone and growth retardation are common complications of glucocorticoid therapy in pediatric patients, but the rate of bone loss is strictly related to dose[36]. Loss of bone occurs most rapidly in the first 6 months of glucocorticoid therapy, predominantly in the cancellous bone. Failure to achieve peak bone mass is thought to result from many factors, including direct effects of steroids on bone, impaired calcium absorption, abnormal renal calcium handling, reduced gonadal steroid secretion and changes in the growth hormone/insulin-like growth factor-I axis[37]. Different rheumatological diseases such as systemic lupus erythematosus and juvenile dermatomyositis have been associated with the reduction of BMD[38]. However, given the widespread therapeutic use of corticosteroids in these conditions, it is difficult to demonstrate an independent effect on bone[39]. The presence of bone loss in patients with abnormal pubertal development demonstrates the critical impact of pubertal hormone changes on normal bone mineral acquisition[40]. McCune-Albright syndrome is classically defined by the clinical triad of fibrous dysplasia of bone, involving single or multiple skeletal sites, café-au-lait skin spots and hyperfunction of multiple endocrine glands leading to pseudo-precocious puberty: occasionally this disease might start with pathologic fractures due to a defective bone mineralization[41]. Lastly, patients with all thalassemia syndromes and other hematologic disorders display hypogonadism, bone marrow hyperplasia, increased bone turnover, variable states of osteopenia and increased fracture risk,

whilst patients with different solid tumours might present a paraneoplastic syndrome with parathormone ectopic secretion and objective pictures of osteopenia[42].

How to Study Bone Mineral Density in Children

BMD evaluations require undoubtly a peculiar attention in pediatrics. Children studied for bone health need firstly to be evaluated for their height, weight, pubertal stage, calcium intake, type of physical activity, eventual history of fractures and serum 1,25-dihydroxyvitamin D (normal value in children is 20-80 pg/ml), though vitamin D repletion is better assessed by serum levels of 25-hydroxyvitamin D (normal value: 20-100 ng/ml). The first instrumental system used to evaluate bone mass *in vivo* has been standard radiography, which is not sensitive enough to detect bone loss until 25 to 40% of BMD has been lost. As annual variations of bone mass do not exceed 6-7%, even in the course of diseases with high bone turnover, newer tools of evaluation with a major precision had to be investigated. Dual energy X-ray absorptiometry (DXA) is the most widely available method of measuring bone densitometry (X-rays are used, but the radiation dose is less than during a chest X-ray) and can be applied in different skeletal sites, though the lower spine and total upper femur are mainly studied to evaluate respectively cancellous and cortical bone[43]. Routinely DXA is frequently used for assessing BMD also in pediatrics and many Authors have carried out BMD normality curves for the pediatric age[44-48]. It has to be emphasized that in children and adolescents BMD values are expressed as Z-scores by the comparison with gender/age-matched healthy subjects. DXA measurements identify only an "areal" BMD (g/cm^2, i.e. the ratio of bone mineral content to the projection area) instead of a true volumetric BMD (g/cm^3, i.e. the ratio of bone mineral content to bone volume): the consequence is an overestimation of greater bone sizes and an underestimation of smaller ones. Many correction formulas have been proposed to take into account body size, though there is no definite agreement about the one with the most acceptable correcting effect[49]. Peripheral quantitative computed tomography (pQCT) is the most accurate BMD test, which is not dependent on bone size and is preferably applied to peripheral bones as radius, femur and tibia, though reference data are not yet sufficient for diagnostic purposes. This technique is used to evaluate separately cancellous and cortical bone, but might offer useful information about bone strength too. A precise volumetric evaluation can be obtained through pQCT especially in the forearm, but its pediatric applicatory interest is poor due to costs and higher radiation doses, 10 times superior to DXA[50]. New methods of measuring BMD using ultrasound have also been developed with smaller and less expensive systems than traditional DXA ones. Quantitative ultrasound bone densitometry (QUS) uses sound waves to analyze bone tissue of different skeletal sites as heel, phalanges of the hand, radius and tibia. Phalangeal QUS is an accurate method to assess bone mineral status and fracture risk in children and adolescents with bone and mineral disorders, as well as in healthy children. Most used phalangeal QUS parameters are amplitude-dependent speed of sound and bone transmission time, reflecting both BMD, bone elasticity and architecture: reference curves for phalangeal QUS variables according to age, height, weight, body mass index and pubertal stages are available from early childhood to young-adulthood[51].

Therapy in Children's Low Bone Density

The results of the densitometric evaluation help healthcare providers in making recommendations about either prevention or treatment of reduced BMD, but no guidelines deriving from controlled clinical studies are actually available. Therapeutic interventions should not be instituted on the basis of a single DXA measurement. The effective control of an underlying disease (as celiac disease through a strict gluten-free diet or juvenile dermatomyositis through an adequate immunosuppressant therapy) is the rational approach to restore bone mass in many cases of secondary reduced BMD. Patients on long-term corticosteroid therapy should receive the minimum effective dose to control the underlying disease[52]. Pubertal retardation or hypogonadism require a specific correction with hormonal therapy[53]. The first step in the therapeutic management of children with reduced BMD is control of calcium, phosphate, protein and vitamin D intake and their adjustment according to the recommended dietary allowance[54]. Calcium supplementation has been shown to improve BMD, but it is unclear whether the effect is sustained once supplementation is stopped. Whether calcium or other micronutrient supplementation can lead to an improvement in peak bone mass remains unknown[55]. Calcium-rich foods should be preferred,

Table VI.

Pharmacological modulators of osteoclast activity in adults	Pharmacological modulators of osteoblast activity in adults
• Bisphosphonates • Oestrogens • Selective oestrogen receptor modulators • Calcitonins • Strontium ranelate • Blocking RANKL system (osteoprotegerin, soluble RANK, RANKL-antibodies)	• Parathyroid hormone 1-34 (teriparatide) • Strontium ranelate • Other potential stimulators (prostaglandins, fluoride, vitamin D and calcitriol analogues, RANK ligand, androgens, growth factors)

because calcium salts (as calcium carbonate) are often refused by most children and long-term compliance is difficult to obtain[56]. The availability of vitamin D is mainly dependent on the cutaneous production of cholecaciferol induced by the exposition to sunlight, but in diseases as systemic lupus erythematosus ultraviolet rays might lead to the exacerbation of clinical symptoms and many patients with chronic disabilities live in charitable institutes with poor possibility of exposition to the external environment. The recommended dose of vitamin D is 400 IU/day in children and adolescents, remembering that its therapeutic index is narrow and there is great interindividual variation in the dose that will lead to chronic toxicity and hypercalcemia; thus periodic monitoring of serum calcium, phosphate, magnesium and alkaline phosphatase is recommended. The available different vitamin D analogs on sale (calcitriol: 1,25-dihydroxyvitamin D; calcifediol: 25-hydroxyvitamin D; alfacalcidol: 1-α-hydroxyvitamin D) have not been compared systematically[57]. If an increased risk of fractures is established there is the possibility of administering drugs, which might increase BMD. Anti-resorption therapy is aimed at preventing further bone loss (whilst anabolic therapy is aimed at building new bone tissue): final goals of any treatment strategy must be obviously the reduction in fracture risk and the preservation of an adequate quality of life. Table VI lists all pharmacologic modulators acting on osteoclast and osteoblast activity in adults. There is scanty experience for the anabolic therapy in the pediatric age, while anti-resorption therapy with bisphosphonates is actually under discussion. With the exception of osteogenesis imperfecta, there are very few controlled studies in children, mostly related to small numbers of patients. Put on the market more than 25 years ago, bisphosphonates are synthetic analogues of pyrophosphate with great affinity to hydroxyapatite and power to cause dramatic changes in bone physiology by the inhibition of osteoclast-mediated bone re-

Table VII. Comparison of old and new generation-bisphosphonates.

Drug	Generation	Oral dosage	Parenteral dosage
Etidronate (hydroxy-etiliden-bisphosphonate)	I	300-600 mg/day	–
Clodronate (dichloromethylen- bisphosphonate)	I	400-800 mg/day	100-200 mg/2-4 weeks
Pamidronate (amino-hydroxyipropiliden-bisphosphonate)	II	150 mg/day	0.5-1 mg/kg for 3 days
Alendronate (amino-hydroxyibutan-bisphosphonate)	II	5-10 mg/day aut 70 mg/week	–
Risedronate (hydroxy-pirinidil-etiliden-bisphosphonate)	III	5 mg/day aut 35 mg/week	–
Neridronate (amino-hydroxy-etiliden-bisphosphonate)	III	–	25-50 mg every 1-2 months
Ibandronate (hydroxymethylpentilamino-propiliden-bisphosphonate)	III	150 mg/month	3 mg every 3 months
Zoledronate (hydroxy-imidazol-phosphonoethyl-bisphosphonate)	III	–	0.020-0.025 mg/kg

Table VIII. Side-effects of bisphosphonates.

Oral or intravenous bisphosfonates	Hypocalcemia with hyperparathyroidism
	Skin rash
	Atrial fibrillation
	Bone pain
	Delay in tooth eruption (in children with osteogenesis imperfecta)
Oral bisphosfonates	Upper gastrointestinal irritation
	Esophageal ulceration
Intravenous bisphosfonates	Influenza-like illness
	Transient leukopenia
	Acute renal failure and nephrotic syndrome
	Jaw osteonecrosis (unreported in children)

sorption[58]. In Table VII bisphosphonates of old and new generation used in the clinical practice are listed. Etidronate is one of the first drug used against osteoporosis by the inhibition of the dissolution of hydroxyapatite crystals and their amorphous precursors[59]. Intravenous pamidronate has been used in most cases, but zoledronate is the most potent bisphosphonate actually available, being 850 times more powerful than pamidronate and 16,000 times more powerful than clodronate as inhibitor of osteoclast function[60]. Oral bisphosphonates must be administered in the morning, on an empty stomach, in orthostatism, at least one hour before starting any usual daytime activity. In particular, aminobisphosphonates can be administered once a week per os: alendronate is the first bisphosphonate for which clinical studies were available, defining a significant increase of BMD in the lumbar column: 8% after 4 years of treatment[61]. Neridronate has been more recently introduced and successfully administered in patients with neoplastic hypercalcemia: it induces the differentiation of osteoblast precursors and reduces fracture risk in patients aged 5-17 years with osteogenesis imperfecta[62]. Side effects and general contraindications of bisphosphonates are listed in Tables VIII and IX. Periodic controls of BMD during treatment is advised at least after 6-12 months since startment in order to catch significant differences, whilst markers of bone formation and resorption (listed respectively in Tables X and XI) have only been studied in adults, who can be identified as uncompliant or unresponsive patients. Studies in animals have shown fetal abnormalities in bone induced by bisphosphonates, so it is unethical to study bisphosphonates in pregnant women or women who might become pregnant[63]. Currently there are many doubts about administering bisphosphonates in mild primary forms of low BMD or in cases of recognized low BMD with no history of fracture, because long-term efficacy and safety data are still not available. However, due to the difficulty in defining the correct dose and the overall duration of treatment, the prescription of bisphosphonates should be reserved to specialists experienced in pediatric bone biseases[64].

Table IX. General contraindications of bisphosphonates.

- Pregnancy
- Chronic kidney disease (stages 4 or 5)
- Hypocalcemia
- Osteomalacia and vitamin D deficiency
- Esophageal disease (for oral bisphosphonates)
- Bedrest with impossible upright position (for oral bisphosphonates

Table X. Markers of new bone formation.

- Total alkaline phosphatase (bone-specific isoenzyme)
- Osteocalcin
- N-terminal propeptide of type 1 procollagen 1 (P1NP)

In conclusion, much also remains to be done, despite the recent and remarkable advances in bringing osteoporosis and reduced BMD to the public attention, in understanding their pathogenesis and in improving diagnosis and treatment. It is now well established that bone strength is not only dependent on bone mass, but also on bone quality, which depends on several parameters, including bone macro and microarchitecture, bone matrix proteins and mineral content through the balanced activity of formation and resorption during bone remodeling. At the cellular level this balance is largely dependent on cell number and activity, which are controlled by hormones and autocrine/paracrine signalling. Optimization of skeletal health is a process which has necessari-

Table XI. Markers of bone resorption.

- Tartrate-resistant acid phosphatase
- Deoxypyridinolines
- C-terminal telopeptide of type I collagen

ly to be kept in mind for the whole life duration, pediatric age enclosed, because inadequate achievement of peak bone mass can predispose to pathological levels of BMD in the long term and increased risk of fractures, which are their most dreadful consequence. The available clinical data indicate that behavioural and lifestyle changes, as regular weight-bearing exercise, avoidance of smoking or reducing alcohol intake, have a slight impact on the absolute reduction of fracture risk, while there is general agreement that calcium and vitamin D supplementation should be an integral component of the management strategy, along with specific osteoporosis treatment.

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