OSTEOPENIA IN CHILDHOOD AND ADOLESCENCE

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ABSTRACT

Osteopenia, term of child pathologies, is a decrease in bone mass relative to chronological age, being an intermediate state between normal bone mass and osteoporosis. It has multiples etiological factors, comprising a heterogen group of diseases of the connective tissue with genetic determinism and osteopenia gained in various pathological conditions affecting bone homeostasis. Early diagnosis is determined by measuring bone density through non invasive imaging methods, the most common being dual-energy x-ray absorbtiometry (DEXA) and quantitative ultrasonography. Treatment in children customize through the need to adapt the intake of calcium and vitamin D to physiological growth needs and to requirements of some diseases. Specific drug treatment with nitrogen bisphosphonates was introduced to the children but is not yet well acted. Attention to be given to this bone pathologies in children and adolescents is warranted of its prognostic value for the rest of his life, to the peak bone mass of 20-21 years of age.

Keywords: osteopenia, children, diagnosis, treatment

Genetic (present in 80% of cases), endocrine, autocrine and nutritional factors ensure the constant renewal of bone (resorption and replacement). The process is very active during fetal and postnatal growth, until 18-20 years; at the age of 25 years peak bone mass is obtained, necessary to bone health and long-term prognosis (1).

Modelling of bone in children and in adults is performed by the basic multicellular unit (UMB), a temporary structure that last for 6-9 months. This is a unique structure, consisting of a team which comprises: osteoclasts (two weeks life), osteocytes, osteoblasts (three months life), the central capillary, nervous fibres, connective tissue. UMB is measured by the amount of bone replaced.

UMB activators factors (PTH, IgF-I, IL-1, IL-6, TNFα, PGE, NO, calcitriol) and the estrogenic inhibitory factors influence the lifetime of UMB (6-9 months). A unit UMB is measured by the amount of bone replaced, has a displacement speed of 25 micrometers/day, redesigning the same site in 2-5 years. 10% of the turnover of the entire skeleton takes place in 12 months (2-4).

Bone turnover remains open to the further investigations; have recently been found as participant factors involved in osteoclast differentiation and proliferation the role of one receptor activator of nuclear factor kB (RANK) and its ligand (RANKL) and the osteoprotegerin (OPG) as an inhibitor of this process. Gene mutations, proinflammatory cytokines and glucocorticoid excess can increase system RANK/RANKL (5).

Osteopenia is a decrease in bone mass relative to chronological age shown histological by deficiency of bone tissue and radiological by decreased bone density. It is an intermediate state between normal bone mass and osteoporosis and is common in children and adolescents. Bone density is lower than the average healthy adult with 1-2 SD; associate clinically history of fractures.

In osteoporosis, the strong negative balance of the remodelling process reduces bone density with more than – 2 SD and increase the risk of fractures. A single leg long bone fracture, two upper limb fractures or one vertebral fracture by compaction have clinical significance. Peak bone mass at the

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end of adolescence is the primary determinant of bone health in adults (6).

ETIOLOGY AND CLINICAL FEATURES

Osteopenia in a children and adolescents have multiples etiological factors. Primary forms are either the result of the primary disease of the connective tissue affecting bone and/or other supporting tissues, or is known as juvenile idiopathic osteoporosis.

Gene mutations, most known, causes a heterogeneous group of connective tissue diseases that affect the quality and quantity of collagen type I: osteogenesis imperfecta, Cole-Carpenter dysplasia, Sigleton-Merton dysplasia, osteopenia with mandibles lesions, osteoporotic pseudogliomal dysplasia, Ehlers-Danlos syndrome, Marfan syndrome, Bruck syndrome, homocystinuria, geoderma osteodysplasticum, Menkes syndrome (3,6).

Osteogenesis imperfecta (brittle bone disease) has an incidence of 1/10000 and is characterized by increased bone fragility with recurrent minimal trauma fractures. Recent studies have identified the involvement of multiple genetic loci, including those of VNT ligands, of signalling molecules between different cellular compartments, including these between the hematopoietic compartments and the osteocytic lines (VNT1 effectors). VNT signals are essential for normal skeletal development and bone homeostasis; VNT 1 mutation was correlated with the severe form of osteogenesis imperfecta (prenatal onset osteoporosis) (Glass 2005 cited by 7).

Juvenile idiopathic osteoporosis is a rare discovery, casual, in children with bone pain and fractures (long bones, spine), rarely with kyphosis or scoliosis. The diagnosis requires exclusion of secondary osteopenia. The disease affects both sexes, often starts 2-3 years before puberty with insidious pain in the back and lower limbs, gait disorders, fractures near the joints that support the weight. Often family history is positive for bone diseases. Histological morphometry evidences the decrease of the bone turnover and of trabecular mineralization. There is no characteristic biochemical picture. Quantitative computerized tomography shows a reduced lumbar trabecular and femoral cortical bone mineral density (8). Pathogenesis kept unknown; was involved the polymorphism low-density lipoprotein gene receptor co related toprotein 5, which lowers the performance of osteoblast; is associated the vitamin D deficiency and the hyperparathyroidism (9). Treatment with bisphosphonates is under study.

Osteopenia/acquired osteoporosis is the result of disturbance factors involved in bone homeostasis, deficiency or excess, or the intervention of different drugs, that affect the bone remodelling process. Secondary osteopenia frequency is more frequent than reported in practice. Can accompany:

– *Chronic inflammatory diseases*: SLE, juvenile idiopathic arthritis (JIA), DM, inflammatory bowel disease, nephrotic syndrome.

– *Reduced physical activity*: traumatic, cerebral palsy, muscular dystrophy.

– *Endocrine disorders*: hypogonadism (gonadal digenesis), hypo/hyperthyroidism, Cushing's syndrome, GH deficiency, delayed puberty.

– *Catabolic syndromes/poor nutrition malabsorption*: malignancies (ALL, lymphoma), vitamin D deficiency, cystic fibrosis, mental illness (anorexia nervosa, bulimia), chronic malabsorption, HIV, intense physical activity in women (athletes).

– *Drugs*: glucocorticoids (chronic therapy), anticonvulsants, heparin, dose methotrexate in oncologic doses (10).

The frequency of secondary osteopenia is not negligible. Applying ultrasound (sometimes verified by DEXA and dosing 25-OHD) in children with chronic diseases diagnosed in IV and II Pediatric Clinic – Emergency Hospital for Children "Sf. Maria" in a period of six years revealed the presence of osteopenia with following percentage frequency: AJI 48.57% (105 cases), chronic hepatitis 38.5% (82 cases), persistent asthma 35% (182 cases), intestinal malabsorption 32.2% (118 cases), impairment chronic renal 75% (346 cases). The frequency of secondary osteopenia mentioned is close to other reports (11).

Pathogenesis of osteopenia in chronic diseases is very complex, intertwining the effects of proinflammatory cytokines, the hormonal disturbances involved in bone metabolism, with the nutritional deficits by low input or severe organic suffering (hepatic, renal, malabsorption). UMB failure is compounded by drug treatments (12,13,14). Multitude of disease states that requires repeated treatment with corticosteroids and the need for frequent long course makes this product to be a partner in the production of pathogenic feared osteopenia in young people.

The effects of glucocorticoids in the cell nucleus level is reflected in the increase of RANKL and OPG decrease, which extends the life of osteoclasts, osteoblasts and decreases the differentiation rhythm of osteoblasts inducing the apoptosis, increases the osteocytes apoptosis with a decrease resistance and bone mass (15).

Indirect effects of glucocorticoids on bone are: inhibition of calcium uptake in the intestine and renal tubules causing hyperparathyroidism, transrepression of osteocalcin and collagen 1 (bone matrix proteins) thus lowering mineralization and induces bone fragility, cortisone myopathy (increased risk of fracture).

Glucocorticoid-induced osteopenia begins after the first month of treatment, evolving rapidly in the first year (3.5% loss), and slow after (0.5-1% per year). After 6 months of treatment, 30% of patients present the trabecular bone osteopenia. Aggravating factors are: the evolution of the underlying disease, immobilization, obesity, smoking. Prevention with bisphosphonates in child is recommended in more than 3 courses of systemic corticosteroids per year. 12 months of treatment with bisphosphonates reduces the risk of fractures (15,16).

Osteopenia of preterm newborn is pathogenetic particular through a combination of inadequate reserves, loss of essential minerals by organic immaturity and insufficient intake (difficult) to replace losses and to restore reserves. Mineral content and bone density is positively correlated with gestational age. On the other hand preterm and term infants with low weight could be affected by placental pathology that limited the transfer of phosphate (physiological placenta converts vitamin D to 1,25-dihydroxycholecalciferol). Disruption in mineral metabolism is aggravated by renal losses, by the effects of parenteral nutrition combined with copper deficiency and the impact of treatment with steroids and diuretics. In time, the preterm baby, may be affected by one metabolic bone disease (rickets of prematurity), characterized by abnormal bone modelling and reduced linear growth (17). Breastfeeding by the increased content of growth factor and hormones, as well as monitoring the intake of mineral and vitamin D, contribute to the gradual normalization of bone between 2 and 16 years.

THE DIAGNOSIS OF OSTEOPENIA/OSTEOPOROSIS

Early diagnosis of osteopenia is determined by *measuring the bone density* – safest method – measure the bone density in gr./cm^2 and, in children, determine the Z score, representing the number of SD from the mean of a healthy child of the same age, sex and ethnicity. Different types of methods to assess bone mineral density are non-invasive dual-energy X-ray absorbtiometry (DEXA), Quantitative computed tomography (QCT), Qualitative ultrasound (QUS), single photon absorbtiometry (SPA), dual photon absorbtiometry (DPA), digital X-ray radiogrammetry (DXR), single energy X-ray absorbtiometry (SEXA). Measurements apply to vertebrae of the lumbar spine, hip, fist; high tissue thickness that covers the bones can generate errors.

Simple plain bone X-ray detected the osteopenia only after 20-40% bone loss.

Quantitative computer tomography (CTQ), progressively improved method, is a technique based on a three-dimensional body scanning standard, separately measuring cortical bone mineral density and the trabecular one; the amount expresses the average density of the peripheral area. In children with idiopathic juvenile osteoporosis, where the histological morphometry revealed decreased trabecular bone turnover and the trabecular mineralization heterogeneity, CTQ detected reduction of bone mineral density of the trabecular bone in both the lumbar spine (important values) and the femoral cortical bone (8).

DEXA is considered the "gold standard" in bone exploration for precision, speed, stable calibration and low dose radiation. SIOC (2007) recommend it in children over 4 years of age and adolescents, applied lumbar and/or the whole body (without cephalic extremity); DEXA exploration introduced the term "low bone mineral content for chronological age". Z score results of the difference in bone mineral density of the patient and a normal individual of the same age and sex/DS. Z value is more accurate than the assessment of Tanner stages of puberty. Disadvantages of this technique: the attenuation coefficient of fat is different from that of muscle and gain errors (3% forearm, column 5%, 6% head and femoral neck), the equipment is expensive and requires special authorization (18).

Quantitative ultrasound explores peripheral skeleton in areas with minimal amounts of soft tissue, using ultrasound transducers and a computerized system for results processing. SIOC in 2007 stated the fidelity by exploring the calcaneus, patella, tibia, radius, phalanx, stressing that the results are similar to DEXA. Advantages of the method: the absence of irradiation technique, easy to apply, small devices, movable, favourable for population studies (19).

The biochemical collagen markers of bone resorbtion with practical value are deoxipiridinolina and the peptides resulted from telopeptides by the action of metaloproteinases on collagen type I. The depxipiridinoline comes from the bone, from the non-helicoidal part of collagen I. The serum value is not influenced by the diet and correlates with DEXA

results. The carboxiterminal peptide resulted from telopeptides signifies the increase of bone density when the osteoporosis treatment is correct, by the decrease of its serum and urinary titer (10, 11).

Biochemical bone turnover exploration comprises determining the biochemical markers of bone synthesis and resorption (non collagen and collagen).

From the biochemical markers of bone synthesis has proved the utility of bone alkaline phosphatase value determined with monoclonal antibodies, is a reliable marker for bone formation (monitor treatment). Osteocalcin, noncollagen protein, synthesized by osteoblasts, bone-specific, and dentin, as well as the extension peptides of the procollagen type I, has little practical value.

From noncollagen biochemical markers of bone resorption enrolles matinal urinary calcium and acid phosphatase, but with reduced practical value. Bone sialoprotein, phosphorylated protein from bone and holds noncollagen matrix, mobilized by osteoclasts, is a short-term marker of bone resorption in adult and child; serum levels decline rapidly after the introduction of bisphosphonate treatment.

Collagen biochemical markers of bone resorption with practical are: deoxypyridinoline and the peptides resulting from telopeptids by the action of metalloproteinases on collagen type I. Deoxyipiridinoline comes almost exclusively from bone, from non-helical portion of type I collagen. Serum value is not influenced by food and correlate with the DEXA results. The carboxyterminal peptide resulted from telopeptids marks increase bone density when osteoporosis treatment is correct, by a decrease in its serum and urine values (10,11).

TREATMENT

Extension of osteodensitometry and thus increasing the life of chronic diseases with repercussion on bone metabolism, leading to more frequent reporting of skeletal fragility in children and adolescents. Effects of chronic disease and of chronic medicines on bone are different between adult and the growth period; affected skeletal site varies with the biological age and the onset of chronic illness (epiphyseal fusions vary). Thus, the experiences gained in the treatment of osteoporosis in adults cannot be extrapolated to children, requiring further in-depth studies.

Prevention of osteopenia in children and adolescents, especially in the age group 12-18, includes physical activity, proper nutrition, fighting the anorexia and obesity, and the administration of the necessary daily calcium and vitamin D.

The daily requirement of calcium is adapted to age: 1-3 years 500 mg/day, 4-8 years 800 mg/day, 9-18 years 1,300 mg/day, pregnancy 1,200 mg/day and lactation 1,000 mg mg/day.

The average daily requirement of vitamin D is 800-1,000 U/day in preterms and dystrophic children, and in recovery treatment 1,500 U/day. Chronic treatment with glucocorticoids requires an intake of 2,000 U/day. 25 OHD levels should be maintained above 50 nmol/L (20 ng/ml.) (20).

Along with adaptation needs of calcium and vitamin D throughout the period of growth, should be identified and corrected any endocrine disorders (thyroid disturbances, hypogonadism), anorexia, obesity etc.

In chronic diseases mobilization, physical therapy, individualized nutritional support and supervised correction of bone metabolism (repeated osteodensitometry, 25 OHD determination), reduce the risk of osteopenia (21).

The calcitonine was proposed in the osteopenia treatment but the dose in child is not well established; approximately 20-100 micrograms/day alternative regimen. The intranasal and parenteral administration was associated with adverse effects (nausea, mucosa dryness etc). Future biological therapies are being used experimentally: denosumabe, catepsine L inhibitors, specific antiscleotine antibodies.

Specific drug treatment of osteopenia/osteoporosis comprising administering nitrogen bisphosphonates: pamidronate, neridronat, olpadronate, alendronate, ibadronat, risedronate, zoledronate. The mechanism of action is modification of the connected to the cell membrane protein, involved in osteoclastic resorption, while decreasing osteoclastogenesis and osteoclast survival (22).

Bisphosphonate treatment in children is not well stated. We have accumulated experience in osteogenesis imperfecta, juvenile idiopathic osteoporosis, Gaucher disease, fibrous dysplasia, mitochondrial myopathy, progressive osificans fibroplasias, anorexia nervosa in adolescents and in osteopenia induced by prolonged corticosteroid (8).

The optimal duration of bisphosphonate therapy in children, in various chronic diseases, is not well established; osteogenesis imperfecta correction in bone mass begins after 2-4 years of treatment.

Side effects are rare, reactions may be transient (1-3 days), consisting of fever, malaise, nausea, di-

arrhea, muscle and bone pain. It have been reported some severe complications installed over time, as uveitis, thrombocytopenia, oral and esophageal ulcers. Bisphosphonates are deposited in bone and released in years. Attention is needed in treat the teenagers, as bisphosphonates can cross the placenta and affect fetal development (23).

Calcitonin has been proposed to treat osteopenia but recommended dose in children is not well established; is indicated 20-100 micrograms/day, alternative regime. Intranasal administration and injection was accompanied by adverse effects (flushing, nausea, dry mucous membranes, etc.).

In experimental studies are future biologic therapies: denosumab, cathepsin K inhibitors, and specific antiscleotine antibodies.

CONCLUSIONS

The term osteopenia, which defines the intermediate condition between the normal and osteoporotic bone, is imposed by its frequency, its evolution and the potential repercussions on the adult bone pathology. The most common is secondary osteopenia as a common manifestation of subgroups of disease with different pathogenesis. Often, in childhood, is the result of medical treatments, especially corticosteroids administration.

Bone density studies is a important marker of the evolution of bone turnover in many diseases, but also it can be use as a screening method to detect osteopenia in adolescents. Peak bone mass that is given up to 20-21 years old is predictive for bone health throughout life.

Treatment is complex and must be adapted to causes of osteopenia. Adequate calcium and vitamin D intake had a positive effect in most cases. In severe forms of primary or secondary osteopenia, bisphosphonate treatment is recommended oriented by clinical experiences.

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