Diagnosis of Osteoporosis in Children and Adolescents

Christine M Laine[1] and Tero Laine[2]

1. Consultant in Endocrinology, Institute of Medicine, Sahlgrenska University Hospital and University of Gothenburg, Gothenburg, Sweden;
2. Senior Consultant in Paediatric Orthopaedics, Department of Orthopaedics, Institute of Clinical Sciences, Sahlgrenska University Hospital and University of Gothenburg, Gothenburg, Sweden

Abstract

Osteoporosis is traditionally regarded as a disease of elderly women. However, this bone disorder occurs in patients of both sexes and of all ages and is also increasingly recognised in the paediatric setting. In particular, patients, including young children, with other chronic diseases are at risk of developing bone fragility. There are also several forms of hereditary osteoporosis, which should be identified at an early stage to ensure adequate treatment. The diagnosis of osteoporosis in children is challenging, since their bone mineral density (BMD) is affected by growth and pubertal development. In addition to low BMD, a child must also exhibit a significant proneness to fractures before the osteoporosis diagnosis can be made. Through early diagnosis and treatment for paediatric bone fragility, we can also ameliorate bone health in adulthood. In this article we review the aetiology, known risk factors and the diagnostic criteria of osteoporosis in the young.

Keywords

Osteoporosis, child, adolescent, dual-energy X-ray absorptiometry

Disclosure: The authors have no conflicts of interest to declare.
Received: 12 April 2013 **Accepted**: 24 May 2014 **Citation**: *European Endocrinology*, 2013;9(2):141–4 *DOI:10.17925/EE.2013.09.02.141*
Correspondence: Christine M Laine, Sahlgrenska University Hospital/Östra Sjukhuset, Department of Internal Medicine, SE-41345 Gothenburg, Sweden.
E: christine.laine@vgregion.se

Osteoporosis and related fragility fractures are a significant cause of morbidity and mortality in developed countries.[1] The lifetime risk of osteoporosis-related fractures exceeds 40 % in women and 20 % in men.[2] According to the definition set by the World Health Organization (WHO), osteoporosis is defined as a "systemic skeletal disease characterized by low bone mass and micro-architectural deterioration of bone tissue, with a consequent increase in bone fragility and susceptibility to fractures",[1] and arises when the amount of bone resorbed exceeds the amount of newly formed bone inducing a net loss of bone mass.

New bone is formed and old bone is degraded continuously throughout life. The most rapid bone mass accrual occurs around puberty, and approximately 90 % of the maximum bone mass in life, the peak bone mass (PBM), is acquired before the age of 20 years.[3,4] The PBM achieved in youth is an important predictor of osteoporosis in adulthood and affects the time of onset of osteoporosis; a 10 % increase in PBM has been estimated to delay the onset of postmenopausal osteoporosis by up to 13 years.[5,6] Therefore, the optimal time to intervene with regards to prevention of osteoporosis is, in fact, in adolescence.

Aetiology

Osteoporosis occurs in both sexes and in individuals of all ages, and is generally divided into primary and secondary osteoporosis (see *Table 1*). The most common form of primary osteoporosis is seen in the elderly, where bone fragility is age-related and associated with a decline in sex hormones. In younger patients, primary osteoporosis is mainly hereditary, and genetic factors are estimated to account for up to 80 % of the variance in PBM.[7] The most common form of primary osteoporosis is osteogenesis imperfecta (OI), caused by mutations in the genes encoding collagen type I and related peptides.[8,9] Many other genetic forms have been identified, but these are rare (summarised in *Table 2*). As the genetic cause of most cases remains unknown, these are termed idiopathic. Mutations in two genes, *LRP5* and *WNT1*, have been identified as the cause of dominantly inherited osteoporosis without other phenotypic features, and more causative genes will probably be found in time.[10,11] Genetic screening for mutations in these genes is currently in use mainly in research settings.

Secondary osteoporosis is due to underlying chronic illness or its treatment, which decreases bone strength and predisposes the patient to fragility fractures. The most common form of secondary osteoporosis arises from long-term use of glucocorticoids, which even at low dosages causes a significant decrease in BMD.[12] Other conditions associated with an increased fracture risk and osteoporosis in children include endocrine disturbances, inflammatory diseases, certain forms of cancer and associated treatments, immobilisation and haematological disorders (*Table 1*). Additional risk factors, such as limited physical activity and nutrition (especially low intake of vitamin D, calcium and proteins) also affect bone mass accrual in both healthy and chronically ill children.[6,13,14]

The Use Of DXA in Children and Adolescents

Dual-energy X-ray absorptiometry (DXA) is the most commonly used method for evaluating bone mineral density (BMD) and bone mineral content (BMC). The criteria for diagnosing osteoporosis were originally developed based on epidemiological data regarding fracture risk in postmenopausal women.[1] The comparison of the areal BMD of a postmenopausal woman to the mean areal BMD of healthy young females expressed as

Table 1: Causes of Osteoporosis in Children and Adolescents

Primary Osteoporosis
Connective Tissue Disorders
Ehlers-Danlos syndrome
Homocystinuria
Marfan's syndrome
Osteogenesis imperfecta
Idiopathic (juvenile) osteoporosis
Rare genetic and hereditary disorders
Disorders that Put Children at Risk of Secondary Osteoporosis
Inflammatory Diseases
Juvenile idiopathic arthritis
Systemic lupus erythematosus
Inflammatory bowel disease
Chronic Immobilisation
Cerebral palsy
Meningomyelocele
Myopathic diseases (e.g. Duchenne, spinal muscular atrophy)
Nutritional, Intestinal and Malabsorption Disorders
Coeliac disease and other malabsorption syndromes
Schwachman-Diamond disease
Cystic fibrosis
Malnutrition; vitamin and mineral deficiency
Haematologic Disorders
Leukaemia
Thalassaemia
Endocrine Disturbances
Growth hormone deficiency
Sex hormone deficiency (e.g. hypogonadism, Turner's syndrome)
Hyperthyreosis
Cushing's syndrome
Anorexia nervosa
Secondary to Therapies with Adverse Effects on Bone Health
Following chemotherapy for childhood malignancy
Following solid organ or bone marrow transplant
Glucocorticoids, anticonvulsants, heparin, calcineurin inhibitors
Chronic Kidney Disease
Cholestatic Liver Disease

standard deviations (SDs) is called the T-score. A decrease exceeding 2.5 SD from the reference mean (i.e. a T-score below –2.5) is indicative of osteoporosis, and a T-score of –1.0 to –2.5 indicates osteopenia.[1] The diagnostic use of DXA has since been expanded to all adults as epidemiological studies have shown an association between fracture incidence and densitometric measurements.[15–18]

The diagnostic guidelines used in adults cannot, however, be directly extrapolated to paediatric subjects due to the effect of growth and hormonal development on densitometric measurements and due to the difference in fracture epidemiology between children, adolescents and adults.[19] Contrary to adults, who most commonly fracture at the hip or spine, children sustain most of their fractures in the peripheral skeleton, in particular in the upper extremities. Childhood fractures are common, and in fact their fracture rate is only surpassed by women over the age of 85. Twenty-seven to 40 % of girls and 42–51 % of boys sustain at least one fracture during growth, and the highest fracture rates are seen during the pubertal years.[20,21] There are a few reports which show an association between wrist fractures and low BMD in children, but the link is not as clear as in the adult population due to the high fracture frequency and the difficulty of reliably interpreting BMD results in growing children, and more studies are warranted for before direct conclusions can be made.[22] Therefore, a diagnosis of osteoporosis in a growing child cannot be set based on bone densitometric data alone.[23]

The areal BMD and BMC results in children should be compared to a reference population with regards to age, gender and ethnicity. This comparison, reported as SD from the mean of the reference population, is called the Z-score. T-scores should not be used for children, nor should the term 'osteopenia'. The diagnosis of osteoporosis can only be set if a child has both low areal BMD or BMC and a clinically significant fracture history.[19] The reference data should always be validated for the equipment and software version used.[19]

The recommended sites for assessment with DXA are the lumbar spine and total body less head (TBLH). The spine is recommended due to easy positioning for reliable measurement, high reproducibility and a fair availability of normative data.[24] The TBLH provides a value for the total bone mass, along with data on body composition of soft tissues. Information regarding fat and lean body mass are valuable especially when caring for children with chronic illnesses and bone fragility: e.g. eating disorders, inflammatory and bowel diseases, neuromuscular disorders and long-term glucocorticoid treatment. Children with a low lean body mass may not, for instance, have an increased risk of fragility fractures despite low BMD.[25] The hip region is not considered a reliable measurement site due to the variability in skeletal development, the difficulty in correct positioning for the screening and the low reproducibility of results in growing children.[24] The use of forearm DXA could be a good screening alternative in the future, but due to the scarcity of reference data, this method is currently only recommended for follow-up measurements and comparison to baseline data of a particular individual.[24] BMD measurement with quantitative computed tomography (qCT) is a good complement to traditional DXA, since this method is not influenced by body or skeletal size.[26] Valid reference data have been published for some ethnicities, but this method is yet to be included in the official criteria for osteoporosis in children and adolescents.[27] Peripheral qCT is considered a safe screening method for children.

Since children with chronic illnesses can have a significant delay in growth, skeletal maturity and pubertal development, several models have been developed for correction of BMD and BMC with respect to height, pubertal stage and lean body mass.[24,25] The major limitation regarding the use of such corrections is the lack of reference data. Comparisons according to both chronological age and bone age, which corresponds better to the skeletal maturation in chronically ill children with growth delay, may be of value. The clinician must take into account corrections based of the clinical profile of the child and consider whether the correction is made to understand the aetiology of the low BMD or to assess the fracture risk of the child; e.g. in a child of short stature and delayed puberty, the bone mass may be underestimated and fracture risk overestimated without correction.[26] The benefits and pitfalls of such corrections are discussed in depth by Gordon et al.[24]

The Diagnosis of Osteoporosis in Children and Adolescents

According to the official positions of the International Society for Clinical Densitometry (ISCD), the cut-off value for low areal BMD or BMC Z-scores is less than or equal to –2.0, and defined as "low BMC or areal BMD for chronological age".[23] This diagnosis can be used if the child has no relevant fracture history; the term 'osteopenia' should not be used. A

Table 2: Known Genetic Skeletal Disorders Causing a Decrease in Bone Mineral Density, Excluding Bone Fragility from Osteomalacia

Disorder	Inheritance	Clinical Features and Notes
OI type 1–13	AD/AR	In addition to osteoporosis, features may include grey/blue sclerae, dentinogenesis imperfecta, hearing loss, growth deficiency
Bruck syndrome 1-2	AR	OI-like phenotype with pterygia
Mutations in *LRP5*	AD/AR	Decreased bone mineral density, osteoporosis pseudoglioma syndrome in biallelic carriers
Mutations in *WNT1*	AD/AR	Decreased bone mineral density, OI-like phenotype in biallelic carriers
Singleton-Merten dysplasia	AD	Widened medullary cavities of bone, aortic calcification, abnormal dentition and muscular weakness
Geroderma osteodysplasticum	AR	Wrinkly skin and osteoporosis
Calvarial doughnut lesions, bone fragility	AD	Pathological fractures, lumps on the head, elevated serum alkaline phosphatase levels and dental caries
Idiopathic juvenile osteoporosis	Unknown	Heterogenous group of osteoporotic children, some with bone pain but without other distinct clinical features
Cole-Carpenter dysplasia	Unknown	Bone fragility with craniosynostosis, ocular proptosis, hydrocephalus, distinctive facial features
Spondylo-ocular syndrome	AR	Moderate osteoporosis, platyspondyly, advanced bone age, cataract, retinal detachment, facial dysmorphism, short trunk, immobile spine, kyphosis
Cleidocranial dysplasia	AD	Persistent fontanels, hypoplasia/aplasia of clavicles, wide pubic symphysis, dental and digital anomalies, in some cases severe osteoporosis, scoliosis
Gnathodiaphyseal dysplasia	AD	Frequent fractures in adolescence, purulent osteomyelitis of the jaws in adulthood
Hadju-Cheney syndrome	AD	Osteoporosis, facial abnormalities, acro-osteolysis, hearing loss, renal cysts

AD = autosomal dominant; AR = autosomal recessive; OI = osteogenesis imperfecta. Adapted and updated from Superti-Furga et al., Am J Med Genet A, *2006:143A(1):1–18.*

diagnosis of osteoporosis in a child or adolescent requires the presence of both a clinically significant fracture history and low areal BMD or BMC for chronological age (see *Table 3*).[28] Therapeutic interventions should not be initiated based on one DXA measurement alone.[29]

Additional Considerations in Clinical Practice

Initiation of and Follow-up with DXA Scan Measurements

When meeting a child with suspected bone fragility or at risk of bone fragility based on clinical history, when should DXA measurements commence? According to the recommendations of ISCD,[29] a DXA screening should be performed at clinical presentation of primary osteoporosis (mainly OI or idiopathic osteoporosis), or of a disease that puts the child at risk of secondary osteoporosis, e.g. endocrine disturbances, chronic inflammatory diseases, after organ transplantation and childhood cancer. The screening should include spine and TBLH areal BMD and BMC when technically feasible. In children with chronic immobilisation or significant motor disability, DXA screening should be performed at fracture presentation. Data regarding the risk of fragility fractures in children with thalassaemia are in part contradictory, and screening is recommended to begin at fracture presentation or at the latest at the age of 10 years. Women with Turner's syndrome rarely fracture in childhood and therefore no general screening is recommended in childhood or adolescence based on the genetic diagnosis.[29]

There are no clear-cut recommendations in terms of the frequency or length of DXA follow-up measurements. Children with idiopathic osteoporosis may show a spontaneous normalisation of BMD after puberty,[30] while adolescents with anorexia nervosa and related endocrine disturbances may never achieve a normal PBM and have an increased risk of fracture up to 40 years after the diagnosis.[31,32]

A baseline value prior to bone-active treatments, such as bisphosphonates and growth hormone, should be obtained and follow-up measurements performed to monitor treatment response at clinically appropriate intervals. The recommended minimum time interval for follow-up measurements during treatment or disease progress is six months to avoid excessive exposure to radiation.[29]

Table 3: Diagnostic Criteria for Osteoporosis in Children and Adolescents According to the International Society for Clinical Densitometry[23]

1. A clinically significant fracture history (one or more of the following)
   a. Long bone fracture of the lower extremities
   b. Vertebral compression fracture
   c. Two or more long-bone fractures of the upper extremities
2. Low spinal or total body less head areal bone mineral density or bone mineral content, defined as a Z-score less than or equal to –2.0 adjusted for age, gender and body size, as appropriate

Many clinics have adapted follow-up intervals of six months when on treatment and of 12 months when not treated with bone-active agents, but no official recommendations other than the stated minimum time interval of six months exists.

Risk of Vertebral Fractures in Children at Risk of Secondary Osteoporosis

If vertebral fractures unrelated to high-impact trauma are diagnosed in children, these usually signify a significant skeletal pathology. Vertebral compression fractures are surprisingly common in chronically ill children; the prevalence is 8–25 % among children with rheumatoid arthritis, leukaemia, after organ transplants or of children with motor disabilities.[33–37] Compression fractures are underdiagnosed in this group of patients, as most children have no symptoms. New DXA equipment often offers the possibility to assess vertebral morphology, but despite high diagnostic accuracy of this method in adults, up to two-thirds of compression fractures in children are missed.[38] Spine X-rays or magnetic resonance imaging should therefore be considered in chronically ill children with back problems.

Prevention and Treatment of Osteoporosis in Children and Adolescents

Although the main determinants of PBM acquisition are genetic and/or affected by other diseases and related treatments, we can affect the factors amenable to positive intervention in growing children.

Suboptimal PBM acquisition may be prevented by ensuring an adequate intake of calcium and vitamin D, encouraging physical activity, treating under- or overweight, correcting endocrine disturbances and avoiding osteotoxic medication, such as glucocorticoids, when possible.[6,39]

Calcium is the main component of bone tissue and required for the normal mineralisation of the bone matrix. A lack of calcium activates the secretion of parathyroid hormone, which induces the mobilisation of calcium from the bone thereby impairing bone mass accrual. The recommended intake of calcium varies in different age groups and countries, but dependent on the dietary intake, children with osteoporosis may need over 1,000 mg of calcium supplements daily. Calcium should ideally be obtained from dietary intake, as recent studies have shown an association between calcium supplement intake and cardiovascular events in adults. There is also a lack of evidence regarding the possible benefits of calcium supplementation in chronically ill children. Vitamin D deficiency causes a decrease in intestinal uptake of dietary calcium and phosphorous. The recommended daily dose of vitamin D2 or D3 is 600 IU for children (aged one to 18 years) who are at risk of vitamin D deficiency, e.g. due to inadequate exposure to sunlight, malabsorption syndromes and treatment with anticonvulsants.[40] Children (aged one to 18 years) with vitamin D deficiency, i.e. with serum 25-hydroxyvitamin D (25(OH)D) levels below 20 ng/ml (50 nmol/l), are recommended a daily dosage of 2,000 IU for at least six weeks to achieve a blood level of 25(OH)D above 30 ng/ml. The recommended maintenance therapy thereafter is 600–1,000 IU daily, aiming at blood levels of 25(OH)D between 30 and 50 ng/ml. Some patients may need two to three times higher doses to achieve sufficient serum levels.[40]

If the preventative measures are insufficient in terms of osteoporosis and fractures, the question may arise as to whether bone-active agents should be prescribed. While the efficacy and safety of such treatments are rather well documented in the adult population, the data regarding treatment of children are scarcer. The only anabolic bone therapy available, recombinant parathyroid hormone, is not approved for children as it has caused osteosarcoma in growing rodents.[41] A group of anti-catabolic bone-active agents, namely bisphosphonates, remains the only alternative. While treatment with bisphosphonates is becoming quite widespread in children with OI, the effects in children with secondary osteoporosis are less well-known. There is a shortage of data regarding the efficacy, safety, choice of agent, duration of treatment and long-term outcome.[39] Therefore, treatment with bone-active agents in children should be conducted only in large paediatric centres and preferably in the setting of clinical trials.[39]

Conclusions

The diagnosis of osteoporosis in a growing child cannot be set based on bone densitometric measurements only, but requires both a significant fracture history and low areal BMD or BMC.

Vertebral compression fractures are common and underdiagnosed in children with secondary osteoporosis.

The need for supplementation with calcium and vitamin D should be assessed and addressed in all children at risk of osteoporosis. Treatment with bone-active agents, such as bisphosphonates, should be conducted at paediatric centres with sufficient experience of treatment and follow-up of children with metabolic bone diseases. ■

1. World Health Organization Study Group on Assessment of Fracture Risk and Its Application to Screening and Postmenopausal Osteoporosis, Geneva: WHO, 1994.
2. Kanis JA, Johnell O, Oden A, et al., Risk of hip fracture according to the World Health Organization criteria for osteopenia and osteoporosis, *Bone*, 2000;27:585–90.
3. Bonjour JP, Theintz G, Buchs B, et al., Critical years and stages of puberty for spinal and femoral bone mass accumulation during adolescence, *J Clin Endocrinol Metab*, 1991;73:555–63.
4. Bailey DA, McKay HA, Mirwald RL, et al., A six-year longitudinal study of the relationship of physical activity to bone mineral accrual in growing children: the university of Saskatchewan bone mineral accrual study, *J Bone Miner Res*, 1999;14:1672–9.
5. Hernandez CJ, Beaupre GS, Carter DR, A theoretical analysis of the relative influences of peak BMD, age-related bone loss and menopause on the development of osteoporosis, *Osteoporos Int*, 2003;14:843–7.
6. Rizzoli R, Bianchi ML, Garabedian M, et al., Maximizing bone mineral mass gain during growth for the prevention of fractures in the adolescents and the elderly, *Bone*, 2010;46:294–305.
7. Bonjour JP, Chevalley T, Rizzoli R, Ferrari S, Gene-environment interactions in the skeletal response to nutrition and exercise during growth, *Med Sport Sci*, 2007;51:64–80.
8. Roughley PJ, Rauch F, Glorieux FH, Osteogenesis imperfecta--clinical and molecular diversity, *Eur Cell Mater*, 2003;5:41–7; discussion 7.
9. Rauch F, Glorieux FH, Osteogenesis imperfecta, *Lancet*, 2004;363:1377–85.
10. Gong Y, Slee RB, Fukai N, et al., LDL receptor-related protein 5 (LRP5) affects bone accrual and eye development, *Cell*, 2001;107:513–23.
11. Laine CM, Joeng KS, Campeau PM, et al., WNT1 mutations in early-onset osteoporosis and osteogenesis imperfecta, *N Engl J Med*, 2013;368:1809–16.
12. Laan RF, van Riel PL, van de Putte LB, et al., Low-dose prednisone induces rapid reversible axial bone loss in patients with rheumatoid arthritis. A randomized, controlled study, *Ann Intern Med*, 1993;119:963–8.
13. Chevalley T, Bonjour JP, Ferrari S, et al., Skeletal site selectivity in the effects of calcium supplementation on areal bone mineral density gain: a randomized, double-blind, placebo-controlled trial in prepubertal boys, *J Clin Endocrinol Metab*, 2005;90:3342–9.
14. Chevalley T, Bonjour JP, Ferrari S, Rizzoli R, High-protein intake enhances the positive impact of physical activity on BMC in prepubertal boys, *J Bone Miner Res*, 2008;23:131–42.
15. Johnell O, Kanis JA, Oden A, et al., Predictive value of BMD for hip and other fractures, *J Bone Miner Res*, 2005;20:1185–94.
16. Szulc P, Munoz F, Duboeuf F, et al., Bone mineral density predicts osteoporotic fractures in elderly men: the MINOS study, *Osteoporos Int*, 2005;16:1184–92.
17. Kanis JA, Johnell O, Oden A, et al., Ten year probabilities of osteoporotic fractures according to BMD and diagnostic thresholds, *Osteoporos Int*, 2001;12:989–95.
18. Barrett-Connor E, Siris ES, Wehren LE, et al., Osteoporosis and fracture risk in women of different ethnic groups, *J Bone Miner Res*, 2005;20:185–94.
19. Baim S, Leonard MB, Bianchi ML, et al., Official Positions of the International Society for Clinical Densitometry and executive summary of the 2007 ISCD Pediatric Position Development Conference, *J Clin Densitom*, 2008;11:6–21.
20. Cooper C, Dennison EM, Leufkens HG, et al., Epidemiology of childhood fractures in Britain: a study using the general practice research database, *J Bone Miner Res*, 2004;19:1976–81.
21. Ferrari SL, Chevalley T, Bonjour JP, Rizzoli R, Childhood fractures are associated with decreased bone mass gain during puberty: an early marker of persistent bone fragility?, *J Bone Miner Res*, 2006;21:501–7.
22. Clark EM, Tobias JH, Ness AR, Association between bone density and fractures in children: a systematic review and meta-analysis, *Pediatrics*, 2006;117:e291–7.
23. Rauch F, Plotkin H, DiMeglio L, et al., Fracture prediction and the definition of osteoporosis in children and adolescents: the ISCD 2007 Pediatric Official Positions, *J Clin Densitom*, 2008;11:22–8.
24. Gordon CM, Bachrach LK, Carpenter TO, et al., Dual energy X-ray absorptiometry interpretation and reporting in children and adolescents: the 2007 ISCD Pediatric Official Positions, *J Clin Densitom*, 2008;11:43–58.
25. Crabtree NJ, Kibirige MS, Fordham JN, et al., The relationship between lean body mass and bone mineral content in paediatric health and disease, *Bone*, 2004;35:965–72.
26. Wren TA, Liu X, Pitukcheewanont P, Gilsanz V, Bone densitometry in pediatric populations: discrepancies in the diagnosis of osteoporosis by DXA and CT, *J Pediatr*, 2005;146:776–9.
27. Gilsanz V, Perez FJ, Campbell PP, et al., Quantitative CT reference values for vertebral trabecular bone density in children and young adults, *Radiology*, 2009;250:222–7.
28. Bianchi ML, Baim S, Bishop NJ, et al., Official positions of the International Society for Clinical Densitometry (ISCD) on DXA evaluation in children and adolescents, *Pediatr Nephrol*, 2010;25:37–47.
29. Bishop N, Braillon P, Burnham J, et al., Dual-energy X-ray aborptiometry assessment in children and adolescents with diseases that may affect the skeleton: the 2007 ISCD Pediatric Official Positions, *J Clin Densitom*, 2008;11:29–42.
30. Smith R, Idiopathic juvenile osteoporosis: experience of twenty-one patients, *Br J Rheumatol*, 1995;34:68–77.
31. Jayasinghe Y, Grover SR, Zacharin M, Current concepts in bone and reproductive health in adolescents with anorexia nervosa, *BJOG*, 2008;115:304–15.
32. Lucas AR, Melton LJ, 3rd, Crowson CS, O'Fallon WM, Long-term fracture risk among women with anorexia nervosa: a population-based cohort study, *Mayo Clin Proc*, 1999;74:972–7.
33. Valta H, Makitie O, Ronnholm K, Jalanko H, Bone health in children and adolescents after renal transplantation, *J Bone Miner Res*, 2009;24:1699–708.
34. Markula-Patjas KP, Valta HL, Kerttula LI, et al., Prevalence of vertebral compression fractures and associated factors in children and adolescents with severe juvenile idiopathic arthritis, *J Rheumatol*, 2012;39:365–73.
35. Helenius I, Remes V, Salminen S, et al., Incidence and predictors of fractures in children after solid organ transplantation: a 5-year prospective, population-based study, *J Bone Miner Res*, 2006;21:380–7.
36. Laakso S, Valta H, Verkasalo M, et al., Impaired bone health in inflammatory bowel disease: a case-control study in 80 pediatric patients, *Calcif Tissue Int*, 2012;91:121–30.
37. Halton J, Gaboury I, Grant R, et al., Advanced vertebral fracture among newly diagnosed children with acute lymphoblastic leukemia: results of the Canadian Steroid-Associated Osteoporosis in the Pediatric Population (STOPP) research program, *J Bone Miner Res*, 2009;24:1326–34.
38. Mayranpaa MK, Helenius I, Valta H, et al., Bone densitometry in the diagnosis of vertebral fractures in children: accuracy of vertebral fracture assessment, *Bone*, 2007;41:353–9.
39. Bachrach LK, Ward LM, Clinical review 1: Bisphosphonate use in childhood osteoporosis, *J Clin Endocrinol Metab*, 2009;94:400–9.
40. Holick MF, Binkley NC, Bischoff-Ferrari HA, et al., Evaluation, treatment, and prevention of vitamin D deficiency: an Endocrine Society clinical practice guideline, *J Clin Endocrinol Metab*, 2011;96:1911–30.
41. Tashjian AH, Jr., Gagel RF, Teriparatide [human PTH(1-34)]: 2.5 years of experience on the use and safety of the drug for the treatment of osteoporosis, *J Bone Miner Res*, 2006;21:354–65.