Dual X-ray absorptiometry (DXA) in children with kidney diseases – a problematic method of bone analysis

J. FEBER, L. M. WARD

Divisions of Nephrology and Endocrinology, Department of Pediatrics, Children's Hospital of Eastern Ontario, Ottawa, Canada

SUMMARY

Feber J., Ward L. M.: **Dual X-ray absorptiometry (DXA) in children with kidney diseases – a problematic method of bone analysis**

Dual energy X-ray absorptiometry (DXA) has been used in adult medicine to diagnose and monitor various types of osteoporosis. It is a very sensitive and accurate method to detect even small losses of bone mineral. Consequently, its use has been extended to pediatric medicine. The manufacturers provided reference values for healthy children in relation to chronological age. However, children with chronic disease often suffer from height retardation and the use of pre-established reference values in relation to age may yield falsely low bone density results. Therefore, correction for actual height or bone volume is required for accurate interpretation of DXA results in children. Moreover, the amount of bone mineral or bone density may not be the most important parameter for the assessment of bone strength, which is influenced by bone geometry (the ratio between the cortical and trabecular bone as well as composition of trabecular microarchitecture) and muscle mass. DXA provides only limited information in this respect and does not differentiate between cortical and trabecular bone. Caution is warranted in the interpretation of DXA in children with stunted growth. The use of other macromorphometric techniques such as peripheral quantitative computer tomography (pQCT), as well as micromorphometry (bone histomorphometry) may be of advantage. In symptomatic patients the use of a classic X-ray should not be eliminated as a means of diagnosing fractures (such as vertebral compression) despite normal results of DXA scans.

Key words: bone mineral density – children.

SOUHRN

Feber J., Ward L. M.: **Vyšetření skeletu dvouenergiovou rentgenovou absorpční denzitometrií u dětí s onemocněním ledvin – problematická metoda analýzy kostní tkáně**

Vyšetření denzity kostního minerálu (BMD) za pomoci paprsku o dvou energiích (DXA) je běžně používáno u dospělých pacientů k diagnostice a monitorování různých typů osteoporózy. Jedná se o velice přesnou metodu, která je schopna detekovat i minimální ztráty kostního minerálu. Tato metoda byla rozšířena i do dětského lékařství. Výrobci dodali referenční hodnoty pro zdravé děti. Uvedené hodnoty se vztahují ke kalendářnímu věku. Chronicky nemocné děti ovšem často trpí poruchou růstu a jsou oproti svým vrstevníkům menší. Užití referenčních hodnot, které jsou vztaženy pouze k věku kalendářnímu může proto u chronicky nemocných dětských pacientů vést ke stanovení falešně nízkých hodnot BMD. Z tohoto důvodu je nezbytné korigovat naměřené hodnoty BMD na aktuální výšku vyšetřeného dítěte nebo provést přepočet na jednotku kostního objemu. Množství kostního minerálu nebo kostní denzita nemusí být nejvýznamnějším ukazatelem kostní síly. Mechanická odolnost kostní tkáně bývá ovlivněna kostní geometrií (poměrem mezi kortikální a trámčitou kostí, stejně jako složením trámčité kostní mikroarchitektury) a též svalovou hmotou. DXA nám poskytuje pouze omezené informace a nerozlišuje mezi trámčitou a kortikální kostí. Výsledky BMD získané metodou DXA u dětí s opožděným růstem musí být interpretovány s velkou opatrností. Výhodné může být užití dalších makromorfometrických technik, jako například periferní kvantitativní computerová tomografie (pQCT), stejně jako mikromorfometrie (kostní histomorfometrie). U symptomatických pacientů nesmí být podceněna úloha rentgenových snímků, které pomáhají odhalit zlomeniny (např. kompresívní zlomeniny obratlů) v přítomnosti normálních nálezů DXA.

Klíčová slova: denzita kostního minerálu – děti.

Osteologický bulletin 2005;10(4):96–100

Adresa: Janusz Feber, MD, FRCPC, Associate Professor, Pediatrics, Division of Nephrology, Department of Pediatrics, Children's Hospital of Eastern Ontario, 401 Smyth Road, Ottawa, Ontario, K1H 8L1, Canada, tel.: +1 (613) 737 7600 ext. 2441, fax: +1 (613) 738 3254, e-mail: jfeber@cheo.on.ca

Došlo do redakce: 12. 10. 2005

Introduction

Bone densitometry using dual-energy X-ray absorptiometry (DXA) has been widely used in adult and pediatric medicine for a variety of clinical diagnoses. It is considered a gold standard for the diagnosis of osteoporosis, upon which diagnostic guidelines have been based [1]. These guidelines recommend using the T-score (bone density related to young adult age) for the definition of osteoporosis [2]. This approach may be applicable only to adult patients, where the main goal of DXA is to quantify the loss of bone density compared to peak bone mass achieved at young adult age and predict/estimate the risk of subsequent fracture. In children, the situation is rather different due to the skeletal growth as well as increasing evidence that bone density/mass is also related to muscle development [3]. Therefore the use of Z-scores (bone density related to age) has been recommended in children in order to reflect changes of bone density with skeletal growth [4]. However, the definition of osteoporosis based on BMD criteria has not yet been established for children; that is, the fracture rates for a given BMD in health and disease, and at the various ages and pubertal stages, is not precisely known. Thus, if the Z-score is below –2.0 it is only possible to determine „inappropriate low bone mineral density".

Despite these limitations, DXA continues to be used frequently in pediatrics as part of the overall bone health evaluation, in order to detect early bone loss (or, more often, a failure to accrue bone at a normal rate). The aim of this review article is to consider current concepts of bone density analysis in children and summarize several cautions in the use of DXA in children with kidney disease.

Dual energy X-ray absorptiometry

Mazess et al. [5] initially developed dual energy X-ray absor-

ptiometry for the precise measurement of total bone mineral. The method is based on the energy dependence of the attenuation coefficients for photon absorption of bone mineral. Bone mineral contains the high atomic number element calcium, and soft tissue, which contains mostly the low atomic number elements hydrogen, oxygen, and carbon [6]. A polychromatic X-ray beam is converted into a beam that has two main energy peaks of 40 kV and 70 kV. The ratio of soft tissue attenuation (RST) at the two energies is measured. The attenuation of pure fat (RF) and of bone-free lean tissue (RL) is known from both theoretical calculations and human experiments. Given the subject's RST and the known R for fat (RF) and lean (RL), one can solve the equations (one at each X-ray energy) with two unknowns to calculate the proportion of fat (α) and lean tissue (b) in each pixel:

$$RST(40\ kV) = \alpha(RF) + \beta(RL)$$
$$RST(70\ kV) = \alpha(RF) + \beta(RL)$$

This method provides a whole body imaging technique that simultaneously measures bone mineral, fat and lean mass [6].

The precision of DXA is less than 2.5% [7]. The radiation dose for a whole body scan is < 5 mrem, which represents about 1/10 of a normal chest X-ray. The DXA exam takes 20–35 minutes and requires little cooperation from the subject. Therefore, this technique has been successfully used in pediatric patients [8], even in small infants and newborns [7].

Older DXA devices (Hologic QDR-1000/W, 2500) worked with a thin X-ray pencil beam obtained after collimation (diameter 0.23 mm) passes through a calibration disk and scanned either the chosen region of interest in a serpentine x-y pattern, or the entire body. A detector, mechanically connected to the X-ray source and mounted above the patient, feeds the computer with the absorption data recorded pixel by pixel for both soft tissue and bone. When theoretically calculated, the absorption is directly related to the coefficients of absorption and to the amount of each component. Newer DXA scanners use fan beam technology, which is equally or even more accurate (precision of 1%) and significantly shorter exam times are achieved [9]. Using the fan beam technique, spine and femur scan requires only 30s, total body scan can be done in 4–5 min [10].

Results can be expressed as bone mineral content (BMC) in grams of hydroxyapatit or as bone mineral density (BMD) in g/cm^2 of the scanned area. Lean and fat body mass (LBM and FBM, respectively) are obtained in grams. Absolute values are typically transformed to standard deviation scores (SDS) for age (Z score) or, in adult patients, compared to an expected bone density at the age of 20 (T score). The manufacturer provides reference values for a healthy population. The interpretation of DXA results may therefore seem convenient and adequate for the adult population, mainly for postmenopausal women. However, several problems have been identified in children with stunted growth and furthermore, DXA may have other limitations as discussed in the ensuing paragraphs.

DXA in adults

The main indication for DXA in adults is to detect, diagnose and monitor postmenopausal osteoporosis, which is the most common underlying cause of osteoporosis in this population [11]. DXA has also been used in other forms of bone disease such as osteoporosis secondary to chronic illness, including kidney disease and end-stage renal failure [12], and following solid organ transplantation (to name a few) [13]. All these forms of osteoporosis are associated with risk factors for fragility fractures. Hence, attempts have been made to predict the risk of fractures with non-invasive imaging techniques like DXA. In 1999, the World Health Organization (WHO) introduced definitions of osteoporosis and osteopenia using T-scores [14]. The presence of a BMD T-score that is 2.5 standard deviations or greater below the mean for the young adult population has been used for definition of osteoporosis, whereas a T-score between 1 and 2.5 SD below the healthy adult mean defines osteopenia. Similar definitions of osteoporosis and osteopenia have been used in the recently published recommendations for bone mineral density reporting [15]. However, several studies indicate that bone density may not be the only determinant for fracture risk [16]. The most important of these additional risk factors in the post-menopausal population are age and prior fracture history. In addition, the definition of the T-score is based on the assumption that areal bone density increases with growth during childhood that peaks around 20–25 years of age (peak bone mass) and declines thereafter [3]. However, strong bones at a young age do not necessarily lead to fracture-free aging. Moreover, risk of bone fracture may not be dependent on bone density/bone mass only, but also on bone geometry/bone strength. Therefore, the WHO definition of osteoporosis from 1994 may be too simplistic and outdated. In addition, bone geometry/bone strength cannot be assessed by DXA. It requires newer techniques like peripheral quantitative computer tomography (pQCT) and assessment of muscle force.

DXA in children

The use of DXA is much more problematic in children than in adults. First, the child's bone is constantly changing in mass and geometry with growth. It was assumed that bone mineralization increases with age until approximately 20–25 years of age (peak bone mass). Thereafter, bone mineral density was assumed to decline and DXA use was supposed to assess the loss of bone mineral. However, these assumptions were made based on areal bone density (g/cm^2), which is not the true density from a physical perspective. Density of a material/tissue (bone) is defined as the amount of the material/tissue per volume (g/cm^3), which is not directly measured by the DXA machines. The volumetric bone density in g/cm^3 of the lumbar spine can be calculated using a formula, where the spine is considered as a column: BMDvol = areal BMD [4/(π x W)], where W = mean width of vertebral body [17, 18]. As a result we obtain the true bone mineral density in g/cm3, which interestingly enough no longer correlates with age – it remains stable during the whole age range 0–18 years [19]. This would suggest that true bone mineral density does not change with age, but it is the changing size of the bone, when the child is growing, that results in the progressive increases in areal BMD. Therefore, areal density in g/cm^2 correlates with age and reflects bone size – the bigger/longer the bone the higher the areal bone density. On the contrary, shorter bones yield lower areal bone density. In other words, two children of the same chronological age but different heights would have different BMD results: the smaller child would have a lower BMD whereas the taller one would have a higher BMD. Yet, the bone mineral content relative to the volume of bone is the same and the only difference is the size of the bone (height). Therefore, the patient's actual height should be taken into account in the interpretation of BMD results. However, the manufacturers of DXA machines provide us with age-related reference values only and the BMD result is given in g/cm^2.

This has several clinical implications:

1. Age related reference values are not sufficient to properly assess bone density in children.
2. Correction for actual height/bone size is needed.
3. Volumetric bone density is preferred.

Disregarding these notions may lead to misinterpretation of DXA and over-diagnosis of osteoporosis in children [20]. Interestingly enough, the term „osteoporosis" has been widely used even in the pediatric literature. However, at present there are no BMD criteria for osteopenia/osteoporosis in children. Therefore, the term

„bone health“ has been increasingly used in pediatric medicine, which allows a better description of the bone morbidity seen in children. The diagnosis of bone morbidity rests on concrete clinical evidence for bone fragility: low trauma extremity and/or vertebral compression fractures rather than a given BMD Z-scores of T-score.

A DXA scan also yields the **bone mineral conten**t in g. This represents the absolute amount of the bone mineral measured either in the whole body or skeletal sub-regions. BMC increases with chronological age and appropriate age-related reference values are available [21]. It seems logical to assume that a higher BMC renders the bone stronger and therefore less prone to fractures; as the main purpose of bones is to provide enough strength to keep voluntary physical loads from causing spontaneous fractures. However, the relation between the BMC and bone strength is not dependent on chronological age, but rather on muscle development and strain applied to the bone. Therefore, BMC should be interpreted in relation to bone size, body height and muscle force rather than chronological age. This has led to the concept of a „muscle-bone unit“ put forward by Frost and subsequently adapted to the pediatric setting by Schönau [22].

Interpretation of DXA in view of the „muscle-bone unit“ in children

In Schönau's „functional“ view of bone development, the major driving forces of bone development (including bone density), are the mechanical challenges that result in bone tissue strain. The two main mechanical challenges, which stimulate bone development (and which are maximally operative during the pediatric years), are linear growth of the skeleton and muscle forces [3]. The former challenge, increases in bone length, results in concomitant increases in bone width in order to maintain bone strength and stability. In addition, bone strength and stability also adapts in response to muscle forces, as the muscle contractions from everyday activities routinely puts much larger loads on the skeleton than the simple effects of gravity. Based on this muscle-bone unit theory, Schönau proposes a step-wise evaluation of bone density:

1. Analysis of whether muscle mass is adequate for body height.
2. Analysis of whether bone mineral content is adequate for muscle mass.

Using this approach, one can identify primary, secondary and mixed bone defects [23, 24]. This concept of „mechanical competence“ has a significant impact on the interpretation of DXA and the diagnosis of osteoporosis in children. Rather than focusing on Z-scores and T-scores, osteoporosis has been defined as „the situation when the skeleton has not been able to withstand its mechanical challenges (growth and muscle force) due to inadequate bone mass and/or structure, resulting in atraumatic fractures“ [25]. In view of this finding, the focus of bone analysis is shifting from bone mass to bone strength [26, 27]. The term „bone health“ seems to better describe the clinical condition of the bone and encompasses a variety of bone pathologies as compared to the term of „osteoporosis“, which is mainly limited to the clinical scenario where there is demonstrated bone fragility.

„Bone health“ analysis in children with kidney disease

There are two major groups of renal patients whose bone health may be compromised. One group represents children with steroid-resistant, steroid-dependent nephrotic syndrome (NS) and systemic diseases, where the bone disease results from high-dose and long-term use of steroids. These patients suffer from steroid-induced osteoporosis, where the bone is adequately mineralized but the amount of bone tissue is decreased as a result of suppressed bone formation caused by steroids [28]. The other group includes patients with chronic kidney disease (CKD), where the bone suffers from disturbed metabolism of vitamin D and mineral metabolism, resulting in rickets and osteomalacia. In this condition, the amount of bone tissue is adequate but the bone is not adequately mineralized. In both conditions, osteoporosis and osteomalacia, the DXA scan would show decreased BMD. In both groups it is necessary to analyze bone health and recognize early signs of bone disease in order to prevent complications, which may potentially lead to severe deformities and physical handicap if untreated.

Nephrotic syndrome/systemic diseases

Patients with NS and normal glomerular filtration rate (GFR) frequently exhibit abnormalities of calcium and vitamin D homeostasis, mainly hypocalcemia and reduced circulating vitamin D metabolites. They receive high-dose and long-term steroid treatments (3 months for initial manifestation of NS), recurrent treatments for relapses of the NS, so that the cumulative steroid dose may be quite elevated if patients are steroid-dependent or steroid-resistant. It therefore seems logical that this therapy would impact bone health in children with nephrotic syndrome or systemic diseases. In one study, 22 out of 100 children (22%) developed osteoporosis defined as a BMD value evaluated by DXA of the lumbar spine with a Z-score of 2.5 SD less than the mean [29]. Children with greater steroid doses were likely to have low BMD on follow-up [30]. However, another recent study showed that intermittent treatment with high-dose glucocorticoids during growth does not appear to be associated with deficits in the bone mineral content of the spine or whole body relative to age, bone size, sex, and degree of maturation [31]. In addition, glucocorticoid-induced increases in body mass index were associated with increased whole-body bone mineral content and maintenance of the bone mineral content of the spine [31]. These rather controversial results confirm that there may be problems with DXA interpretation in children and that the amount of bone mineral may be influenced by other factors such as body weight, lean body mass and body mass index, which should be taken into account during analysis of bone health. In fact, other authors [32, 33] also recognized the importance of lean body mass in the interpretation of total body densitometry in children.

In most studies on steroid-induced osteoporosis in nephrotic syndrome authors used DXA with Z-scores with its inherent biases and interpretation problems as described above. Therefore, the real incidence of steroid-induced osteoporosis may be overestimated by using only the DXA technique. In only one study, bone health was analyzed by a bone biopsy in 8 children with NS and normal GFR [28]. Bone histomorphometry displayed focal osteomalacia (OM) and mild increased bone resorption in most patients. The mineralization lag time, an indicator of the degree of osteomalacia, correlated with the time elapsed since the original diagnosis of NS. While the OM appears to be related to the disease process, the alterations of bone formation and the adynamic changes are likely the result of the corticosteroid therapy.

The main cause of bone disease in these patients is the prolonged use of steroids, which have several and well described adverse effects on bones and cause growth retardation. In addition, steroids may also affect muscle mass and muscle force, which may play a significant role for bone health as suggested by the new concept of the muscle-bone unit. Therefore, the correct assessment of bone health should include bone size and muscle mass in addition to bone mass. Assessment of the bone mass alone may not be sufficient to predict the risk of fractures in these patients. These concepts can be confirmed by anecdotal reports of patients with steroid-induced vertebral fractures detected on classical X-ray whereas the DXA Z-scores of the lumbar spine were completely normal [34].

Chronic kidney disease/kidney transplantation

Recent analysis showed that bone disease remains a significant

problem in children with chronic kidney disease (CKD) [35]. Nearly one third of children with end-stage renal diseases (ESRD) have clinical signs of metabolic bone disease and this accounts for both dialysis and transplant recipients. Metabolic bone disease represents a spectrum of skeletal lesions that range from high-turnover to low-turnover bone disease [36]. Bone disease manifestations in children with CKD include metabolic acidosis, renal osteodystrophy, malnutrition, and disturbances in the insulin growth factor (IGF)/growth hormone (GH) relationship, growth retardation and the development of bone deformities.

Osteopenia was documented in 61.9% of pre-dialysis patients and 59.1% patients with ESRD [37]. However, bone density was assessed by DXA and results may be again biased by interpretation problems as also pointed out by Chesney [38]. DXA does not allow the differentiation between cortical and trabecular bone. It is therefore not clear whether reduced bone density measured by DXA is due to reduced density of the trabecular or cortical bones. To answer this question, one has to use peripheral quantitative computer tomography (pQCT), which measures bone density of the peripheral skeleton and this technology can differentiate between the cortical and trabecular bones. Using this method, Ruth et al. [39] showed that the radial bone had an inadequately thin cortex in relation to muscular force in pediatric renal transplant recipients. As a consequence of cortical thinning, the Strength-Strain Index that reflects the combined strength of trabecular and cortical bone was reduced in these patients. Yet, bone mineral density of the forearm was not decreased. This is in contrast to several papers concluding that there is loss of bone density after kidney transplantation [40–42]. However, the perceived prevalence of osteopenia among pediatric kidney transplant recipients differs using analysis based on chronological age, height-age, or gender-matched reference data [43]. Also, long-term analysis showed that volumetric bone density is not severely affected at 5 to 10 years post kidney transplantation [44]. All these controversial literature reports raise the question whether the analysis of bone density/bone mass with DXA is clinically relevant. It seems that the recently proposed term „bone health“ is more appropriate and better describes the condition of the bone. A proper assessment of bone health cannot be done using DXA only. Other methods like pQCT are needed to better assess bone quality and geometry. This method also enables us to obtain information on muscles, which seem to play a significant role in bone development and bone health. A two-step diagnostic algorithm has been proposed by Schönau et al. to differentiate between primary bone or muscle disease [23].

Conclusion

DXA has been widely used for the diagnosis of osteoporosis. Children with kidney disease often present with growth retardation, which necessitates the correction of DXA results by actual height. Even after correction for height and bone size, DXA may not be the optimal method for bone analysis in children, as it does not differentiate between cortical and trabecular bones. DXA results should be interpreted with caution in children with kidney diseases. Only limited information can be obtained from DXA on muscle mass, which seems to play a significant role for bone density and bone strength. The use of modern devices such as pQCT is recommended to better assess bone health in children. In all circumstances, clinical correlate is mandatory and the existence of the classical X-ray should not be forgotten.

Acknowledgment

The author thanks Darlene Poulin, administrative assistant to the Division of Pediatric Nephrology at the Children's Hospital of Eastern Ontario, for her editorial assistance in the preparation of this manuscript.

References

1. Geusens PP. Review of guidelines for testing and treatment of osteoporosis. Curr Osteoporos Rep 2003;1:59–65.
2. Faulkner KG, Orwoll E. Implications in the use of T-scores for the diagnosis of osteoporosis in men. J Clin Densitom 2002;5:87–93.
3. Schönau E. The peak bone mass concept: is it still relevant? Pediatr Nephrol 2004;19:825–31.
4. Leib ES, Lewiecki EM, Binkley N, et al. Official positions of the International Society for Clinical Densitometry. J Clin Densitom 2004;7:1–6.
5. Mazess RB, Peppler WW, Chesnut CH, et al. Total body bone mineral and lean body mass by dual-photon absorptiometry. II. Comparison with total body calcium by neutron activation analysis. Calcif Tissue Int 1981;33:361–3.
6. Roubenoff R, Kehayias JJ, Dawson-Hughes B, Heymsfield SB. Use of dual-energy x-ray absorptiometry in body-composition studies: not yet a „gold standard“. Am J Clin Nutr 1993;58:589–91.
7. Braillon PM, Salle BL, Brunet J, et al. Dual energy x-ray absorptiometry measurement of bone mineral content in newborns: validation of the technique. Pediatr Res 1992;32:77–80.
8. Chan GM. Performance of dual-energy x-ray absorptiometry in evaluating bone, lean body mass, and fat in pediatric subjects. J Bone Miner Res 1992;7:369–74.
9. Fukunaga M, Tomomitsu T, Ono S, et al. Determination of vertebral bone mineral density with new dual energy X-ray absorptiometry using multiple detectors: fundamental studies. Radiat Med 1992;10:39–43.
10. Mazess RB, Hanson JA, Payne R, et al. Axial and total-body bone densitometry using a narrow-angle fan-beam. Osteoporos Int 2000;11:158–66.
11. Selby P. Postmenopausal osteoporosis. Curr Osteoporos Rep 2004;2:101–6.
12. Miller PD. Treatment of osteoporosis in chronic kidney disease and end-stage renal disease. Curr Osteoporos Rep 2005;3:5–12.
13. Maalouf NM, Shane E. Osteoporosis after solid organ transplantation. J Clin Endocrinol Metab 2005;90:2456–65.
14. Genant HK, Cooper C, Poor G, et al. Interim report and recommendations of the World Health Organization Task-Force for Osteoporosis. Osteoporos Int 1999;10:259–64.
15. Siminoski K, Leslie WD, Frame H, et al. Recommendations for bone mineral density reporting in Canada. Can Assoc Radiol J 2005;56:178–88.
16. McClung MR. The relationship between bone mineral density and fracture risk. Curr Osteoporos Rep 2005;3:57–63.
17. Braillon PM. Volumetric bone mineral density derived from dual-energy X-ray absorptiometry measurements. Nucl Med Commun 1999;20:106.
18. Kröger H, Kotaniemi A, Vainio P, Alhava E. Bone densitometry of the spine and femur in children by dual-energy x-ray absorptiometry. Bone Miner 1992;17: 75–85.
19. Glastre C, Braillon P, David L, et al. Measurement of bone mineral content of the lumbar spine by dual energy x-ray absorptiometry in normal children: correlations with growth parameters. J Clin Endocrinol Metab 1990;70:1330–3.
20. Gafni RI, Baron J. Overdiagnosis of osteoporosis in children due to misinterpretation of dual-energy x-ray absorptiometry (DEXA). J Pediatr 2004;144:253–7.
21. Braillon PM, Cochat P. Analysis of dual energy X-ray absorptiometry whole body results in children, adolescents and young adults. Appl Radiat Isot 1998;49: 623–4.
22. Frost HM, Schönau E. The „muscle-bone unit“ in children and adolescents: a 2000 overview. J Pediatr Endocrinol Metab 2000;13:571–90.
23. Schoenau E. The „functional muscle-bone unit“: a two-step diagnostic algorithm in pediatric bone disease. Pediatr Nephrol 2005;20:356–9.
24. Schoenau E. From mechanostat theory to development of the „Functional Muscle-Bone-Unit“. J Musculoskelet Neuronal Interact 2005;5:232–8.
25. Ward LM, Glorieux FH. The spectrum of osteoporosis. In: Pediatric bone diseases. Eds F.H.Glorieux, H.Juppner and J.Pettifor. Elsevier Science, 2003, 401–442.
26. Seeman E. From density to structure: growing up and growing old on the surfaces of bone. J Bone Miner Res 1997;12:509–21.
27. Seeman E. Periosteal bone formation—a neglected determinant of bone strength. N Engl J Med 2003;349:320–3.
28. Freundlich M, Jofe M, Goodman WG, Salusky IB. Bone histology in steroid-treated children with non-azotemic nephrotic syndrome. Pediatr Nephrol 2004;19: 400–7.
29. Gulati S, Godbole M, Singh U, et al. Are children with idiopathic nephrotic syndrome at risk for metabolic bone disease? Am J Kidney Dis 2003;41:1163–9.
30. Gulati S, Sharma RK, Gulati K, et al. Longitudinal follow-up of bone mineral density in children with nephrotic syndrome and the role of calcium and vitamin D supplements. Nephrol Dial Transplant 2005;20:1598–603.
31. Leonard MB, Feldman HI, Shults J, et al. Long-term, high-dose glucocorticoids and bone mineral content in childhood glucocorticoid-sensitive nephrotic syndrome. N Engl J Med 2004;351:868–75.
32. Högler W, Briody J, Woodhead HJ, et al. Importance of lean mass in the interpretation of total body densitometry in children and adolescents. J Pediatr 2003; 143:81–8.
33. 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.
34. Feber J, Ward LM, Rauch F, et al. Bone mineral density assessed by DXA may not be reduced in children with bone fragility due to steroid-resistant nephrotic syndrome. Pediatr Nephrol 2005;20:C9.