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Quantifying Bone Disease in Pediatric Rheumatic Patients and It's Problems

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Abstract

It is well known, that, due to different reasons, children with rheumatic diseases as well as children with other chronic inflammatory diseases suffer from bone disease like osteopenia or osteoporosis. To measure bone mineral density (BMD) or bone mineral content (BMC), Dual X-Ray Absorptiometry (DXA) is used as golden standard. In this review we will show several problems appearing in measuring bone density in children due to multiple reasons, discuss the necessity to have a closer look on bone and muscle as well as on length and bone age on the examined child and end with the few recommendations there are concerning bone disease in pediatric rheumatology patients.

Bone Disease in Children with Rheumatic Diseases

It is well known, that pediatric patients with chronic rheumatic diseases suffer from bone disease. This was shown in different studies and summarised in an excellent review by Uziel et al. [1] cited in the following chapter. As one example individuals with juvenile onset SLE are more likely to suffer from decreased bone mineral density (BMD) and hence osteoporosis (OP), compared to age mates or compared with other pediatric rheumatology patients [2,3]. Factors recognized to be responsible for these effects are various cytokines and use of Glucocorticoids (GC), especially via the receptor activator of nuclear factor κB (RANK) and its ligand (RANKL) as well as the osteoprotegerin (OPG) system. Compeyrot- Lacassagne et al. [4] found prevalence values for osteopenia and OP among patients with juvenile systemic lupus erythematodes (SLE) with rates for osteopenia of 37.5% and OP of 20.3%. They saw an association with duration and severity of disease, use of GC as well as other cytotoxic drugs and the prevalence of nephritis. In a large cohort of 1000 adult patients followed for 10 years OP rates were slightly lower at 12.1% [5]. Similar findings have been reported for dermatomyositis [6]. In a cohort of 118 children with different rheumatic diseases screened for incident vertebral fractures (IVF) one year after initial GC therapy Rodd et al. found 7 children with IVF all suffering from systemic diseases like dermatomyositis (2 children), SLE (3 children) and one each with systemic vasculitis and mixed connective tissue disease in a very recent study [7]. In addition to that Lim et al. found low BMD in about 15% of newly diagnosed pediatric SLE patients [8].

Concerning Juvenile Idiopathic Arthritis - JIA

Most patients with rheumatic disease in childhood however suffer from juvenile idiopathic arthritis (JIA). Luckily most of them need not to be treated with systemic GC and they represent a very heterogeneous group of patients, which makes it hard to enrol in studies. However there are data that outline low BMD in JIA patients.

In adult patients previously diagnosed with juvenile idiopathic arthritis (JIA) Aggarwal et al. [9] found decreased BMD. These data are confirmed by another study with 30 JIA patients [10] - with mostly patients from the polyarticular group - suffering from low BMD. The authors did not find a statistic significance for disease duration, but BMD and Z score were associated with lower insulin-like growth factor I (IGF-I) levels, maybe as a sign for restricted growth and bone development in these patients. For prepubertal and postpubertal JIA patients Henderson et al. [11,12] described low total body BMD (Z score lower than -1SD) in 29.2%. Notably, none of the JIA patients or controls had ever received GC. Low BMD was seen in patients with greater disease severity and higher levels of inflammatory markers. An important cytokine, beside tumour necrosis factor alpha (TNF α), which is know to interact directly with the RANK-RANKL system, is interleukin-6, seen especially in systemic JIA. It is known to stimulate osteoclast activity and via this way it could be a major player in the development of OP. This was demonstrated by De Benedetti et al. [13] in an interleukin-6 transgenic mice model

As in adults OP may present clinically with a bone fracture often associated with mild or no trauma. Though in a child with a chronic disease such as JIA or SLE back pain or fractures can be a link for OP. Although Osteoporosis in the pediatric age group carries little mortality; however, it does bring a considerable burden of morbidity, especially due to pain, interference with regular activities, and long-term sequel.

But is Osteoporosis in Children the same as in Adults?

In adults, OP is commonly defined as a bone density of 2.5 standard deviations (SD) below the mean in DXA [14]. In between 1.0 and 2.5 SD below the young adult mean we talk about osteopenia. For children there's another definition.

In 2007 the International Society for Clinical Densitometry (ISCD) published a position paper concerning. In this paper the ISCD claims that the diagnosis of osteoporosis in children should not be made on the basis of densitometric criteria alone. Beside a low bone mineral content or density, meaning a z-score of -2.0 or less, adjusted for age, gender and body size, it requires a history of clinical significant fractures. To meet the criterion of a clinical significant fracture it needs either one significant fracture in a long bone of the lower limb, or two fractures in the long bone of an upper extremity, or one vertebral compression fracture [15].

Bone density varies greatly with age. This is the reason the densitometry Z-score is used in the pediatric population and not the

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T-score usually used in adults. Z scores of -2 SD define OP [16]. The problem with pediatric DXA studies is the over- diagnosis of OP in children due to misinterpretation of data based on adult references [17].

What does the BMC or BMD tell us about the bone or it's bearer? Does a Z-score of -2 SD, although age related, tell us the whole truth?

To answer these questions we have to go a bit more into detail. On the one hand we have to take a closer look on the growing bone and it's surrounding - the muscles and it's host. Is she or he tall enough for her or his age or lead the ongoing disease to retardation of puberty and skeletal development? As we will show further on, this might be of interest to interpret the results we get from the DXA device.

On the other hand we will have to take a look on the method itself. Where are the pitfalls of DXA measurements? Is a "small bone" a "bad bone"?

Understanding the Growing Bone

The peak bone mass concept

The central tenet of this concept is that attainment of peak bone mass during childhood and adolescence will prevent fractures in later life, and is based on the observation that areal bone density reaches a peak at around 20 years of age and then decreases. Two possibilities may account for the occurrence of fractures in later life: either such individuals have lost more bone than those without fractures, or their peak bone mass was lower in young adulthood and thereafter they lost bone mass at the same rate and for the same length of time as those without fractures [18]. In this context, it is important to distinguish between bone mass and density: bone mass equals the weight of the bone, which depends on bone size, while the physical bone density represents the BMC relative to the outer bone volume and is independent of size. A normal small bone will have a lower areal density than a larger one, even if their physical densities are identical, and so a presumed bone mass deficit may disappear when the results are corrected for body height or bone size [18].

Moreover, heavy bones will increase energy expenditure and decrease running speed and are therefore unlikely to have conferred an evolutionary advantage [19]. Furthermore, serum calcium remains stable even in the presence of severe osteopenia, and hence maximization of calcium stores through increased skeletal weight is unlikely to be functionally advantageous [20]. Therefore, the most critical property of bone for survival is now thought to be its strength rather than its weight. Since fracture of a bone would have resulted in death in the wild, it is logical that humans would develop mechanisms during the evolutionary process that would encourage bone development to produce bones of optimal strength [19].

Harold frost's mechanostat hypothesis

The combination of factors that make healthy load bearing bones satisfy the needs of all amphibians, birds, mammals, and reptiles of any size, age, and sex was named the mechanostat. It combines the modeling and remodeling mechanisms, their thresholds, the marrow mediator mechanisms, the signalling mechanisms that connect them, and perhaps other things. For mechanical reasons, the resulting negative feedback system determines whether, when and where bones need more strength, or when bone is not needed. Various non mechanical factors, including hormones and other humoral agents, might modulate ('help or hinder') the mechanostat's effects on bone strength. The mechanostat could be compared with the combination of a car's steering, brakes, and accelerator. Osteoblasts and osteoclasts could be analogous to the car's wheels, and mechanical usage its driver (Figure 1) [21-23]. The development of muscle and bone during growth is influenced by forces associated with gravity and physical activity [22,24,25]. It is the muscle forces that create the peak forces acting on bone. Thus, growth in the presence of unloading results in both a muscle that lacks functional capacity, and a bone that lacks the specific shape that is unique for its function [26]. This intrinsic relationship between muscle and bone is described by the mechanostat theory which postulates that increasing maximal muscle force during growth or in response to increased loading will affect bone mass, size, and strength. Unloading (disuse or immobilization) will lead to reduced muscle development (and muscle force) and have a negative effect on the mass, size, and strength of bone. The proper functioning of the mechanostat depends on the normal state of all its cells (osteocytes, osteoblasts, and osteoclasts), the customary mechanical usage of the skeleton, and the endocrine metabolic environment [27]. The fine-tuning of the mechanostat is achieved by physiological set points that act as thresholds for the initiation or inhibition of bone modeling and remodeling. Mechanostat set points are genetically determined and are regulated by the endocrine environment. For instance, it is proposed that reduced estrogen concentrations increase the set points for bone modeling and remodeling. The endocrine environment affects the mechanostat sensitivity with which bone adapts its mass, geometry, or structural properties to bone deformations caused by loading [27]. Exercise and nutrition are key environmental factors known to affect muscle and bone development. Exercise acts directly through muscle action and indirectly through endocrine regulation; during growth, exercise is thought to influence bone modeling and thus bone geometry.

Development of the 'Functional Muscle–Bone Unit'

Figure 2 shows the relationships between age and trabecular density; between BMC and bone strength index (BSI); between muscle area and trabecular density, and BMC and BSI in a healthy reference population. Anthropometric data and results obtained with Peripheral Quantitative Computed Tomography (PQCT) in these individuals have been reported previously [28-30]. Trabecular density as an index of tissue density is dependent on neither age nor muscle development, whereas BMC and BSI appear to be dependent on age during childhood only. By contrast, BMC and BSI show a strong linear correlation with muscle development in childhood and adulthood. These data show that bone density is more or less 'constant', and that BMC and BSI are a

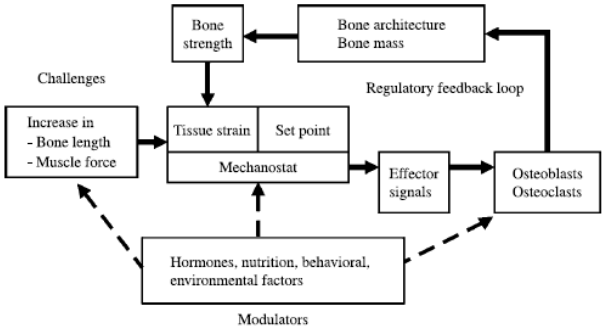

Figure 1: A functional model of bone development based on the mechanostat theory. The central piece of bone regulation is the feedback loop between bone deformation (tissue strain) and bone strength. During growth, this homeostatic system is continually forced to adapt to external challenges. The factors shown below modulate various aspects of the central regulatory system. From Rauch & Schoenau [20], with permission.

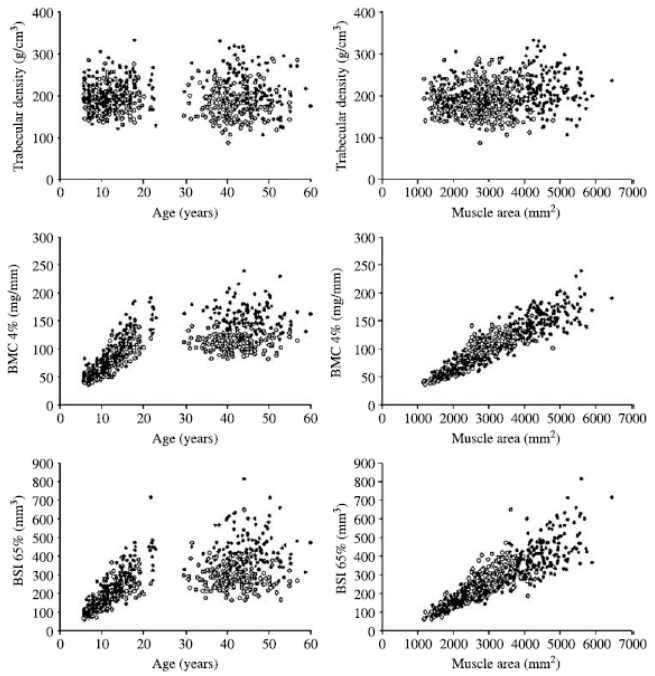

Figure 2: (a) Trabecular density, (b) bone mineral content (BMC), and (c) bone strength index (BSI) in relation to age and muscle area in a healthy reference population at the distal radius. From Schoenau [30], with permission.

function of muscle development. Based on these considerations, some years ago we recommended relating analyzed bone data with surrogates of muscle development. Instead of using age-related reference data, analysis of the so-called 'functional muscle-bone unit' (Figure 3) should improve understanding of the physiology and pathophysiology of bone development.

Knowing all that a two-stepped diagnostic algorithm to characterize metabolic bone diseases in children and adolescents should be used (Figure 4) [31-33]. This algorithm includes two important aspects of the skeletal development in children and adolescents – the relationship of bone mass with body height and muscle force. In the first step, muscle mass is referred to height. In the second step, the ratio of bone mass to muscle force (expressed by cross-sectional muscle area or maximal force) indicates whether the individual is characterized by intact bone or a primary bone disease (e.g. osteogenesis imperfecta, juvenile idiopathic osteoporosis) or a secondary bone disease (e.g. due to chronic inflammatory diseases, endocrine disturbances). Thereby, bone parameters are measured by densitometric methods under consideration that the volumetric approach is preferred in children and adolescents. Suitable muscular parameters are maximal forces, e.g. maximal isometric grip force (MIGF), or a related parameter, e.g. the cross-sectional muscle area. A strong functional relationship between skeletal element and muscle are essential to obtain valid results.

Problems in the Interpretation of Bone Density Scans Using DXA in Children

In the past decade there has been considerable interest in the assessment of bone density in children. This has partly been driven by the recognition that the risk of osteoporosis in adults is influenced by peak bone mass which is largely achieved during childhood and adolescence. However, the main reason for such an interest has been the availability of techniques such as DXA because of its speed, precision and low radiation dose. There have been extensive publications reporting DXA in both healthy children and those with a variety of chronic diseases. However, it is important to remember that DXA is a technique that was originally developed for use in adults, particularly the diagnosis and management of postmenopausal osteoporosis. Children are not just small adults and therefore the assessment and interpretation of DXA scans in children need to be undertaken with caution. In contrast to adults there are considerable changes in the size and shape of children's bones as they grow and mature (Figure 5). In addition there can be large differences in body size and physical maturity in children of the same age which need to be accounted for when trying to interpret a bone density scan result generated by a DXA scanner. Currently the diagnosis of osteoporosis in adults is based on measurements of BMD using DXA with criteria defined by the WHO [34]. A T score (i.e. the observed BMD expressed as a standard deviation (SD) in relation to the young adult mean) of less than –1.0 is defined as osteopenia, whilst a T score of less than –2.5 is defined as osteoporosis. Such definitions have been shown to predict a future risk of fractures in large epidemiological studies in which a 1-SD reduction in BMD is said to predict a two- to threefold increase in the risk of fractures [35]. As said before, defining a child's bone density in relation to the young adult mean as a T score is meaningless and equivalent to comparing a child's height to that of an adult. Similarly the use of a Z score (i.e. the observed BMD expressed as a SD in relation to the mean for the child's age) could be inappropriate

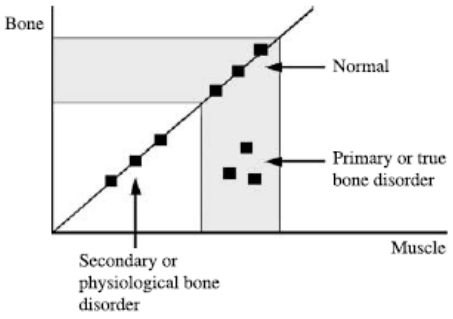

Figure 3: The 'functional muscle–bone unit'. In the cases of 'primary bone disease', the bone structure/mass is not adapted to muscle development. In the cases of 'secondary bone disease', there is disturbed muscle development, but a normal adapted skeleton.

From Schoenau [31] with permission.

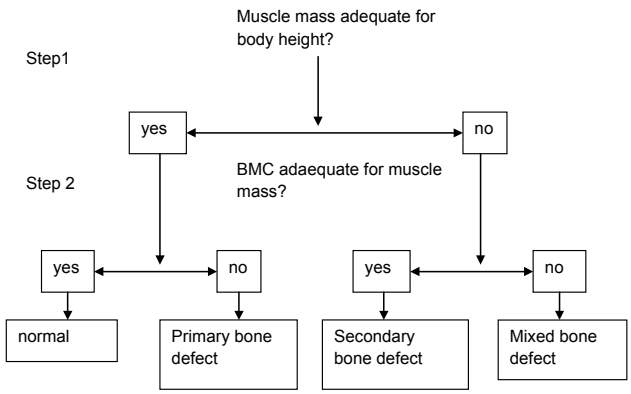

Figure 4: Proposed diagnostic two-step algorithm. Reproduced from Schoenau et al. [31] with permission of the American Society for Bone and Mineral Research.

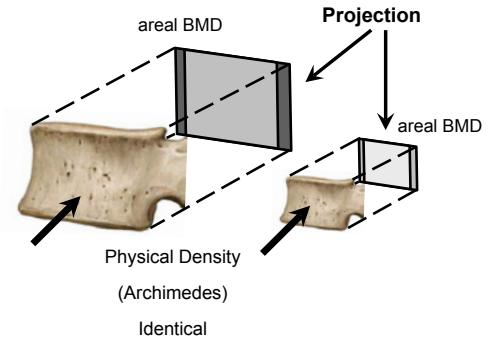

Figure 5a: Difference in Projection from Bones of different size with the same physical density in DXA.

in trying to make a diagnosis of osteoporosis in children. This is for two reasons: Firstly the relationship between BMD and bone fragility in children is not established such that an individual Z score cannot predict the risk of fractures either now or in the future. The second reason relates to the technique of DXA such that small children will have an artificial reduction in BMD. DXA scanners measure BMC and bone area (BA) and calculate BMD as BMC/BA. However, this is not a true density (BMC/bone volume) but a two-dimensional measurement (areal bone density) that is affected by the subject's size [36]. As a consequence there is a strong correlation between the measurement of BMD using DXA in healthy children and their height and weight. As the pediatric reference data that are currently available on DXA scanners relate a child's bone density to that expected for his/her age it can readily be seen that a child who is significantly smaller than his/her age-related peers will have a BMD result that is low in relation to age and may easily have a Z score of –2.5 or less. This may lead to an inappropriate label of 'osteoporosis' and unnecessary treatment (Figure 5 b). Such a problem is particularly evident in children with chronic diseases who will often be small for their age. There are many examples in the pediatric literature in which a group of children with a particular chronic disease have been identified as having a low bone density using DXA. However, closer examination of the data often reveals that these children are usually also small for their age and no adjustment has been made for this difference in body size.

A variety of different approaches have been used to correct for the impact of body size and bone size on DXA scan results. These methods of normalization have concentrated on the individual aspects of the problem either making an adjustment for the bone size or adjusting mineralization to body size.

One approach has been to calculate a volumetric or bone mineral apparent density (BMAD) using the BA and average width of the lumbar vertebrae to produce a measure of bone volume. There are currently two principal methods to achieve this, one being that of Kroger et al. [37] in which it is assumed that the spine is a stack of cylinders, and that of Carter et al. [38] which have assumed each vertebra is a cube. Although such an approach makes a clear adjustment for the effect of bone size, it fails to take into account all issues concerning body size resulting in an over approximation of bone mass for children with large wide bones.

Another approach involves adjustment of BMC for projected BA, body height, weight and Tanner stage of puberty using a regression model as recommended by Prentice et al. [36] and was used in the normative data of Warner et al. [39]. A similar approach has been proposed by Ellis et al. [40] calculating a predicted BMC using regression analysis of the log-transformed variables height, age, gender and pubertal stage.

A third approach proposed by Molgaard et al. [41] uses a three-stage algorithm to evaluate whole body BMC which considers height for age, BA for height and BMC for BA. These three steps were suggested to correspond to three different reasons for reduced bone mass, short bones, narrow bones and light bones. This approach allows the clinician to separately determine if the child's reduced bone density is due to a reduction in the size of the bones or the amount of BMC within the periosteal envelope or both of these factors. Currently normative data for this approach are only available for whole body BMC.

A further problem highlighted by Leonard et al. [42] is that the use of different published normative pediatric DXA data for assessment of areal BMD in children with chronic disease can lead to significant inconsistencies in the diagnosis of osteopenia. They have also demonstrated that the use of different versions of analysis software provided by DXA manufacturers can result in significantly different values for lumbar spine BMC, BA, and therefore areal BMD in children [43]. Thus there are considerable problems in relation to the pediatric normative data that are currently provided on DXA scanners even before considering the issue of adjusting for body size. Although there is now increasing recognition of the problem of interpreting areal BMD scan results in children using DXA, there is currently no consensus as to which technique is the most appropriate. There may in fact be a need to adopt different approaches depending on the clinical question being asked, for example the impact of corticosteroids on bone is more likely to be seen in the spine, whereas the impact of immobility is often more apparent in the whole body and limbs. Currently there has been little attempt to relate BMD values in children to bone fragility as measured by fracture incidence as an outcome. Such studies would obviously require large numbers of subjects followed longitudinally for several years. However, it is important that such studies are undertaken if we are going to continue to use DXA as an assessment of bone density in children.

Recommendations for routine diagnostics concerning osteoporosis in children with JIA or other rheumatic diseases are few. The American College of Radiologists (ACR) presumed that there should exist specific reasons for evaluating children before performing bone density measurement. For the reasons we described above the ACR sees a potential for misdiagnosis. Corticosteroid treatment, eating disorders, amenorrhea, and genetic disorders are among the reasons to evaluate this group. The expert group discussed that the reporting results may include bone age using hand x-ray, and corrections using height and

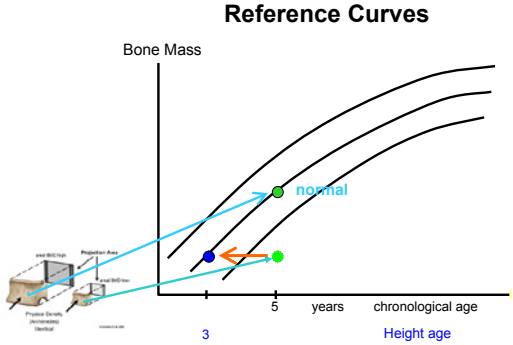

Figure 5b: the bone of a small for its age child is measured with a low bone mass. Corrected for it's height, for example due to a delayed bone age, or just corrected for height, the bone mass is normal.

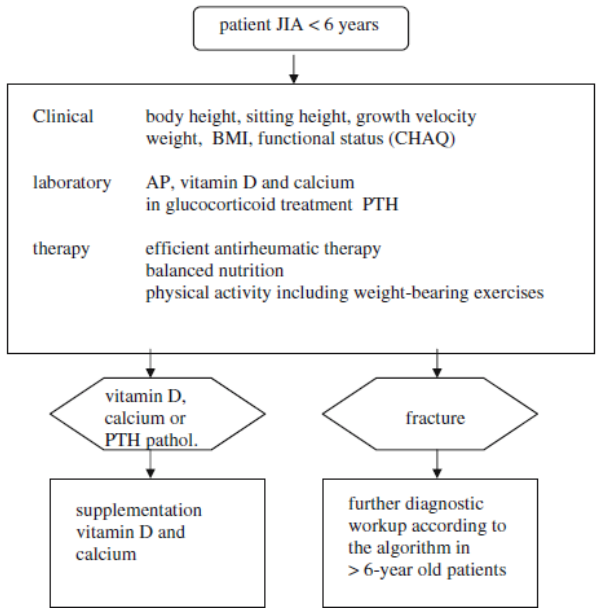

Figure 6a: Flow-sheet for children younger than 6 years with rheumatic diseases from Roth et al. [45] with permission .

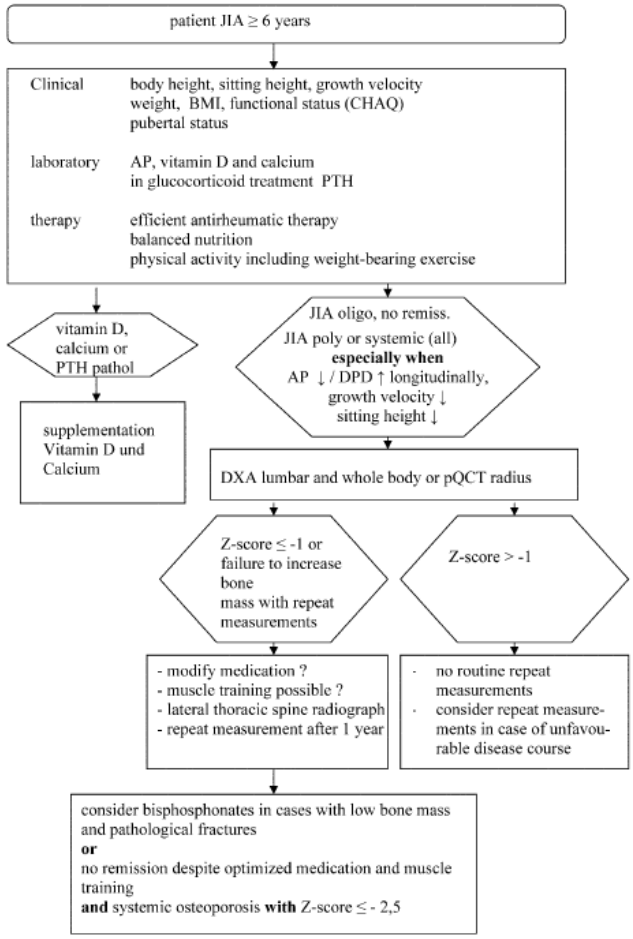

Figure 6b: Flow sheet for Children older than 6 years with rheumatic diseases from Roth et al. [45] with permission.

height age for the scans, especially when there is linear growth or maturation delay of an individual patient. DXA is the preferred method of assessment. [44].

The German pediatric rheumatology association (Gesellschaft für Kinder-und Jugendrheumatologie – GKJR) has tried to establish quite precise recommendations as published by Roth et al. [45] all for children with JIA. Although these recommendations are originally made for JIA patients in special, they could easily be used for all forms of pediatric rheumatic diseases. The algorithms are shown in the Flow sheets in Figure 6a and Figure 6b below.

Conclusion

Due to multiple reasons children with chronic rheumatic diseases can suffer from osteopenia or OP. The disease its self (cytokine action) the treatment (GC), immobility, malnutrition and others can lead to decreased bone density and OP. Data show that even the 'less ill' patients like children with JIA may have a reduced bone density.

There is still no real consensus in between the different associations whom to screen for bone disease, but as shown in Figure 6 there are very good attempts in this direction. If a child with inflammatory disease is screened for OP you have to have in account that these patients often have a reduced body height [46] and often have delayed puberty and retarded bone age. In order not to underestimate bone density in these patients, the results should be interpreted from a 'bone experienced' pediatric rheumatologist, pediatric endocrinologist or pediatric radiologist and may be corrected.

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