Bone Mineral Content per Muscle Cross-Sectional Area as an Index of the Functional Muscle-Bone Unit

ECKHARD SCHOENAU,1 CHRISTINA MARIA NEU,1 BODO BECK,1 FRIEDRICH MANZ,2 and FRANK RAUCH1

ABSTRACT

Bone densitometric data often are difficult to interpret in children and adolescents because of large inter- and intraindividual variations in bone size. Here, we propose a functional approach to bone densitometry that addresses two questions: Is bone strength normally adapted to the largest physiological loads, that is, muscle force? Is muscle force adequate for body size? To implement this approach, forearm muscle cross-sectional area (CSA) and bone mineral content (BMC) of the radial diaphysis were measured in 349 healthy subjects from 6 to 19 years of age (183 girls), using peripheral quantitative computed tomography (pQCT). Reference data were established for height-dependent muscle CSA and for the variation with age in the BMC/muscle CSA ratio. These reference data were used to evaluate results from three pediatric patient groups: children who had sustained multiple fractures without adequate trauma (n = 11), children with preterminal chronic renal failure (n = 11), and renal transplant recipients (n = 15). In all three groups mean height, muscle CSA, and BMC were low for age, but muscle CSA was normal for height. In the multiple fracture group and in renal transplant recipients the BMC/muscle CSA ratio was decreased (p < 0.05), suggesting that bone strength was not adapted adequately to muscle force. In contrast, chronic renal failure patients had a normal BMC/muscle CSA ratio, suggesting that their musculoskeletal system was adapted normally to their (decreased) body size. This functional approach to pediatric bone densitometric data should be adaptable to a variety of densitometric techniques. (J Bone Miner Res 2002;17:1095–1101)

Key words: bone density, bone mass, growth, musculoskeletal, muscle

INTRODUCTION

Bone densitometry currently is one of the mainstays in the evaluation of systemic bone diseases in adults1 and also is increasingly used to assess bone disorders in children and adolescents.2 The purpose of doing densitometric studies in such circumstances is to measure densitometric indicators of bone stability.3 Following procedures that were established for diagnosing adult osteoporosis, a decrease in densitometric surrogates of bone stability usually is interpreted as indicating increased fracture risk.

All authors have no conflict of interest.

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Areal BMD is defined as the mineral mass of a bone divided by its projection area in a given direction (g/cm²) and is related directly to the mean path length that the radiation beam takes through the bone.

With increasing awareness of these problems with BMC and areal BMD, methods to determine total volumetric BMD (vBMD) have recently gained popularity. Total vBMD is defined as the mass of mineral divided by the volume enclosed by the periosteal bone surface. The appeal of this parameter derives from the fact that it is not influenced by bone size. However, it is clear from everyday life that total vBMD cannot be expected to be a good indicator of stability, at least of long bones. A thick rod is more stable than a thin rod that is made of the same material (and consequently has the same volumetric density). The same can be shown formally using information that is available from textbooks of mechanics (Fig. 1). Total vBMD will correlate with bone strength when size differences are negligible, but this condition is not met in children and adolescents.

How then can densitometric data in children and adolescents be evaluated in a rational way? We propose a functional approach to this fundamental problem, which takes into account the balance between bone strength and the forces that normally challenge bone stability. The largest physiological loads on a bone result from muscle contraction. Even during everyday activities muscle contraction routinely puts much larger loads on the skeleton than the simple effect of gravity, because muscles have to move the body around by using quite unfavorable lever arms. Therefore, bone stability needs to be adapted to muscle force. This functional muscle-bone relationship could be used for diagnostic purposes, when densitometric surrogates of bone strength are compared with indicators of muscle force.

Thus, when the musculoskeletal system is analyzed as a functional unit, the question arises of how “normality” should be defined. Bone strength may be adapted adequately to local muscle force, but if muscle force is abnormally low, this means that bone strength is decreased also. Therefore, it is necessary to not only evaluate the adaptation of bone strength to muscle force, but also to test whether muscle force is normal. Because muscle force is largely determined by body height, muscle parameters should be related to body height. Using muscle cross-sectional area (CSA) as a surrogate of muscle force rather than actual force, measurements might be advantageous in children, because muscle CSA can be measured more precisely and does not depend on motivation and mood.

The aim of this study was to develop a simple diagnostic algorithm to evaluate musculoskeletal adaptation and thus create an index of the “functional muscle-bone unit.”

Although this investigation was performed using pQCT, the algorithm should be sufficiently simple to be adaptable to other densitometric methods. Therefore, we used BMC as an indicator of bone strength because this probably is the most basic densitometric parameter. We established height-dependent reference ranges for muscle CSA at the forearm and muscle-related reference data for radial BMC at the same site. These data were used to test the proposed diagnostic approach in various pediatric disorders with skeletal manifestations.

MATERIALS AND METHODS

Healthy subjects

The reference population comprised 349 healthy children and adolescents aged 6–19 years (183 girls and 166 boys). Anthropometric data and age-dependent pQCT results of these individuals have been described previously. The children and adolescents were participants of the Dortmund Nutritional and Anthropometric Longitudinally Designed (DONALD) Study, an ongoing observational study investigating the interrelations of nutrition, growth, and metabolism in healthy children. This study was performed at the Research Institute for Child Nutrition in Dortmund, Germany. The cohort was initially recruited for an anthropometric study in a representative sample of school children of Dortmund and later through personal recommendation of parents whose children were already participating. Overall, the study population mostly comprised middle class families and all participants were of white origin. On an annual basis, all participants undergo a full medical history and examination starting in infancy.

The stage of pubertal development was determined in all study participants by physical examination using the grading system defined by Tanner for breast development in girls and genital status in boys. Height was determined to the next succeeding 1 mm using a Harpenden stadiometer. Weight was measured to the nearest 0.1 kg using digital electronic scales with the children clothed in underwear. Age at testing was calculated to two decimals. Forearm length was measured at the nondominant forearm as the distance between the ulnar styloid process and the olecranon using a caliper. Informed consent was obtained from the children’s parents or from the subjects aged 18 years or older. In addition, written assent was obtained from subjects between 14 and 17 years of age.
**Patient groups**

The patient population comprised ambulatory outpatients of the Cologne University Children’s Hospital. Inclusion criteria were age between 7 and 19 years and body height between 120 and 170 cm for girls and 120 and 180 cm for boys. All patients belonging to one of the diagnostic groups described in the following paragraphs and who were referred to the Pediatric Densitometry Unit between January 2000 and February 2001 were included in this evaluation.

Eleven patients (2 girls and 9 boys) were referred to the densitometry unit because they had sustained at least two fractures due to low-velocity trauma but otherwise appeared healthy. These were analyzed together as a “multiple fracture group.”

Eleven patients with chronic renal failure (6 girls and 5 boys) were examined. They had a current creatinine clearance between 10 and 78 ml/minute per 1.73 m² (median, 19 ml/minute per 1.73 m²). These patients had not undergone dialysis or transplantation before but were receiving standard chronic renal failure care, including oral 1,25-dihydroxyvitamin D₃ substitution. Current parathyroid hormone levels ranged from 16 to 212 pg/ml (median, 60 pg/ml). None of these patients had clinical or radiological signs of hyperparathyroid bone disease.

The third group comprised 15 patients (3 girls and 12 boys) who had received a kidney transplant from 3 months to 8.7 years before this study (median, 3.5 years). Current creatinine clearance ranged from 15 to 110 ml/minute per 1.73 m² with a median of 78 ml/minute per 1.73 m². Current parathyroid hormone levels ranged from 6 to 212 pg/ml (median, 60 pg/ml).

**Peripheral quantitative computed tomography**

Peripheral quantitative computed tomography (pQCT) measurements were performed at the proximal nondominant forearm, as described in detail before.(15,16,18) Briefly, an XCT-2000 scanner (Stratec, Inc., Pforzheim; Germany) was used, which is equipped with a low-energy (38 keV) X-ray tube. The effective radiation is ~0.1 μSv from a radiation source of 45 kV at 150 μA. The measurement was performed at a site in which the distance to the ulnar styloid process corresponded to 65% of forearm length. This site of measurement was chosen to analyze the forearm at its maximum circumference. Preliminary measurements in 317 subjects from 6 to 40 years of age had shown that the circumference at this site averaged 99.5% of the maximum circumference of the forearm. A 2-mm-thick single tomographic slice was sampled at a voxel size of 0.4 × 0.4 × 2 mm. Image processing and the calculation of numerical values were performed using the manufacturer’s software package (version 5.40).

The outer contour of the radius was detected at a threshold of 710 mg/cm³. Voxels peripheral of the bones’ outer edges with an absorptiometric density between 20 and 60 mg/cm³ were interpreted as representing muscle. BMC of the entire radial cross-section and muscle CSA were calculated by the manufacturer’s software. BMC represents the mass of mineral per millimeter slice thickness.

<table>
<thead>
<tr>
<th>Height range (cm)</th>
<th>n</th>
<th>Girls</th>
<th>n</th>
<th>Boys</th>
</tr>
</thead>
<tbody>
<tr>
<td>120–129</td>
<td>27</td>
<td>15.8 ± 1.4*</td>
<td>26</td>
<td>17.1 ± 2.0</td>
</tr>
<tr>
<td>130–139</td>
<td>22</td>
<td>18.1 ± 2.4*</td>
<td>17</td>
<td>20.3 ± 2.5</td>
</tr>
<tr>
<td>140–149</td>
<td>18</td>
<td>20.8 ± 2.5</td>
<td>22</td>
<td>22.4 ± 3.7</td>
</tr>
<tr>
<td>150–159</td>
<td>38</td>
<td>24.8 ± 3.0</td>
<td>27</td>
<td>24.6 ± 4.0</td>
</tr>
<tr>
<td>160–169</td>
<td>43</td>
<td>27.4 ± 3.5*</td>
<td>21</td>
<td>30.5 ± 4.8</td>
</tr>
<tr>
<td>170–179</td>
<td>24</td>
<td>28.0 ± 3.3*</td>
<td>31</td>
<td>36.6 ± 6.3</td>
</tr>
<tr>
<td>180–189</td>
<td>12</td>
<td>40.8 ± 5.1</td>
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</tbody>
</table>

Values are mean ± SD.

* Significant difference between results in girls and boys of the same height group (p < 0.01 in each case). The variation between height groups was significant at p < 0.0001 in both genders (Kruskal Wallis test).

**Statistical analysis**

Results in patients were converted into sex- and age- or height-specific Z scores using the formula Z score = (t test result for a patient) − (age/height- and sex-specific mean in the reference population)/(age/height- and sex-specific SD in the reference population).

To evaluate whether a parameter was significantly different from the result in controls, the difference of the mean Z score to zero was assessed. A significant difference was assumed when the 95% CI of the mean Z score did not include zero. For comparisons between two groups t-tests were used. Throughout, a value of p < 0.05 was considered significant. All statistical analyses were performed using the SPSS, Inc. software package (version 6.0 for Windows; SPSS, Inc., Chicago, IL, USA).

**RESULTS**

Regression analysis between body height and muscle CSA at the proximal forearm revealed a power relationship between the two parameters (regression equations: girls, muscle CSA [cm²] = 0.0021 * height¹.35 [cm], r = 0.90; boys, muscle CSA = 0.0004 * height².20, r = 0.90; p < 0.0001 each). Mean and SD of muscle CSA were calculated for height groups spanning 10 cm each (Table 1). These are limited to the range from 120 to 180 cm in girls and from 120 to 190 cm in boys, because there was an insufficient number of smaller (6 girls and 6 boys) or taller subjects (5 girls, 179 cm; 4 boys, 189 cm). Muscle CSA was larger in boys than in girls from 120 to 139 cm and from 160 to 179 cm.

There was a linear relationship between muscle CSA and BMC of the radial diaphysis (Fig. 2). Possibly, the simplest indicator of the muscle-bone relationship that can be derived from these data are the ratio between BMC and muscle CSA. Table 2 shows the variation with age in this ratio. BMC/muscle CSA did not vary significantly between 6 and 19 years of age in boys but increased in girls between...
the age groups of 12–13 years and 14–15 years. Consequently, the BMC/muscle CSA ratio was significantly higher in girls than in boys after age 13 years. In accordance with this age variation, there was no gender difference in the BMD/muscle CSA ratio until pubertal stage 3, but girls had significantly higher values thereafter (Fig. 3).

These reference data were applied to results in children and adolescents who had sustained multiple fractures, in pediatric patients with chronic renal failure, and in pediatric renal transplant recipients (Table 3). The original results of these patients were first converted into age-dependent Z scores, using previously established reference data.\(^{14–16}\) In all three groups the average height, BMC, and muscle CSA were low for age.

The height-related muscle CSA and the muscle-related BMC of individual patients are shown in Fig. 4. Muscle CSA was within or even above the height-dependent reference range in all but two patients. These were a 13.3-year-old boy with chronic renal failure and a 12.7-year-old boy who had received a renal transplant. The mean height-dependent Z score of muscle CSA was not significantly different from zero in any of the patient groups (−0.2 ± 1.0 [mean ± SD] in the multiple fracture group; −0.5 ± 1.1 in chronic renal failure patients; 0.2 ± 1.4 in kidney transplant recipients; \(p > 0.10\) for difference to 0 in each case). In contrast, 3 of the 11 patients with multiple fractures and 4 of the 15 kidney transplant recipients had a BMC/muscle CSA ratio below the reference range. BMC/muscle CSA was significantly decreased in these two groups (age-dependent Z score of BMC/muscle CSA in the group with multiple fractures, −1.3 ± 1.7; in kidney transplant recipients, −1.1 ± 1.2) but was normal in chronic renal failure patients (Z score, 0.0 ± 1.1).

**DISCUSSION**

In this study we present a new diagnostic approach to evaluate densitometric data in children and adolescents. The theoretical background for this approach is provided by the mechanostat theory, which proposes that bones adapt their strength to keep the strain caused by physiological loads close to a set point.\(^{19,20}\) Because the largest physiological loads are caused by muscle contractions, there should be a close relationship between bone strength and muscle force.
or size. This is what was observed in this study and in earlier studies.\(^{18,21,22}\) We are aware that the mechanostat theory still stirs some controversy in the field of bone densitometry and we do not claim that our study "proves" that the theory is correct. Nevertheless, our findings certainly are in accordance with the predictions derived from the mechanostat hypothesis. We found that during puberty, the BMC/muscle CSA ratio increases in girls but not in boys. This mirrors our earlier observation that girls and boys have a similar muscle-bone relationship regarding external bone size, but girls have a relatively smaller marrow cavity.\(^{18}\) These observations are in accordance with the hypothesis that estrogen lowers the mechanostat set point on endosteal bone surfaces.\(^{23}\) A lower set point means that the same loads have a greater osteogenic effect, leading to endocortical apposition. Thus, the changes in BMC/muscle CSA during female puberty could be an example of how hormonal factors can modulate the muscle-bone relationship.\(^{23}\)

Regarding the application of the muscle-bone relationship to clinical practice, we propose the two-step diagnostic algorithm shown in Fig. 5. Required are a measure of muscle force or size and a measure of BMC at a corresponding location. The results can be combined into four diag-

### Table 3. Anthropometric Characteristics and Results of pQCT Analyses in Patient Groups

<table>
<thead>
<tr>
<th></th>
<th>Fractures (n = 11; 2 females; 9 males)</th>
<th>CRF (n = 11; 6 females; 5 males)</th>
<th>RTX (n = 15; 3 females; 12 males)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age (years)</strong></td>
<td>mean ± SD (range)</td>
<td>mean ± SD (range)</td>
<td>mean ± SD (range)</td>
</tr>
<tr>
<td></td>
<td>13.3 ± 2.4 (12.8–18.8)</td>
<td>13.1 ± 2.0 (8.9–16.4)</td>
<td>14.6 ± 3.3 (8.8–19.8)</td>
</tr>
<tr>
<td><strong>Height (cm)</strong></td>
<td>155 ± 15 (123–175)</td>
<td>150 ± 18 (127–176)</td>
<td>147 ± 15 (121–174)</td>
</tr>
<tr>
<td><strong>Weight (kg)</strong></td>
<td>49 ± 15 (29–73)</td>
<td>42 ± 14 (25–74)</td>
<td>47 ± 20 (21–94)</td>
</tr>
<tr>
<td><strong>BMC (mg/mm)</strong></td>
<td>52 ± 21 (48–51)</td>
<td>58 ± 13 (55–81)</td>
<td>51 ± 12 (53–72)</td>
</tr>
<tr>
<td><strong>Muscle CSA (cm²)</strong></td>
<td>26 ± 8 (16–39)</td>
<td>22 ± 5 (15–31)</td>
<td>24 ± 6 (12–37)</td>
</tr>
</tbody>
</table>

**Age-dependent Z scores**

<table>
<thead>
<tr>
<th></th>
<th>Fractures</th>
<th>CRF</th>
<th>RTX</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Height</strong></td>
<td>−1.1 ± 1.3*</td>
<td>−1.2 ± 1.4*</td>
<td>−1.4 ± (−3.2–1.5)</td>
</tr>
<tr>
<td></td>
<td>−0.4 ± 1.1</td>
<td>−0.8 ± 0.6*</td>
<td>−0.9 ± (−1.6–0.5)</td>
</tr>
<tr>
<td><strong>BMC</strong></td>
<td>−2.5 ± 1.7*</td>
<td>−1.6 ± 0.9*</td>
<td>−2.9 ± (−3.1–0.1)</td>
</tr>
<tr>
<td><strong>Muscle CSA</strong></td>
<td>−0.7 ± 0.9*</td>
<td>−1.1 ± 0.5*</td>
<td>−1.4 ± (−2.4–0.4)</td>
</tr>
</tbody>
</table>

**CRF, chronic renal failure group; RTX, renal transplantation recipients.**

* Significant difference of Z score mean value from 0.

**FIG. 4.** Muscle CSA related to height and BMC/muscle CSA ratio related to age in (A) girls and (B) boys with multiple fractures (triangles), chronic renal failure (open circles), and kidney transplant recipients (crosses). The reference ranges (mean ± 2 SD; black lines) and means (gray lines) for healthy children and adolescents are indicated.
nastic groups. In the first situation, muscle force or size is adequate for height. If BMC is adapted normally to the muscle system, the result is interpreted as “normal.” If BMC is lower than expected for muscle force or size, a “primary bone defect” is diagnosed. In the second situation, muscle force or size is too low for height. Even if BMC is adapted adequately to the decreased mechanical challenge, this means that bone mass and presumably strength are still too low for body height. Therefore, a “secondary bone defect” is diagnosed. If muscle force or size is abnormally low and BMC is even lower than expected from a normal muscle-bone relationship, a “mixed bone defect” (primary and secondary) is present. This diagnostic procedure resembles a classification of disorders with low bone mass that was proposed by Frost. That classification distinguished “true osteoporosis,” “physiological osteopenia,” and “combination states.” We prefer the qualifications “primary” and “secondary” to “true” and “physiological,” because even physiological osteopenia may result in serious morbidity.

We used this diagnostic approach in three groups of patients who frequently undergo assessment in pediatric bone densitometry units. The purpose was to exemplify the diagnostic algorithm rather than to provide an in-depth analysis of these conditions. In several of the patients who were referred for multiple fractures, muscle CSA was normal for height, but the BMC/muscle CSA ratio was below the reference range. Therefore, a primary bone disorder is diagnosed in these patients.

The findings in children and adolescents with chronic renal failure are in accordance with earlier results from our group. However, in that previous study we failed to correct muscle force for height and concluded that muscle force was too low for age. In this study, we found that muscle CSA was not significantly decreased when related to height and that BMC/muscle CSA was normal. Thus, in this group of patients without symptomatic bone disease (apart from short stature), bone appeared to be adapted normally to muscle loads and there was no evidence for a specific disease effect on the muscle system. These are preliminary observations in a small and heterogeneous cohort. Obviously, confirmation in more detailed studies is required before firm conclusions can be reached.

Interestingly, kidney transplant recipients differed from patients with chronic renal failure in that they had a decreased BMC/muscle CSA ratio. According to the diagnostic algorithm shown in Fig. 5, this suggests that there is a primary bone problem after renal transplantation. This might be caused by corticosteroids or other medication commonly used after transplantation and requires further study.

It should be possible to adapt the general idea of this diagnostic approach to densitometric techniques other than pQCT. Body height and BMC are routine measures, but probably many pediatric densitometry units do not yet perform concomitant analyses of local muscle force or size. This may be difficult when bone densitometry is performed at the lumbar spine because the biomechanical situation is rather complex at that location. It should be easier to assess the muscle-bone relationship by measuring BMC at limb sites and relate results to parameters of local muscle force or size. Further studies are needed to work out the methodological details when devices other than pQCT are used for this purpose.

In conclusion, we are proposing a new diagnostic approach to pediatric bone diseases, which is based on the analysis of the balance between bone strength and the physiological challenge to bone strength. This approach allows a new classification of bone disorders in children and adolescents. Thus, it is hoped that the more detailed insights gained could help to devise targeted strategies for the prevention and treatment of pediatric bone diseases.

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AN INDEX OF THE FUNCTIONAL MUSCLE-BONE UNIT


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Received in original form June 17, 2001; in revised form January 12, 2002; accepted January 29, 2002.