

From mechanostat theory to development of the "Functional Muscle-Bone-Unit"

E. Schoenau

Children's Hospital, University of Cologne, Cologne, Germany

Abstract

Bone densitometric data are often 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? 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. Because the largest physiological loads are caused by muscle contractions, there should be a close relationship between bone strength and muscle force or size. The proposed two-step diagnostic algorithm requires a measure of muscle force or size and a measure of bone mineral content (BMC) at a corresponding location. The results can be combined into four diagnostic groups. In the first situation, muscle force or size is adequate for height. If the skeleton is adapted normally to the muscle system, the result is interpreted as "normal". If it 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 the skeleton 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. It is hoped that the more detailed insights thus gained could help to devise targeted strategies for the prevention and treatment of pediatric bone diseases.

Keywords: Children, Musculoskeletal, Osteoporosis, Puberty, Mechanostat, Muscle-Bone-Unit

Introduction

Bone densitometry currently is one of the mainstays in the evaluation of systemic bone diseases in adults and is also increasingly used to assess bone disorders in children and adolescents¹. The purpose of doing densitometric studies in such circumstances is to measure densitometric indicators of bone stability. Following procedures that were established for diagnosing adult osteoporosis, a decrease in densitometric surrogates of bone stability is usually interpreted as indicating increased fracture risk. The most basic densitometric parameter is bone mineral content (BMC), which can be

measured with most densitometric techniques. BMC is either defined as the mass of mineral contained in an entire bone (g) or as the mass of mineral per unit bone length (g/cm). Although mineral mass can be expected to be a good surrogate of bone stability, BMC obviously is a size-dependent parameter. This is a drawback, because short children will have a lower BMC than their healthy age-matched peers, even if their (smaller) bones are otherwise completely normal. The same reasoning applies to areal bone mineral density (BMD), which is the most widely used densitometric parameter at present². 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^{3,4}. Similar to BMC, areal BMD is therefore often difficult to interpret in children and adolescents with short stature.

With increasing awareness of the problems related to BMC and areal BMD measurements, methods to determine total volumetric BMD (vBMD) have recently gained popularity. However, it is clear from everyday life that total

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Corresponding author: Eckhard Schoenau, M.D., Children's Hospital, University of Cologne, Kerpener St. 69, 50924 Cologne, Germany
E-mail: Eckhard.Schoenau@uk-koeln.de

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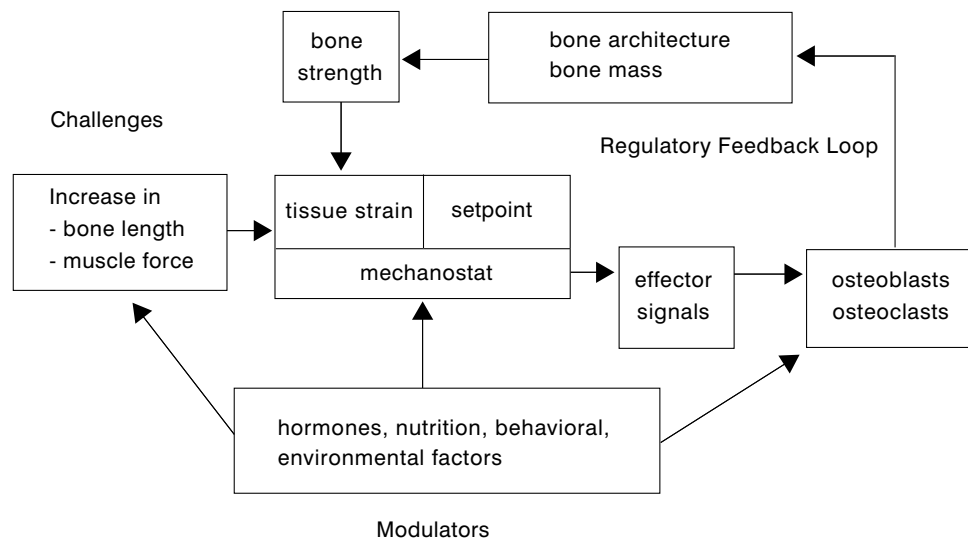


Figure 1. A functional model of bone development based on the mechanostat theory. The central piece of bone regulation is the feedback loop between bone deformation (tissue strain) and bone strength. During growth this homeostatic system is continually forced to adapt to external challenges. Factors shown below modulate various aspects of the central regulatory system [Reproduced from *Pediatric Research* 2001; 50(3):309-314].

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). 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 based on the mechanostat hypothesis.

Harold Frost's mechanostat hypothesis

The combination of factors that makes healthy load bearing bones satisfy needs in all amphibians, birds, mammals and reptiles of any size, age and sex was named the mechanostat. It would combine the modeling and remodeling mechanisms, their thresholds, the marrow mediator mechanisms, the signaling mechanisms that connect them, and perhaps other things. The resulting negative feedback system would determine, for mechanical reasons, whether, when and where bones needed more strength, or when bone was 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 would be like the combination of a car's steering, brakes and accelerator. Osteoblasts and osteoclasts would be analogous to the car's wheels, and mechanical usage its driver (Figure 1)⁵⁻⁷.

Development of the "Functional Muscle-Bone-Unit"

Figure 2 shows the relationship between age, muscle area and trabecular density, BMC and bone strength index (BSI) in a healthy reference population. Anthropometric data and results obtained with peripheral quantitative computed tomography (pQCT) in these individuals have been reported previously⁸⁻¹⁰. Trabecular density as an index of tissue density is neither dependent on age nor on muscle development. BMC and bone strength index seem to be dependent on age during childhood only. In contrast, BMC and BSI show a strong linear correlation with muscle development in childhood and adulthood. These data describe that bone density is more or less a "constant" and BMC and BSI are a function of muscle development. Based on these considerations we recommended some years ago to relate analysed bone data on surrogates of muscle development. Instead of age-related reference data, the analysis of the so-called "muscle-bone-unit" (Figure 3) should improve the understanding of physiology and pathophysiology of bone development.

The "Functional Muscle-Bone-Unit" in clinical practice

Regarding the application of the muscle-bone relationship to clinical practice, we previously proposed a diagnostic algorithm shown in Figure 4¹¹. A measure of muscle force or size and a measure of BMC at a corresponding location are required. If BMC is lower than expected for muscle force or size, a "primary bone defect" is diagnosed. In the second sit-

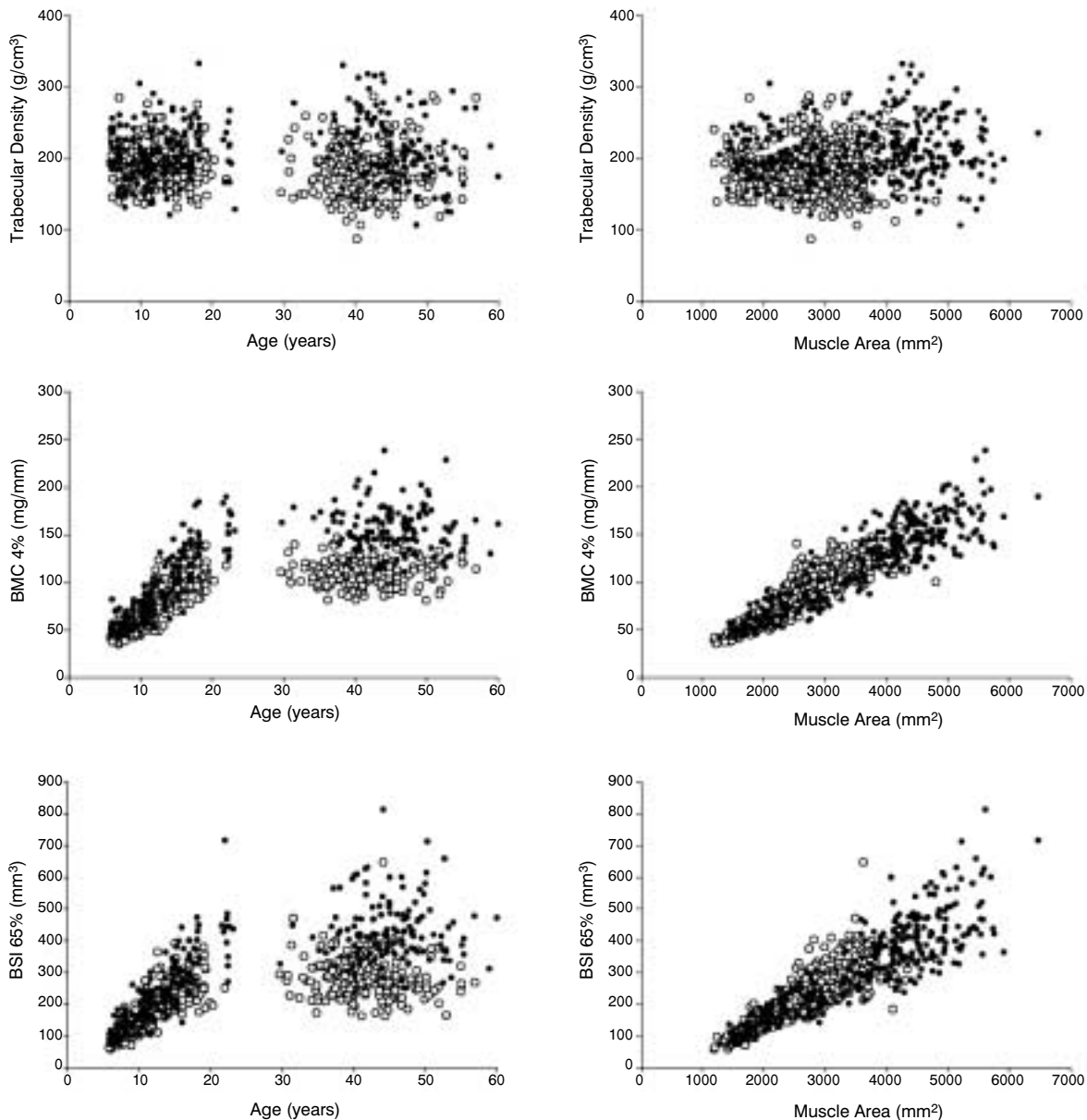


Figure 2. Trabecular density, bone mineral content (BMC 4%) and bone strength index (BSI 65%) in relation to age and muscle area (open circles: females; closed circles: males).

uation, 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 are abnormally low and BMC is even lower than expected from a normal muscle-bone relationship, a "mixed bone defect" (primary and secondary) is present. Height-dependent reference ranges for muscle cross-sectional area at the forearm and muscle-related reference data for radial BMC at the same site have been published⁸. Although this investigation

was performed using pQCT, the algorithm should be sufficiently simple to be adaptable to other densitometric methods. Indeed, Schiessl et al. found identical correlations between muscle and bone mass using dual-energy X-ray absorptiometry (DXA)¹². Therefore, we used BMC as an indicator of bone strength because this probably is the most basic densitometric parameter. These data were used to test the proposed diagnostic approach in children and adolescents with renal diseases¹⁰.

Eleven patients with chronic renal failure (CRF, 6 girls and 5 boys) were examined (see Figure 5). The second group

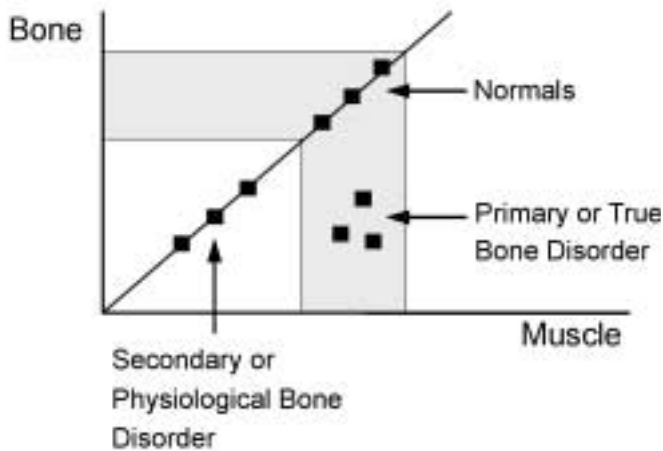


Figure 3. The "functional muscle-bone-unit". Primary bone disease: bone structure/mass not adapted on muscle development. Secondary bone disease: disturbed muscle development but normal adapted skeleton.

comprised 15 patients who had received a kidney transplant (RTX, 3 girls and 12 boys). The patients had undergone transplantation from 3 months to 8.7 years before this study (median 3.5 years). Peripheral QCT measurements were performed on the proximal non-dominant forearm, as described in detail previously^{8-11,13}.

At the radial diaphysis, there was a linear relationship between height and muscle cross-sectional area and BMC and muscle cross-sectional area (Figure 5). The 95% confidence intervals of regression curves showed an overlap between controls and patients with CRF or RTX. The analysis of "Step 1 – Ratio muscle cross-sectional area /Height" showed no difference between the distribution of the plots for patients and controls. The analysis of "Step 2 – Ratio BMC/muscle cross-sectional area" showed that most of the patients' plots were below the regression curve of the control group¹⁴.

The findings in children and adolescents with CRF are in accordance with earlier results from our group¹⁵. However, in that previous study we failed to correct muscle force for height and concluded that muscle force was too low for age. In the present analysis, we found that muscle cross-sectional area was not significantly decreased when related to height and that BMC/ muscle cross-sectional area 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. Interestingly, RTX patients differed from patients with CRF in that they had a decreased BMC/ muscle cross-sectional area ratio. According to the diagnostic algorithm shown in Figure 3, this suggests that there is a primary bone problem after renal transplantation.

In conclusion, these data illustrate 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.

Influence of puberty on the "Muscle-Bone-Unit"

In 1995, H.M. Frost raised the important question: could estrogen make growing females add more bone than needed for physical activities, to store extra calcium for later gestation and lactation (personal communication)? Data from Zanchetta et al. support this¹⁷. This group used DXA to estimate total body bone mineral content and lean body mass in 778 healthy Argentine Caucasian children. These data were re-analyzed by Schiessl et al. who found that bone mass in girls at puberty begins to increase more than in boys with similar lean body masses¹². Because of methodological and analytical uncertainties in using total bone mineral content and lean body mass as indices of bone and muscle strength, and also because of the potential importance of these findings, additional studies seemed necessary for confirmation.

In healthy children and adolescents, aged 6–22 years, and adults who took part in the DONALD Study (Dortmund Nutritional and Anthropometric Longitudinally Designed Study), the cortical area of the radius as an index of bone strength and muscle area representing muscle strength, were measured with pQCT^{16,18}.

There was a strong correlation between muscle area and cortical area of the radius in all children, adolescents, and adults. Figure 6 shows the correlations between muscle area and cortical area in males and females. Before puberty, boys and girls showed the same relation of muscle area and cortical area. But after puberty, in girls the cortical area was greater in relation to muscle area than in boys. At pubertal stage 3, a relatively greater cortical area could be shown in girls. Figure 7 describes the relationship between periosteal, endosteal circumference, and the muscle area. The correlation between muscle area and periosteal circumference was not significantly different between males and females. In contrast, there was a significant gender difference in the relationship between muscle area versus endosteal circumference. These data support ideas about bone development during childhood and adolescence proposed by Frost and the Utah paradigm of skeletal physiology. The largest voluntary loads on bones come from muscles. To adapt bone strength and mass to them, special strain threshold ranges determine where modeling adds and strengthens bone and when remodeling conserves or removes it, just as different thermostat settings control the heating and cooling systems in a house. If estrogens affect the sensitivity of the mechanostat by lowering the remodeling threshold at puberty in girls, bone mass should begin to increase more rapidly than in boys with similar muscle strengths, due to decreased remodeling-dependent bone losses. The results presented here complement studies by Zanchetta et al., Schiessl et al. and Ferretti et al. and support the cited concept^{12,17,19}.

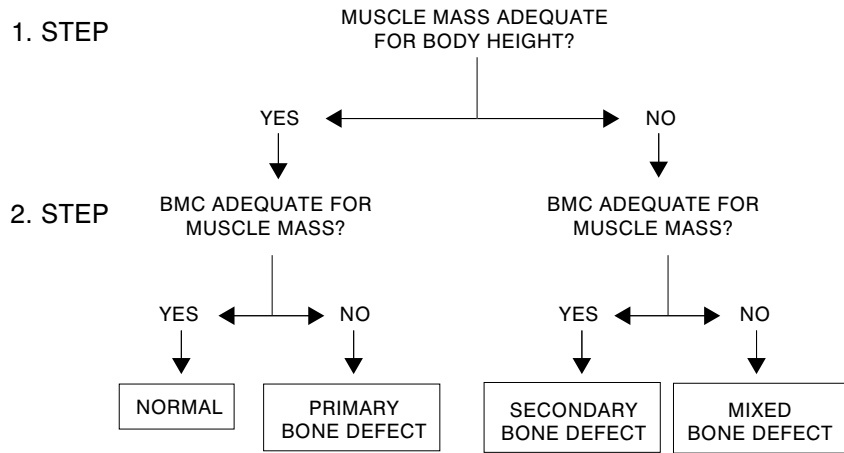
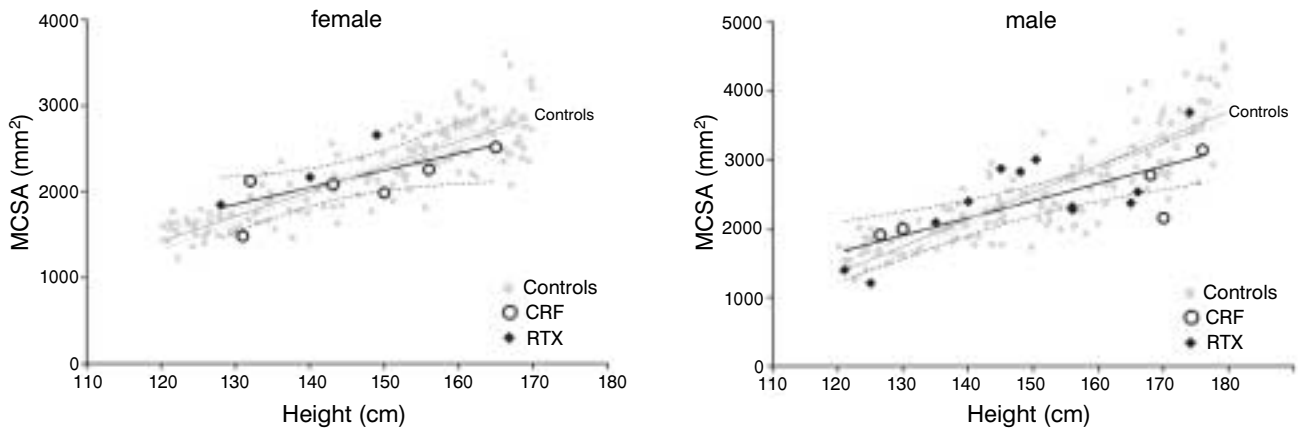


Figure 4. Proposed diagnostic algorithm. [Reproduced from J Bone Miner Res 2002; 17:1095-1101 with permission of the American Society for Bone and Mineral Research]¹⁰.

1. Step: Muscle Mass (MCSA) Adequate For Body



2. Step: BMC Adequate For Muscle Mass

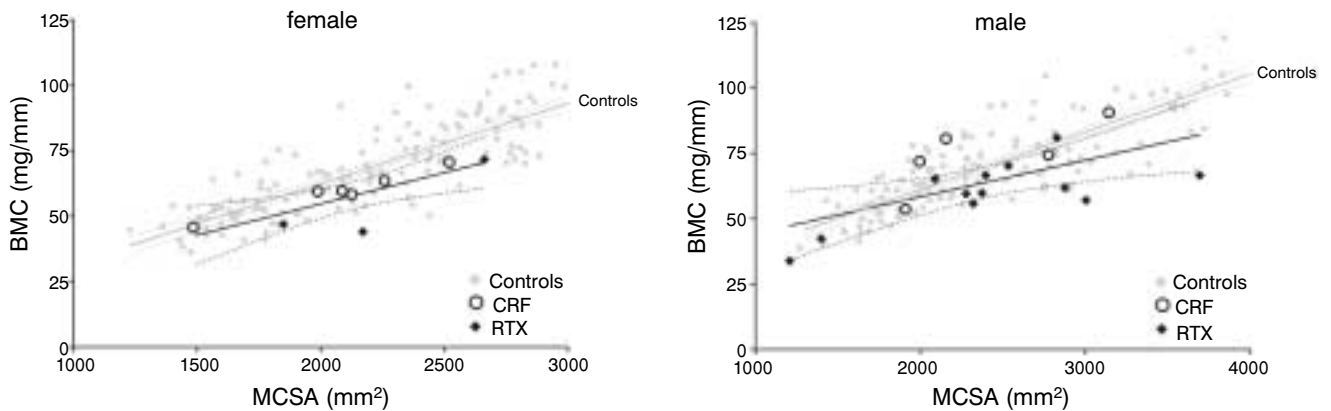


Figure 5. Muscle-bone relationship analyzed by a two-step diagnostic algorithm. CRF chronic renal failure group, RTX renal transplantation recipients: black regression curve and plots; reference group: grey regression and plots [Reproduced from *Pediatr Nephrol* 2005; 20:356-359]¹³.

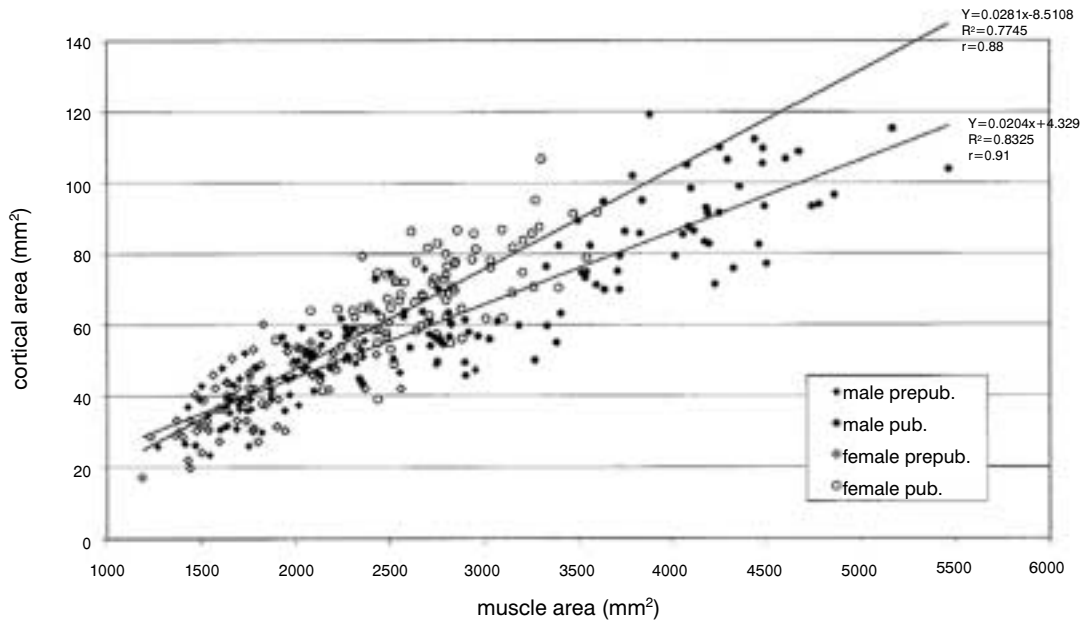


Figure 6. Cortical bone area in relation to muscle area in prepubertal and pubertal boys and girls [Reproduced from Journal of Clinical Endocrinology & Metabolism 2000; 85(3):1095-98. Copyright 2000, The Endocrine Society].

Outlook and new concepts

The following suggestions and recommendations outline a new concept, which is based on the mechanostat theory, but is not proven to be correct in its details.

Bone mass should not be related to age. There is now more and more evidence that bone mass should be related to bone size or muscle function. Thus analyzed, there is no such thing as a "peak bone mass". Many studies are currently underway to evaluate whether these approaches increase sensitivity and specificity of fracture prediction in an individual.

Furthermore, the focus of many bone researchers is shifting from bone mass to bone geometry or bone strength. Bone mass is a surrogate of bone strength, but widely available techniques such as DXA, radiogrammetry, and computed tomography can also be used to measure variables of bone geometry such as cortical thickness, cortical area, and moment of inertia. Future studies will show whether the combined analysis of bone geometry or bone mass in relationship to muscle development improves or removes the peak bone mass concept. At present, bone mass analysis is very useful for epidemiological studies on factors that may have an impact on bone development. However, bone mass can not be regarded as a highly sensitive and specific measure of an individual's fracture risk. The peak bone mass concept was based on the idea that optimal development during childhood and adolescence will prevent fractures in late adulthood. It is clear now that strong bones in the youngster

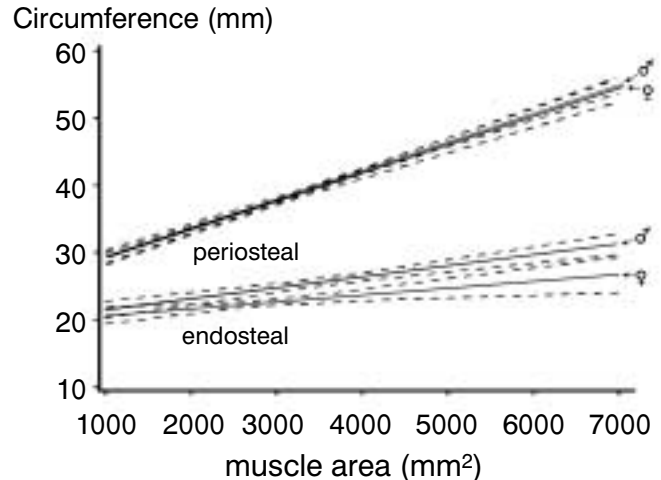


Figure 7. Regression lines and 95% confidence intervals of correlation muscle area vs. periosteal and endosteal circumference [Reproduced from Journal of Clinical Endocrinology & Metabolism, 2000; 85(3):1095-1098. Copyright 2000, The Endocrine Society].

do not automatically lead to a fracture-free old age. However, it might be possible that strong bones keep strong if an individual maintains the healthy lifestyle that made bones strong in the first place. It remains to be seen whether this hypothesis is correct.

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