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Original Article

Hylonome

The muscle-bone unit in adulthood: influence of sex, height, age and gynecological history on the bone mineral content and muscle cross-sectional area

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Abstract

Bone and muscle development are both strongly influenced by sex hormones. The purpose of this study was to examine the changes in bone and muscle parameters (bone mineral content - BMC, muscle cross-sectional area - MA) in 130 men aged 31 -60 years, and in 180 pre-menopausal women aged 30-53 years with respect to age, body height and, with the women, their gynecological history (age-at-menarche, number of pregnancies, duration of lactation and use of oral contraception). The study was performed using peripheral quantitative computed tomography (pQCT) at a 65% site of the forearm length. Both BMC and MA were dependent on body height ($p<0.0001$), but not on age. The BMC/MA ratio was dependent neither on age nor on body height in both genders. MA as well as BMC were found significantly higher in males than in females ($p<0.0001$ for both variables). We observed a significantly higher BMC/MA ratio in females than in males ($p<0.0001$). We found no effect of the analyzed variables of gynecological history on bone/muscle characteristics. The findings highlight the necessity of including height-adjusted parameters and BMC/MA ratio into bone analysis in adults.

Keywords: Bone Mineral Content, Estrogens, Peripheral QCT, Muscle, Osteoporosis

Introduction

Understanding bone physiology is an important milestone for the appropriate and adequate therapy of bone disorders. The metabolism of the skeleton is influenced throughout life by many genetic, hormonal and mechanical factors. The final bone strength, which mirrors the risk of fractures, is a result of the interplay between these factors.

According to the Frost mechanostat hypothesis[1], mechanical loading is the most important determinant of the bone strength. Indeed, both the muscle force[2] as well as the muscle size (muscle cross-sectional area - MA)[3] as surrogates of mechanical loading strongly correlate with bone mineral density (BMD) as well as with bone mineral content (BMC). Moreover, disorders primarily affecting muscles cause osteoporosis due to the inappropriate stimulation of osteoblasts by inactivity. Therefore, the muscle mass should be analyzed together with bone mass.

Involutional osteoporosis is a common chronic disorder affecting both elderly women and men. Osteoporosis-related complications lead to a substantial increase in mortality especially in postmenopausal women. Considering this fact and the high costs expended every year for treating osteoporosis and its complications, procedures enabling the most exact prediction (and subsequent prevention) of osteoporosis in the female population are required. Many hypotheses were postulated to find the target group with an increased risk of osteoporosis, which would profit from an early preventive strategy[4]. Since estrogens are recognized as the most important hormones influencing skeletal development in both sexes[5,6], many studies have been published evaluating the influence of gynecological status with respect to bone density. Although the majority of them failed to find any

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	Women		Men	
	Mean ± SD	Range	Mean ± SD	Range
n	180		130	
Age (years)	40.8 ± 4.4	30 - 53	45 ± 5.2	31 - 60
Height (cm)	167 ± 6.3	152 - 185	180 ± 6.8	156 - 196
Age-at-menarche (years)	12.9 ± 1.4	9 - 18	-	-
Number of deliveries	1.98 ± 0.83	1 - 5	-	-
Total lactation period (months)	15.0	0 - 66	-	-
Oral contraceptive use (years)	8.6 ± 7.3	0 - 27	-	-

Table 1. Characteristics of the study group.

long-term effect of gynecological history on bone density, some studies came to different results[7-13]. To our knowledge, the muscle parameters were not included in the analysis done in the previously published studies.

The aim of our study was to analyze the BMC, MA and BMC/MA ratio, measured using peripheral quantitative computed tomography (pQCT) at the proximal radius with respect to sex, age and body height in pre-senile subjects. In addition, the influence of age-at-menarche, number of pregnancies, duration of lactation and use of oral contraception on the bone and muscle parameters in pre-menopausal women were studied.

Materials and methods

Subjects

We performed a cross-sectional study on 180 pre-menopausal females aged 30-53 years, and 130 males aged 31-60 years. The study population was recruited from the parents of the children who participated in the DONALD (Dortmund Nutritional and Anthropometric Longitudinally Designed) Study described previously[14]. A medical history was obtained from all subjects using a semi-structured questionnaire. Analyzed factors included sex, age, height, use of drugs, and in respect of the women, age-at-menarche, number of deliveries and total lactation period. Body height was determined to the next succeeding 1 mm using a Harpenden stadiometer. Only healthy subjects with no history of osteoporosis and chronic disorders affecting bone metabolism were entered into the study. Women suffering from Crohn's disease (3), colitis ulcerosa (1) and chronic arthritis (1) were excluded. The complete anthropometrical data are summarized in Table 1.

This study was approved by the Ethical Committee of the Medical Faculty University of Cologne and by the "Bundesamt für Strahlenschutz" (Federal Agency for Protection from Radiation, Salzgitter, Germany).

Bone and muscle investigation

Peripheral QCT analysis on the non-dominant forearm was performed using XCT 2000 (Stratec, Germany). The detailed technical data of the device were described earlier[14]. The scanner was positioned at the site of the radius where the distance to the distal radial articular surface corresponded to 65% of forearm length (measured as the distance between the olecranon and the ulnar styloid process). This site of measurement was chosen in order to analyze the forearm at its maximum circumference. A single tomographic slice of 2.0 mm thickness was taken at a voxel size of 0.4x0.4x2 mm. The outer contour of the radius was detected at a threshold of 710 mg/cm^3. Voxels peripheral to the bones' outer edges with an absorptiometric density between 20 and 60 mg/cm^3 were interpreted as representing muscle. Image processing and the calculations of numerical values were performed using the manufacturer's software package. The MA and BMC (the mass of mineral in a 1-mm-thick slice of the bone's cross-section) were determined at the above mentioned site of the radius. A BMC/MA ratio was calculated as an index of functional muscle-bone unit[3].

Statistical analysis

The results from the men and women were analyzed separately. Women were divided into separately analyzed subgroups according to gynecological history. Age - at - menarche (in completed years and one year steps), number of deliveries, total oral contraceptive use (in five year steps) and total duration of lactation period during lifetime (in six month steps) were taken into the statistical analysis as explanatory variables.

Differences between sub-groups were tested using LS-means resulting from a variance analysis. Dependencies between continuous variables were analyzed using linear regression models. In the second step, a multiple linear regression model was built using the significant predictors from the univariate model. P values lower than 0.05 were considered significant. All statistical analyses were performed using the SAS software package (Version 8.02, Cary, NC).

Age (years)	n	Women			n	Men	
		BMC (mg/mm)	MA (cm^2)			BMC (mg/mm)	MA (cm^2)
30.0-34.9	17	100 ± 15	32 ± 4		-	-	-
35.0-39.9	67	98 ± 10	32 ± 4		15	124 ± 17	45 ± 5
40.0-44.9	66	100 ± 14	32 ± 5		49	128 ± 20	46 ± 6
45.0-49.9	24	99 ± 13	33 ± 4		42	128 ± 17	46 ± 6
50.0-54.9	6	102 ± 16	31 ± 4		16	125 ± 26	45 ± 5

Table 2. Variation by age in bone mineral content (BMC) and muscle cross-sectional area (MA) at the proximal radius. Values are mean ±SD. The variation with age is not significant in both genders.

Table 3a

Height (cm)	n	BMC (mg/mm)	MA (cm^2)	BMC/MA
165.0-169.9	6	114 ± 10	43 ± 4	2.7 ± 0.4
170.0-174.9	18	123 ± 21	45 ± 6	2.7 ± 0.4
175.0-179.9	38	128 ± 18	47 ± 6	2.8 ± 0.4
180.0-184.9	34	127 ± 16	46 ± 6	2.8 ± 0.4
185.0-189.9	22	132 ± 18	47 ± 6	2.8 ± 0.3
190.0-194.9	10	128 ± 28	47 ± 5	2.7 ± 0.3

Table 3b

Height (cm)	n	BMC (mg/mm)	MA (cm^2)	BMC/MA
155.0-159.9	24	92 ± 7	30 ± 3	3.1 ± 0.3
160.0-164.9	41	95 ± 10	32 ± 4	3.0 ± 0.3
165.0-169.9	58	97 ± 12	32 ± 5	3.1 ± 0.5
170.0-174.9	35	108 ± 11	33 ± 4	3.3 ± 0.4
175.0-179.9	16	106 ± 16	33 ± 4	3.2 ± 0.5
180.0-184.9	5	107 ± 19	37 ± 4	2.9 ± 0.6

Table 3a, b. Variation by height in bone mineral content (BMC), muscle cross-sectional area (MA) at the proximal radius, and BMC/MA in males (a) and females (b). Values are mean ± SD. Whereas both BMC and MA are strongly dependent on the body height, BMC/MA ratio remains constant with height in both genders.

Results

Age-, sex- and height-related changes in MA and BMC (Table 2, 3, Figure 1)

The mean and SD of MA and BMC were calculated for 5-year age bands and 5-cm height bands. Due to the small numbers of subject in the border categories, the analysis was limited to the age range 30-55 for females and 35-55 for males, and to the height range 155-185 cm for females and 165-195 cm for males. The cross-sectional areas of muscle and bone were not dependent on age. However, we observed a significant increase in these parameters with increasing body height in both males and females ($p<0.0001$ for all). The BMC/MA ratio was dependent neither on the age nor on the body height in both genders.

Both BMC and MA were significantly higher in males than in females. After adjusting for age and height, LS mean of MA was 45.2±0.72 cm^2 in males, and 33.3±0.52 cm^2 ($p<0.0001$) in females, LS mean of BMC was 123±2.2 mg/mm in males and 105±1.6 mg/mm ($p<0.0001$) in females. In addition, we found a significantly higher BMC/MA ratio in females than in males (LS means 3.16±0.04 vs. 2.74±0.06, $p<0.0001$).

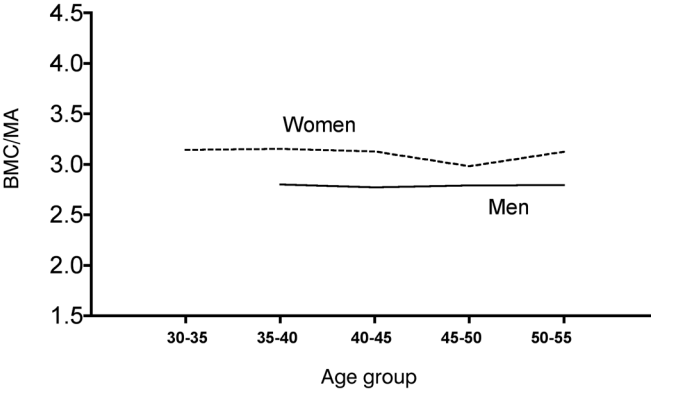

Figure 1. Age variation within the bone mineral content (BMC)/ muscle cross-sectional area (MA) index at the proximal radius in men and woman. The variation between sex categories is statistically significant ($p<0.0001$).

Gynecological history and muscle/bone analysis

The results illustrating the impact of age - at - menarche, number of deliveries, duration of lactation period and use of oral contraceptive on the MA, BMC and BMC/MA ratio are

		n	BMC (mg/mm)	MA (cm^2)	BMC/MA
Age-at-menarche (years)	<10	8	102 ± 16	34 ± 5	3.03 ± 0.31
	10-11	17	99 ± 13	33 ± 6	3.04 ± 0.51
	11-12	37	101 ± 16	32 ± 4	3.15 ± 0.49
	12-13	63	99 ± 11	32 ± 5	3.11 ± 0.45
	13-14	29	99 ± 13	31 ± 4	3.2 ± 0.3
	>14	23	95 ± 12	31 ± 4	3.07 ± 0.38
Number of deliveries (n)	1	53	101 ± 14	32 ± 5	3.19 ± 0.35
	2	89	98 ± 13	32 ± 4	3.06 ± 0.40
	>2	38	100 ± 12	32 ± 5	3.17 ± 0.56
Lactation period (months)	0-6	58	101 ± 13	33 ± 5	3.11 ± 0.45
	7-12	37	99 ± 12	32 ± 4	3.14 ± 0.42
	13-18	35	98 ± 13	32 ± 4	3.12 ± 0.44
	19-24	20	99 ± 9	33 ± 4	2.98 ± 0.37
	>24	30	99 ± 15	31 ± 5	3.20 ± 0.42
Oral contraceptive use (years)	0	47	100 ± 13	32 ± 5	3.17 ± 0.43
	1-5	21	101 ± 17	32 ± 5	3.16 ± 0.36
	6-10	49	100 ± 10	32 ± 4	3.12 ± 0.35
	>10	63	98 ± 13	32 ± 5	3.07 ± 0.50

Table 4. Association between age-at-menarche, number of deliveries, lactation period and oral contraceptive use with bone mineral content (BMC) and with muscle cross-sectional area (MA) at the proximal radius. Values are in mean ± SD. For all parameters, the variation among all analyzed variables is not significant.

shown in Table 4. No effect from all of the analyzed variables of gynecological status on the bone/muscle characteristics was found.

Multiple regression model

To adjust for the influence of MA on the relation between height and BMC, a multiple linear regression model was built: the BMC was the dependent variable, while the height and MA were the predictors. The model explained 22% of the overall BMC variability, having a P value of less than 0,0001. Both height (beta = 0,36 mg/mm per cm height), and MA (beta = 1,45 mg/mm per cm^2) were significantly associated with BMC.

Discussion

We performed a cross-sectional study investigating the influence of sex, height and gynecological history on bone and muscle parameters in pre-senile adults.

Several studies have reported that bone mineral content and muscle cross-sectional area are highly correlated[3,15,16]. This finding is in accordance with the mechanostat hypothesis which assumes that muscle strength is one of the major regulation factors of bone metabolism in humans[1]. We used MA as a surrogate of muscle strength. It is, however, important to note that the analysis of muscle strength is more complex and this method does not reflect the functional status of the entire muscle system, including muscle length, contraction velocity, structure and co-ordination.

As presented earlier[3], bone and lean mass increase similarly in both sexes until pubertal stage 2. In later puberty, the BMC/MA ratio (as a main index of the functional muscle-bone unit) is stable in boys, but increases significantly in girls, probably as a result of estrogen-modulated endocortical apposition. The present study performed on pre-senile subjects shows that this sex difference remains stable during adulthood until menopause/andropause. These results are in accordance with a previous study using DEXA[15]. Expressed in other terms, women produce from early puberty until menopause more bone tissue than is functionally necessary. The rationale for this could be that this physiologically "redundant" pool of bone may be used as a reserve for pregnancy and lactation periods when increased bone resorption is apparently present. This explanation is in accordance with numerous experimental studies (reviewed by Jarvinen et al.[6]).

In our study, we present a significant positive correlation between body height and both BMC and MA in both genders. In view of this, an interpretation of these parameters in clinical practice has to be performed with great caution, and preferably with adjustment for body height. Traditionally, height-related standards are limited to the growing period. Our results taken from pre-senile subjects clearly illustrate that these differences remain clinically relevant even in adulthood. Therefore, the BMC/MA ratio, which is independent both of body height and of age, seems to be a very

useful parameter especially when analyzing subjects of different heights. Whether this ratio can be used as an indicator of bone health, or as a predictor of osteoporotic fractures, has to be proven by subsequent longitudinal studies.

Estrogens have for a long time been known as hormones that substantially influence the bone metabolism in mammalians. Therefore, it has been hypothesized that the course of puberty, the number of pregnancies and the duration of lactation (as periods with large changes in estrogen levels) can influence skeletal properties in the elderly. The age-at-menarche is an objective parameter reflecting the duration of estrogen action in females. Since the physiological level of estrogens has a positive effect on bone formation, greater BMC should be expected in women with earlier age-at-menarche. Indeed, in our previous study investigating age-at-menarche and bone cortex geometry, we found a longer endosteal cortical perimeter in women with late age-at-menarche[17]. However, this effect was small and the other analyzed bone parameters were not influenced by the age-at-menarche. Grainge et al.[18], reported that earlier age-at-menarche is weakly associated with higher BMD at the AP spine and greater trochanter. However, they found no link between age-at-menarche and the whole body BMC. The lack of any association between age-at-menarche and BMC at the proximal radius observed in the present study supports a theory that earlier or later age-at-menarche do not play an important role in achieving normal peak bone mass. Nevertheless, only a small number of women with a truly late menarche (>15 years) were included in the analysis, which could limit the power of our results.

Dramatic changes in bone metabolism have been described during pregnancy and lactation. There are reports of up to a 4% decrease in lumbar BMD immediately after delivery, and an additional 4-6% during lactation and/or postpartum amenorrhea[10,11,19,20]. Although these changes can have clinical correlations in increasing fracture rates during the delivery/lactation period, most studies described a complete recovery within several months after the end of lactation, even in multiparous women with an extended lactation period[9,19,21]. On the other hand, the positive effect of lactation and multiple pregnancies on lumbar BMD was also found in a limited number of studies[12,13]. The results of our study performed using peripheral QCT are in agreement with the studies that found no effect of the duration of delivery/lactation period on the functional muscle-bone-unit. Indeed, even the BMC/MA ratio remains constant irrespective of the gynecological history. Therefore, based on our results, it is rather improbable to characterize women as being at risk of osteoporosis using gynecological history.

Conclusions

Taken together, there is a strong gender difference in the bone mineral content/muscle mass ratio arising in early puberty which remains constant until menopause/andropause. Gynecological history has no detectable effect on the bone/muscle parameters at the proximal radius in premenopausal women. This study supports the importance of the functional approach in the bone health assessment. In our opinion, bone mineral content per muscle cross-sectional area as an index of the functional muscle-bone unit should be involved in the bone analysis especially when comparing subjects of different body height.

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References:

1. Frost HM. Bone "mass" and the "mechanostat". A proposal. Anat Rec 1987; 219:1-9.
2. Hasegawa Y, Schneider P, Reiners C. Age, sex and grip strength determine architectural bone parameters assessed by peripheral quantitative computed tomography (pQCT) at the human radius. J Biomech 2001; 34:497-503.
3. Schoenau E, Neu CM, Beck B, Manz F, Rauch F. Bone mineral content per muscle cross-sectional area as an index of the functional muscle-bone unit. J Bone Miner Res 2002; 17:1095-1101.
4. Melton LJ III. Who has osteoporosis? A conflict between clinical and public health perspectives. J Bone Miner Res 2000; 15:2309-2314.
5. Riggs BL, Khosla S, Melton LJ III. Sex steroids and the construction and conservation of the adult skeleton. Endocr Rev 2002; 23:279-302.
6. Jarvinen TLN, Kannus P, Siervanen. Estrogen and bone — a reproductive and locomotive perspective. J Bone Miner Res 2003; 18:1921-1931.
7. Reid IR. The skeleton in pregnancy and lactation. Intern Med J 2002; 32:433.
8. Paton LM, Alexander JL, Mowson CA, Margerison C, Frame MG, Kaymakci B, Wark JD. Pregnancy and lactation have no long-term deleterious effect on measures of bone mineral in healthy women: a twin study. Am J Clin Nutr 2003; 77:707-714.
9. Karlsson C, Obrant KJ, Karlsson M. Pregnancy and lactation confer reversible bone loss in humans. Osteoporos Int 2001; 12:828-834.
10. Naylor KE, Iqbal P, Fledelius C, Fraser RB, Eastell R. The effect of pregnancy on bone density and bone turnover. J Bone Miner Res 2000; 15:129-137.
11. More C, Bettembuk P, Bhattoa HP, Balogh A. The effects of pregnancy and lactation on bone mineral density. Osteoporos Int 2001; 12:732-737.
12. Fox KM, Magaziner J, Sherwin R, Scott JC, Plato CC, Nevitt M, Cummings S. Reproductive correlates of bone mass in elderly women. J Bone Miner Res 1993; 8:901-908.

13. Kritz-Silverstein D, Barrett-Connor E, Hollenbach KA. Pregnancy and lactation as determinants of bone mineral density in postmenopausal women. Am J Epidemiol 1992; 136:1052-1059.
14. Neu CM, Manz F, Rauch F, Merkel A, Schoenau E. Bone densities and bone size at the distal radius in healthy children and adolescents: a study using peripheral quantitative computed tomography Bone 2001; 28:277-232.
15. Ferretti JL, Capozza RF, Cointry GR, Garcia SL, Plotkin H, Alvarez-Figueira ML, Zanchetta JR. Gender-related differences in the relationship between densitometric values of whole-body mineral content and lean body mass in humans between 2 and 87 years of age. Bone 1998; 22:683-690.
16. Rittweger J, Beller G, Ehrig J, Jung C, Koch U, Ramolla J, Schmidt F, Newitt D, Majumdar S, Schiessl H, Felsenberg D. Bone-muscle strength indices for the human lower leg. Bone 2000; 27:319-326.
17. Rauch F, Klein K, Allolio B, Schoenau E. Age-at-menarche and cortical bone geometry in premenopausal women. Bone 1999; 25:69-73.
18. Grainge MJ, Coupland CAC, Cliffe SJ, Chilvers CED, Hosking DJ. Reproductive, menstrual and menopausal factors: which are associated with bone mineral density in early postmenopausal women? Osteoporos Int 2001; 12:777-787.
19. Matsushita H, Kurabayashi T, Tomita M, Honda A, Takakuwa K, Tanaka K. The effect of multiple pregnancies on lumbar bone mineral density in Japanese women. Calcif Tissue Int 2002; 71:10-13.
20. Kalkwart HJ, Specker BL. Bone mineral loss during lactation and recovery after weaning. Obstet Gynecol 1995; 86:26-32.
21. Henderson PH III, Sowers M, Kutzko KE, Jannausch ML. Bone mineral density in grand multiparous women with extended lactation. Am J Obstet Gynecol 2000; 182:1371-1377.