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ORIGINAL ARTICLE

Interaction of body fat percentage and height with appendicular functional muscle-bone unit

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Abstract

Summary The interaction of body fat percentage and height with appendicular BMC for LBM was analyzed. Only body fat had significant negative correlation with the appendicular BMC for LBM.

Purpose/introduction For the clinical evaluation of the functional muscle-bone unit, it was proposed to evaluate the adaptation of the bone to the acting forces. A frequently used parameter for this is the total body less head bone mineral content (TBLH-BMC) determined by dual-energy X-ray absorptiometry (DXA) in relation to the total body lean body mass (LBM). Body fat percentage seemed to correlate negatively and height positively with TBLH-BMC for LBM. It was supposed that appendicular BMC for LBM is a more accurate surrogate for the functional muscle-bone unit since appendicular LBM does not incorporate the mass of internal organs. The aim of this study was to analyze the interaction of body fat percentage and height with appendicular BMC for LBM.

Methods As part of the National Health and Nutrition Examination Survey (NHANES) study, between the years 1999 and 2004, whole-body DXA scans on randomly selected Americans from 8 years of age were carried out. From all eligible DXA scans, three major US ethnic groups were evaluated (non-Hispanic Whites, non-Hispanic Blacks, and Mexican Americans) for further statistical analysis.

Results For the statistical analysis, the DXA scans of 8190 non-Hispanic White children and adults (3903 female), of 4931 non-Hispanic Black children and adults (2250 female), and 5421 of Mexican American children and adults (2424 female) were eligible. Only body fat had a significant negative correlation with the appendicular BMC for LBM.

Conclusions Only body fat had significant negative correlation with appendicular BMC for LBM, and thus, should be addressed when evaluating functional muscle-bone unit.

Keywords Appendicular functional muscle-bone unit · Bone mineral content · Body fat percentage · Mechanostat · Children · Adults

Abbreviations

BMC	Bone mineral content
CDC	Centers for Disease Control and Prevention
DXA	Dual-energy X-ray absorptiometry
fMBU	Functional muscle-bone unit
LBM	Lean body mass
LOESS	Locally weighted scatterplot smoothing
NHANES	

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	National Health and Nutrition Examination Survey
TBLH	Total body less head

Introduction

Recent studies reveal a complex interaction of muscle and bone. The task of this functional unit is to ensure the stability and mobility of the human body. Different hormones, such as the IGF-1, sex hormones, or bone morphogenetic proteins, as well as the sympathetic nervous system and some neuropeptides regulate the growth of bones and skeletal muscles and affect their interaction [1–4].

It is known that bones adapt to the force acting on them [5]. A presumed mechanostat in bone tissue registers the forces regulating bone formation to keep habitual strains within a constant window [6]. The forces generated by the skeletal muscles are superior to the ones associated with gravity [7], and thus, the muscle and bone represent a *functional unit* (functional muscle-bone unit, fMBU) [8]. Therefore, the ratio of the bone mineral content (BMC) determined by dual-energy X-ray absorptiometry (DXA, usually by *total body less head* scan (TBLH)) to the lean body mass (LBM, usually by *total body* scan) is a frequently assessed parameter to describe the muscle-bone interaction [9]. BMC presents a surrogate parameter for bone strength. LBM correlates highly (Pearson's $r = 0.82$) with muscle mass and is therefore a surrogate parameter for the muscular forces acting in everyday life [10].

The parameter BMC for LBM depicts the mass balance of bone remodeling resulting from the biomechanical control of the bone stiffness exerted by the bone mechanostat. This value could reflect the mass-related aspect of the mechanical equilibrium achieved by the system as a function of its strain-related setpoint.

Recently, we described a negative correlation of body fat percentage with TBLH-BMC for LBM [11]. Children and adults with a Z-score for body fat percentage of two standard deviations showed on average decrease of the Z-score for TBLH-BMC for BMC by one standard deviation. Also, it can be shown a lesser positive correlation of height with TBLH-BMC for LBM.

But we should keep in mind that total LBM is a fat-free and bone mineral-free component including muscle but also other component such as the mass of internal organs, skin, and tendons. For example, the total body muscle mass makes only approximately 53% of the total LBM [12]. Therefore, some authors recommend to assess appendicular LBM rather than the total LBM as surrogate for the muscle mass [13, 14].

Indeed, the first description of the parameter BMC for LBM for evaluating the functional muscle-bone unit was based on measurements using peripheral quantitative computed tomography of the forearm [15]. Until now, there are only a few studies analyzing the functional muscle-bone unit of appendicular sites [16, 17].

The aim of the study was to analyze the effect of body fat percentage and height on: $\frac{\text{appendicular BMC}}{\text{appendicular LBM}}$.

Methods

Study population

Within the framework of the National Health and Nutrition Examination Survey (NHANES) study, whole-body DXA scans were performed on randomly selected civilian and non-institutionalized Americans from 8 years of age in the years 1999–2004 [18]. Study participants were selected through an already described complex, multistage, probability study design [19].

DXA scans were not carried out on females whose pregnancy test was positive at exam time or who declared pregnancy. Further, participants over the weight and height limit of the Hologic DXA system (weight > 136 kg or height > 196.6 cm) were also excluded from the study.

From all eligible DXA scans, three major US ethnic groups were assessed (Non-Hispanic Whites, Non-Hispanic Blacks, and Mexican Americans). We also excluded the DXA data of individuals older than 85 years, since the exact age was not recorded in this patient group. Missing height or weight measurements were also exclusion criteria for our study.

We divided the study population into pediatric (up to 19 years of life) and adult (20 to 85 years of life). The participants' age was documented in months.

Terminology

In the following, the term appendicular functional muscle-bone unit ($fMBU_{app}$) describes the relation of appendicular (both arms and legs, including the pectoral and pelvic girdle) BMC to appendicular LBM. The parameter assessing this relationship is defined as:

$$\frac{\text{appendicular BMC}}{\text{appendicular LBM}}\,(\text{app.BMC for LBM}).$$

According to the latest recommendations of the International Society of Clinical Densitometry to evaluate the (total) functional muscle-bone unit ($fMBU_{tot}$), typically, the following parameter is used:

$$\frac{\text{total body less head BMC}}{\text{total LBM}}\,(\text{TBLH}-\text{BMC for LBM}) \quad [20].$$

DXA measurement and data acquisition

Whole-body DXA scans were performed using Hologic QDR-4500A fan-beam densitometer (Hologic, Inc., MA, USA) in combination with the Hologic software v826:a3. The DXA scans were analyzed using the software Hologic Discovery v12.1 in the years 1999–2004.

Based on the results of an analysis of QDR-4500A DXA data from seven research laboratories [21], the NHANES DXA LBM was decreased by 5% and fat mass was increased by 5% so total mass did not change.

The DXA dataset was downloaded directly from the CDC servers (https://wwwn.cdc.gov/Nchs/Nhanes/Dxa/Dxa.aspx) on the 21.08.2017.

For the $fMBU_{tot}$, we calculated and published age-specific reference percentiles of $\frac{\text{total body less head BMC}}{\text{total LBM}}$ for children and adults for the three mentioned ethnicities using the NHANES data set [11]. We used these data for calculating the Z-scores for TBLH-BMC for LBM. For calculating Z-scores for height for age, the growth charts of the CDC were applied [22].

Generation of age- and gender-specific reference centiles of appendicular BMC for LBM

We used the LMS (lambda-mu-sigma) method to generate reference centile curves for appendicular BMC for LBM [23], to further analyze the effect of body fat percentage and height on $fMBU_{app}$, age, gender, and ethnicity specific. We calculated Z_{LMS}-scores using a modified Box-Cox transformation (a corresponding to age):

$$Z_{\mathrm{LMS}} = \frac{1}{S(a) \times L(a)} \times \left[\left(\frac{g}{M(a)} \right)^{L(a)} - 1 \right] \text{ for } S(\mathrm{a}), L(\mathrm{a}) \text{ and } M(\mathrm{a}) \neq 0 \quad (1)$$

$$Z_{\mathrm{LMS}} = \frac{\ln\left(\frac{g}{M(a)} \right)}{S(a)} \text{ for } L(\mathrm{a}) = 0 \text{ and } S(\mathrm{a}), M(\mathrm{a}) \neq 0 \quad (2)$$

The median value (M(a)), the coefficient of variation (S(a)), and the centile skewness (L(a)) were adjusted to the data with the maximum likelihood estimate, applying cubic spline interpolation. Therefore, the functions M(a), S(a), and L(a) are age-related and can jointly determine the Z-score of a given data pair of age (a) and TBLH-BMC/LBM. We used the Q-Test by Royston and Wright and Worm Plot by van Buuren and Fredriks to assess for goodness of fit [24, 25].

Analysis of the effects of body fat percentage and height on $fMBU_{app}$

We calculated locally weighted scatterplot smoothing (LOESS) regressions between Z-score for appendicular BMC for LBM and Z-score for body fat percentage and height, respectively, and analyzed the effects of body fat percentage and height on appendicular BMC for LBM. We decided to use LOESS regression because of the non-linear regression of body fat and appendicular BMC for LBM. For the sake of clarity, only the data of non-Hispanic White NHANES population (1999–2004) were presented in the main text. The date of non-Hispanic Black and Mexican American NHANES populations (1999–2004) was also analyzed. The effects of body fat percentage and height in these populations were comparable to the results of the non-Hispanic White population and were presented in the Supplement (eFigure 2–5).

Comparison of the $fMBU_{app}$ and $fMBU_{tot}$

Bland-Altman diagram was used to illustrate the agreement of the two methods evaluating the functional muscle-bone unit.

Statistical analysis

The NHANES investigators used a multiple-imputation methodology to replace missing values and published five random and independent sets of data without missing values, to account for bias arising from missing DXA values. We averaged the computed datasets in one final dataset, since no methodology is known to create an average of a series of independent references centiles or LOESS regressions.

The analysis was performed with IBM SPSS Statistics for Windows version 25 (IBM Corp, NY, USA) and RStudio version 1.1.463 in conjunction with R version 3.5.1 (R Foundation for Statistical Computing, Vienna, Austria) and the statistical packages *GAMLSS* (version 5.1.2) [26]. Unless otherwise stated, results are presented as mean (± standard deviation (SD)) or count (relative frequency).

Study population

In Table 1, the description of the study populations of the three analyzed ethnicities were given. In children and adolescents, there were more males than females; in adults the gender ratio was balanced.

For the sake of clarity, in the following, the results of non-Hispanic White population is presented. The tabulated reference centiles for all ethnicities were given in the online-only supplement (eTable 1–6).

Table 1 Study population by age and gender for NHANES populations (1999–2004)

	Non-Hispanic White NHANES population			
	Age			
	< 20 years		≥ 20 years	
	Female	Male	Female	Male
Number	873	1153	3030	3134
Age, years	14.7 (3.30)	14.5 (3.30)	52.7 (18.7)	52.4 (18.46)
Height, cm	157.6 (11.54)	164.1 (17.10)	163.4 (6.60)	176.6 (7.38)
BMI, kg/m^2	22.3 (5.41)	22.0 (5.30)	27.8 (6.71)	28.0 (5.32)
	Non-Hispanic Black NHANES population			
	Age			
	< 20 years		≥ 20 years	
	Female	Male	Female	Male
Number	972	1461	1278	1220
Age, years	14.4 (3.4)	14.5 (3.2)	47.7 (16.7)	47.2 (16.8)
Height, cm	156.9 (11.5)	164.1 (16.2)	162.8 (6.6)	176.5 (7.2)
BMI, kg/m^2	24.0 (7.0)	22.4 (6.2)	31.3 (7.8)	27.9 (6.3)
Data are presented as mean (± SD) and count				
	Mexican American NHANES population			
	Age			
	< 20 years		≥ 20 years	
	Female	Male	Female	Male
Number	1010	1537	1414	1460
Age, years	14.9 (3.3)	14.6 (3.3)	48.3 (17.3)	47.3 (17.6)
Height, cm	154.1 (10.9)	161.1 (15.1)	156.5 (6.4)	169.3 (6.8)
BMI, kg/m^2	23.1 (5.9)	23.1 (5.8)	29.3 (6.3)	28.0 (4.8)
Data are presented as mean (± SD) and count				

Results

The effect of age and gender on the $fMBU_{app}$

In both genders, app. BMC for LBM increased approximately to 20 years (Fig. 1). In younger children (age < 12 years), app. BMC for LBM was similar in both genders. Approximately by the age of 12 years, app. BMC for LBM was higher in females (Fig. 2). In male individuals, app. BMC for LBM app. BMC for LBM remained stable until the age of 85 years. In females, app. BMC for LBM decreased by age of approximately 40 years and became lesser than in males by the age of approximately 65 years. The evolution of app. BMC for LBM was similar to the evolution of the TBLH-BMC for LBM (Fig. 1). But the absolute values for app. BMC for LBM were higher than for TBLH-BMC for LBM ($p < 0.001$).

The effect of body fat percentage on $fMBU_{app}$

The LOESS regression detected a significant ($p < 0.001$) correlation of the body fat percentage for age and the app. BMC for LBM Z-scores among children and adolescents (< 20 years), regardless of gender. Children and adolescents with higher body fat percentage had lesser app. BMC for LBM Z-scores than their peers with lesser body fat percentage (Fig. 3, $p < 0.001$). A similar effect was also seen in adults (age ≥ 20 years, $p < 0.001$). The coefficients of determination are presented in Fig. 3.

The effect of body height on $fMBU_{app}$

The LOESS regression detected a significant ($p < 0.001$) correlation of the height for age and the app. BMC for LBM Z-

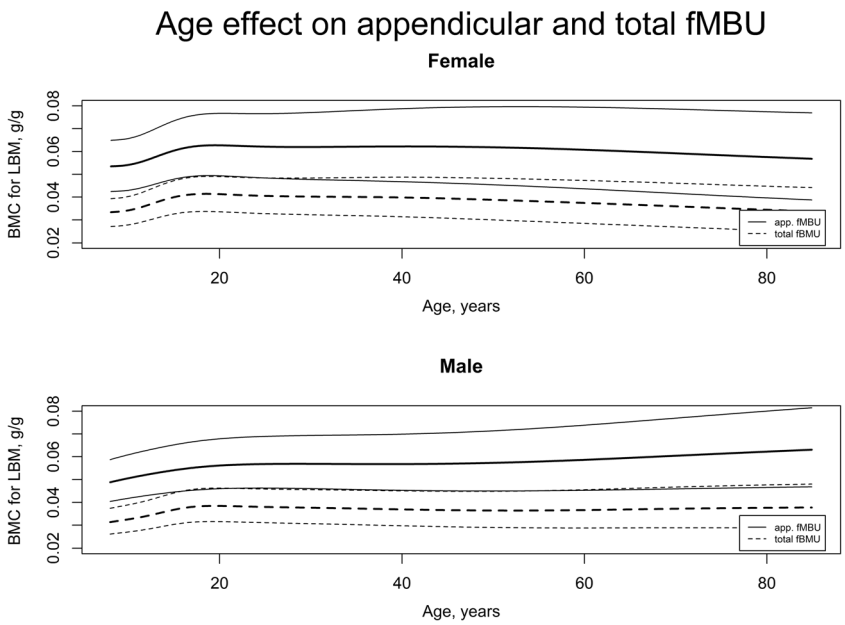

Fig. 1 Age effects on appendicular and total functional muscle-bone unit. Lines indicate 3rd, 50th, and 97th centiles of the age-related distribution of app. BMC for LBM and TBLH-BMC for LBM. Data from the "non-Hispanic White" NHANES population (1999–2004) are shown. The DXA scans of 8190 non-Hispanic White children and adults (3903 female) were eligible

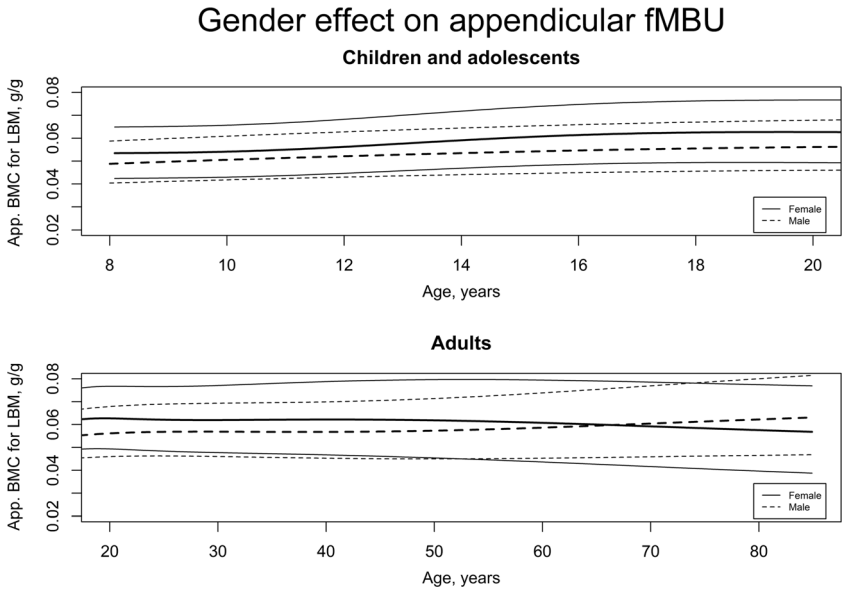

Fig. 2 Gender effects on appendicular functional muscle-bone unit. Lines indicate 3rd, 50th, and 97th centiles of the age-related distribution of app. BMC for LBM. Data from the "non-Hispanic White" NHANES population (1999–2004) are shown. The DXA scans of 8190 non-Hispanic White children and adults (3903 female) were eligible

scores among children and adolescents (< 20 years), regardless of gender. Tall children and adolescents had higher app. BMC for LBM Z-scores than their smaller peers (Fig. 4, $p < 0.001$).

In adults (age ≥ 20 years), body height had also a significant ($p < 0.001$) correlation with the app. BMC for LBM Z-scores: Taller adults tended to have higher app. BMC for LBM Z-scores (Fig. 4, $p < 0.001$). The coefficients of determination are presented in Fig. 3.

Agreement of Z-scores for $fMBU_{app}$ and $fMBU_{tot}$

The Pearson's correlations coefficient r between TBLH-BMC for LBM Z-score and app. BMC for LBM Z-score was 0.919 for females and 0.914 for males. The lower and upper limits of the Bland-Altman diagram for female non-Hispanic were − 0.79 and 0.79 (Fig. 5). The lower and upper limits of the Bland-Altman diagram for male non-Hispanic were − 0.81 and 0.81.

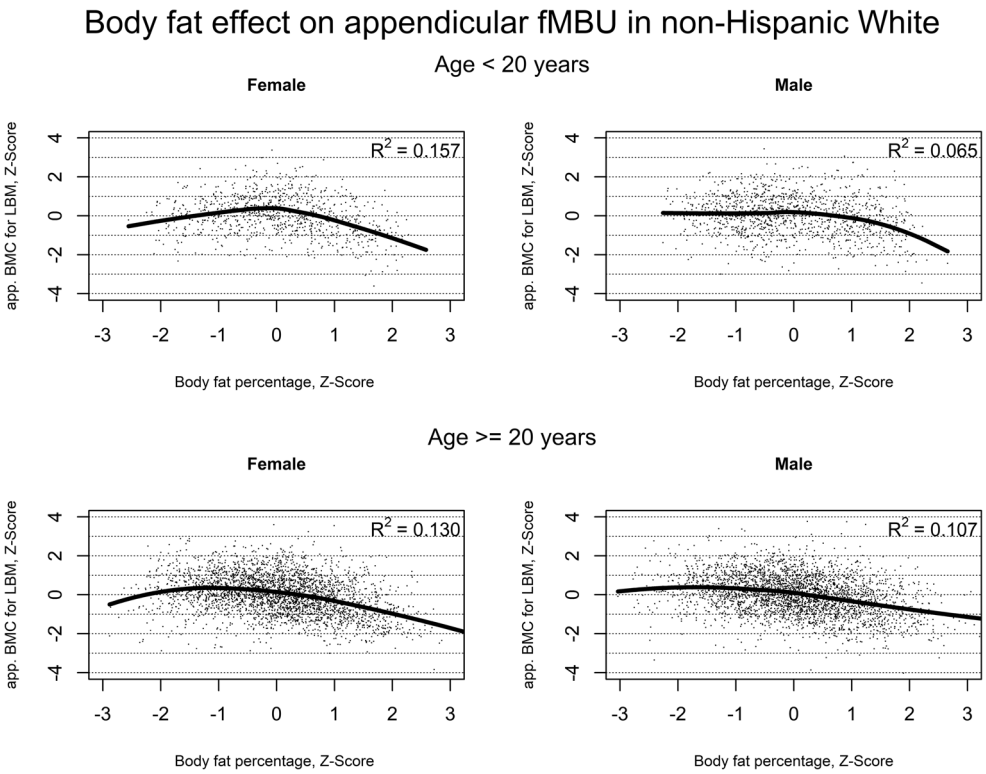

Fig. 3 Body fat effect on appendicular functional muscle-bone unit. Each dot indicates a single proband. The LOESS regression curve is depicted. Data from the non-Hispanic White NHANES population (1999–2004) are shown. LOESS locally weighted scatterplot smoothing

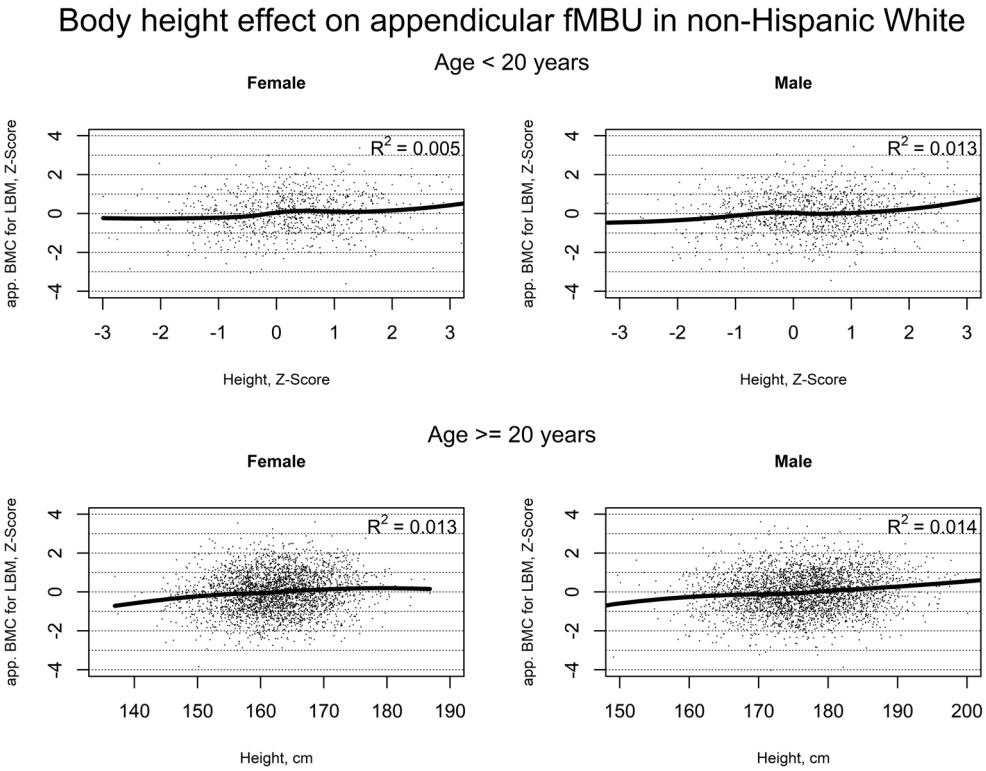

Fig. 4 Body height effect on appendicular functional muscle-bone unit. Each dot indicates a single proband. The LOESS regression curve is depicted. Data from the non-Hispanic White NHANES population (1999–2004) are shown. LOESS locally weighted scatterplot smoothing

Discussion

The results of this study confirm the relevant, negative correlation of body fat percentage with the functional muscle-bone unit assessed by app. BMC for LBM.

The analysis of the NHANES DXA data collected from 1999 to 2004 showed that the evolution of app. BMC for LBM was very similar to the evolution of the already described evolution of the TBLH-BMC for LBM [11]. This evolution includes the following characteristics:

- Prepubertal boys and girls (age < 12 years) had similar app. BMC for LBM (Fig. 1).
- In both genders, app. BMC for LBM increased during puberty and was higher within the reproductive period than before puberty.
- Premenopausal female adults (20 years ≤ age ≤ 50 years) had higher app. BMC for LBM than male adults at the same age.
- Postmenopausal women (age > 50 years) had lower values of app. BMC for LBM than premenopausal women.

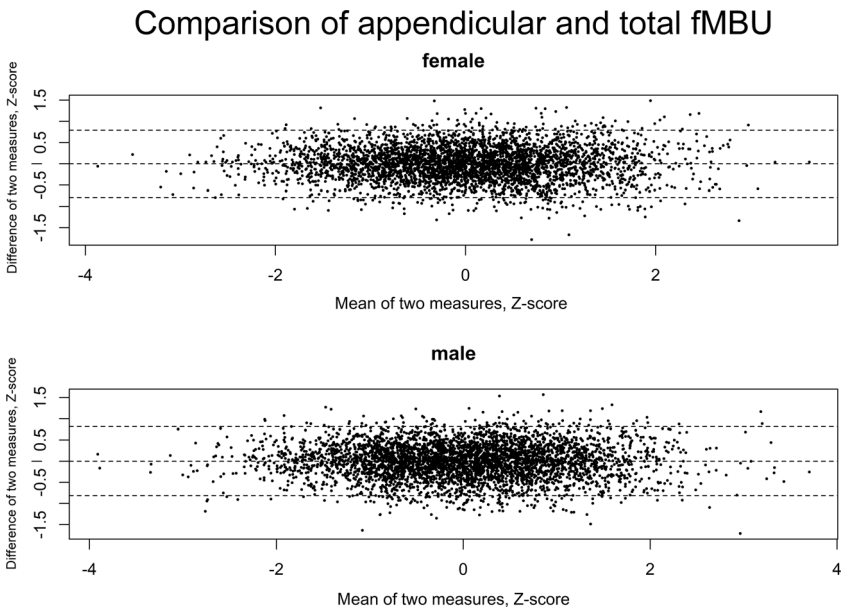

Fig. 5 Comparison of appendicular and total functional muscle-bone unit. The Bland-Altman diagram of the Z-scores for app. BMC for LBM and TBLH-BMC for LBM are depicted. The difference of two measures was calculated as Z-scores for TBLH-BMC for LBM–app. BMC for LBM. The upper and lower limits of the Bland-Altman diagram were set to 1.96-fold of the standard deviation of the differences. Data from the "non-Hispanic White" NHANES population (1999–2004) are shown

- Men showed no relevant age effect on the app. BMC for LBM relationship after puberty.
- Postmenopausal women (age > 65 years) had lower values of app. BMC for LBM than men at the same age.

Similar results according the evolution of TBLH-BMC for LBM was reported by different authors [27–29]. The evolution of the app. BMC for LBM was not studied until yet. Our findings support again the thesis that estrogens influence the setpoint of the mechanostat towards more BMC for LBM by inhibition of bone remodeling [30]. In the last years, several molecular mechanisms were discovered on how estrogens influenced strain-induced bone modeling and remodeling [31].

As expected, the reference centiles for app. BMC for LBM were shifted to higher values than the reference centiles for TBLH-BMC for LBM (Fig. 1). The reason for this is that total body LBM incorporates, next to the axial LBM, more non-muscular lean mass than the appendicular LBM [12]. In addition, our results showed that body fat percentage and height had a significant effect on app. BMC for LBM as on TBLH-BMC for LBM [11]. These effects will be described in detail in the following.

The effect of body fat percentage on app. BMC for LBM

Regardless of gender, body fat percentage correlated negatively with app. BMC for LBM (Fig. 3). For example, children and adults with a Z-score for body fat percentage (for age) above approximately two standard deviations (SD) showed one standard deviation lower Z-scores for app. BMC for LBM. Lower body fat percentage seemed to have no relevant effect on app. BMC for LBM. The same effect of body fat on TBLH-BMC for LBM was already reported by us [11]. The coefficients of determination lie between 6.5 and 15.7% (Fig. 3), indicating that this portion of the variance of app. BMC for LBM was related to the variance of body fat percentage.

Recently, a prospective study of 64 premenopausal women reported the same [32]. The authors concluded that high body fat percentage alters the functional muscle-bone unit. Adiposity may influence bone remodeling by secretion of cytokines or leptins that influence bone, by production of adipokines that alter the central nervous system thereby changing sympathetic impulses to bone, and by paracrine effects [33, 34].

Appendicular LBM was in our study the major determinant of appendicular BMC. These results are in concordance with other studies [35, 36]. Appendicular LBM explained 75.6% of the variance of appendicular BMC in male and 56.7% of the variance of app. BMC in female. These results were higher than the reported values for TBLH-BMC and total LBM (50–55%) [37]. Again, the reason for this might be that total LBM incorporates more non-muscular lean mass than the appendicular LBM. The reasons why appendicular LBM was higher correlated to appendicular BMC in male than in females are unclear, but this difference was also reported by others [38, 39].

The fact that women, who are on average smaller and have a larger body fat percentage than males (Table 1), nevertheless have a higher app. BMC for LBM than men could reflect the ability of estrogens to increase the setpoint of the mechanostat.

The effect of height on app. BMC for LBM

Regardless of gender, the height was positively correlated to app. BMC for LBM (Fig. 4). This means that larger individuals tended to have higher app. BMC for LBM than smaller ones. This confirms the findings of Ferretti et al. [27]. A possible interpretation might be that larger individuals with the same muscle mass exert a greater force on the bone due to the longer lever arms. Since, according to the mechanostat model, the bone adapts to the greatest forces [40], this would explain the higher app. BMC for LBM values in larger individuals. Another possible explanation could be the thicker cortical bone in taller individuals [41]. But overall, the effect of body height on the app. BMC for LBM was relatively small and only got significant because of the large study population. In accordance with this, the coefficients of determination were very low (1.3–2.1%) (Fig. 4). Especially in height for age Z-scores around ± 2.0, there were almost no effect on app. BMC for LBM.

The effect of ethnicity of app. BMC for LBM

The evolution of app. BMC for LBM were very comparable in the three analyzed ethnicities (non-Hispanic White, the non-Hispanic Black, and Mexican American population, eFigure 1). In previous studies, it was reported that in male non-Hispanic Black population, TBLH-BMC for LBM was higher than in non-Hispanic White and Mexican American male [11, 42]. The reason why this difference could not be verified in app. BMC for LBM is not clear.

Nevertheless, we provided in the supplement the gender- and ethnicity-specific reference centiles for app. BMC for LBM, applicable for Hologic QDR-4500A (Hologic Inc., USA, software version Discovery 12.1).

Clinical application of the results

The negative correlation of body fat percentage with the functional muscle-bone unit could be confirmed also in the fMBUapp. This interaction of bone and adipose tissue has consequences for the diagnosis and treatment of bone diseases.

For the differential diagnosis of bone diseases, it was proposed that clearly decreased BMC for LBM would be characteristic for a primary bone disease, such as osteogenesis imperfecta. On the other hand, normal or only slightly decreased BMC for LBM would be indicative for a neurological cause of altered parameters of the functional muscle-bone unit (secondary bone defect) [15, 28, 43, 44]. This differentiation is clinically meaningful, since it might influence therapeutic decisions, such as rather recommending regular loading exercise in secondary bone defect than bisphosphonates. When assessing appendicular BMC for LBM, the effect of body fat should be addressed.

Despite the very similar characteristics of app. BMC for LBM and TBLH-BMC for LBM, there were also some relevant differences when evaluating individuals. The Bland-Altman diagrams in Fig. 5 illustrate the agreement of the two methods (appendicular vs. TBLH). On an individual basis, the Z-score for app. BMC for LBM and the Z-score for TBLH-BMC for LBM could differ approximately ± 0.8 (1.96-fold standard deviation of the observed differences). Since in clinical diagnostics the parameter TBLH-BMC for LBM is used to distinguish between a primary and a secondary bone defect [43], this difference might be clinically relevant. We derive in this study age-, gender-, and ethnicity-specific reference centiles for appendicular BMC for LBM.

Already now, it was shown that TBLH-BMC for LBM was the single DXA parameter with the best diagnostic odds ratio in predicting fractures of the long bones in a sample of children at risk for osteoporosis [9]. Whether app. BMC for LBM has better diagnostic performance than TBLH-BMC for LBM in predicting fracture have to be evaluated in further studies.

In addition, knowledge of the described interaction of bone and adipose tissue might open up the possibilities of a therapeutic approach to promote bone health by reducing body fat. Further studies are needed to investigate how this interaction is mediated and whether reducing the body fat percentage really improves bone health.

In conclusion, the results indicate a negative correlation of body fat percentage with appendicular BMC for LBM. This interaction should also be addressed while evaluating the functional muscle-bone unit, especially in children with obesity.

Limitations

Since body composition measurements are technology and calibration dependent, the presented results are only applicable for measurements with the Hologic QDR-4500A (Hologic Inc., USA, software version Discovery 12.1) [45] calibrated according to Schoeller [21].

The clinical relevance of a measurement parameter, e.g., app. BMC for LBM, should be based on clinical endpoints, such as a correlation to increased fracture tendency. Further studies are needed to evaluate the clinical relevance of app. BMC for LBM. Unfortunately, data on fractures of the included participants in our study were not available.

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Compliance with ethical standards

Conflicts of interest None.

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