·临床研究·

体脂量是绝经后女性股骨近端骨强度的决定因素

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Fat mass is a positive predictor of the proximal femur strength in healthy postmenopausal women

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Abstract: **Objective** To clarify the determinative role of lean mass (LM) and fat mass (FM) on geometric indices of the hip bone strength in healthy postmenopausal women. **Methods** A cross-sectional study was performed. One hundred and one healthy postmenopausal women, ageing from 48.8 to 82.6 years old, were involved. Bone mineral density (BMD) of the femoral neck (FN_BMD), the total hip (TH_BMD), and the proximal femur was detected using dual energy X-ray absorptiometry. Total FM and total LM were derived from the whole body scan. Multivariate linear regression models were used to assess the relationship. **Results** In univariate analysis, there was a significant negative correlation between advanced age, years since menopause and FN_BMD, TH_BMD, and the hip geometric parameters (CT, CSA, SM, and SI) ($P < 0.05$ for all). Height, body weight, FM and LM had a positive relationship with bone data. In multiple liner regression analysis, both LM and FM were significant predictors of the hip BMD and hip structural geometric properties after controlling of age, height, years since menopause. However, when both LM and FM were included in the multivariate regression model after controlling for confounders above, the relationships between LM and bone data disappeared. Only FM was an independent predictor for bone mass and hip strength ($P < 0.001$ for all). Variation explained by FM for FN_BMD, TH_BMD, and hip strength parameters (CT, CSA, SM, and SI) was 19.9%, 16.1%, 31.3%, 30.3%, 34.0%, and 24.4%, respectively. **Conclusion** These data suggest that FM, rather than LM, is independently associated with measures of the proximal femur strength in healthy postmenopausal women.

Key words: Bone mineral density; Hip bone strength; Lean mass; Fat mass

Lower body weight or body mass index (BMI) has been known to be higher risk of developing osteoporosis and low-energy fractures via mechanical loading and other factors in both men and women[1]. Recently, there have been new insights into the relationships between body composition and bone health. However, most of the previous studies regarding the relative effect of body composition on bone mass yielded inconsistent and often conflicting results, which remains an area of active investigation. Some studies have suggested that fat mass (FM) but not lean mass (LM), had the closest positive association with bone mineral density (BMD)[2-4]. However, others have shown a detrimental influence of FM on bone mass after adjusting for confounders[5]. Still other studies have found that both FM and LM were equally important contributors to an increase in bone mass, and lower fracture risk[6]. additionally, when considering total FM, subcutaneous fat was beneficial to bone structure

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and strength, while visceral fat was deleterious[7].

BMD alone can only account for about 50 - 70% of total bone strength[8-9]. Bone strength is related not only to bone mass but also to bone structural geometry. DXA allows the measurement of geometric contributions to bone strength in the proximal femur. Hip strength analysis (HSA) indices are expected to be valid indicators of bone strength along with BMD, and some HSA indices have been reported to predict hip fracture risk independently of BMD[10-11]. The fat-bone connection is complicated and the effect of adipose tissue on hip bone strength is far from clear. Thus, the present study was designed to investigate the relevance of body composition to geometric indices of hip bone strength in a group of healthy postmenopausal women.

1 Materials and Methods

1.1 Study Subjects

The study was a cross-sectional, retrospective study, in which we recruited 120 healthy postmenopausal women from Yueyang Hospital, Shanghai University of Traditional Chinese Medicine between January 1st 2011 and June 30th 2012 to perform BMD measurement. 19 subjects were excluded from the study because they did not meet the criteria of enrollment. Therefore, we finally analyzed data of 101 healthy postmenopausal women (aged 48.8-82.6 years). None of the subjects currently/past use any medication and nutritional supplements known to influence bone metabolism (such as diuretics, glucocorticoids, anticonvulsants, immunosuppressive medications, nonsteroidal anti-inflammatory drugs, asthma medications with corticosteroids), and lacking of diagnosed or self-reported malignancy, cardiovascular, pulmonary, metabolic, renal, hepatic, or orthopedic medical conditions. Written informed consent for each study was obtained independently, and the study was approved by the appropriate institutional research ethics committee.

1.2 Data collection

Standardized interviews and self-reported questionnaires were used to obtain the following information: age (years), smoking status (current, ex-smoker, or never smoking), Years since menopause (YSM) for postmenopausal women. Regular menstruation was defined as the 25 - 35-day interval between menstrual on-set. Menopause was designated if there was a complete natural cessation of menses for more than 12 months[12]. Hysterectomy patients were excluded from the study.

Body weight was measured to the nearest 0.1 kg on a portable electronic beam scale, wearing light clothing and no shoes. Height was measured to the nearest 0.5 cm using a stadiometer. Body Weight and height were each measured twice per time point, and the average of the two measures was used.

1.3 DXA measurements of BMD, BMC and body composition

Bone mineral content and bone mineral density were determined for each individual with Dual-energy X-ray absorptiometry (DXA; Software Version enCORE 13.40.038; Lunar Prodigy, GE Healthcare, USA) at the left proximal femur (including femoral neck and total hip) and whole body. FM and LM were derived from the whole body scan.

1.4 Hip structure analysis

The HSA software derives geometry of the load supporting surface by employing a projection principle first described by Martin and Burr[13]. This is a computational algorithm applied to 2- dimensional projected images of the hip generated from DXA scans, following conventional bone mineral analysis. The program uses the distribution of mineral mass in a line of pixels across the bone axis. The femoral neck at its narrowest region were analyzed and used in this study. the HSA program computed the following variables used in this analysis as described previously[8,10-11]: ① Cross-sectional moment of inertia (CSMI, mm^4); ② Cross-sectional area (CSA, mm^2); ③ Section modulus (SM, mm^3); ④ Mean cortical thickness (CT, mm); ⑤ Femoral strength index (SI, unitless).

Coefficient of variability (CV) of DXA measurements at the femoral neck, total hip, and whole body was < 1% for BMC and BMD, < 1.3% for fat and lean mass, < 2.8% for structural parameters evaluated by duplicate measurements in ten women from the study cohort as described previously[8].

1.5 Statistical analysis

All data analysis was performed using the Statistical Package for the Social Sciences Windows, version 17.0 (SPSS, Chicago, IL, USA). Descriptive statistics consisted of the mean ± SD. Correlation analyses between anthropometrics, body composition and bone mass, geometric indices of hip bone strength were performed with Pearson's correlation analysis. Stepwise linear regression analyses was performed to evaluate the strength of the relationship between body composition (including LM and FM, treated as independent factors) and hip BMD and hip structural parameters (treated as outcome variable) to explore what are the important variables influencing the outcome. A predictor was entered into the model at $P < 0.05$ and was removed at $P > 0.10$. $P < 0.05$ was considered statistically significant.

2 Results

2.1 Anthropometry, body composition, and bone measurements of the subjects

101 healthy postmenopausal women were recruited who fulfilled the study criteria. The demographic, clinical characteristics of anthropometry, body composition (including FM, percent FM, LM) and bone mass (FN_BMD, TH_BMD) and the average values for hip geometric parameters (CT, CSA, SM, and SI) are displayed in Table 1.

2.2 Associations between anthropometry, body composition, and bone mass, proximal femur strength

In univariate analysis, both FN_BMD and TH_BMD showed significantly positive correlations with CT, CSA, SM, and SI ($P < 0.001$ for all), and the relationship between CSA and hip BMD was strongest ($r = 0.737 - 0.765$, $P < 0.001$). FM was positively correlated with LM ($r = 0.623$, $P < 0.001$). As shown in Table 2, there was a significantly negative correlation between advancing age, years since menopause and FN_BMD, TH_BMD, and hip structural geometric properties (CT, CSA, SM, and SI) ($P < 0.05$ for all). Height, Weight, FM and LM had a positive relationship with FN_BMD, TH_BMD, and hip geometric parameters ($P < 0.05$ for all). Among the body composition parameters, FM showed higher correlation with bone data than that of LM except for CSA and SM.

表 1 研究对象基本特征

Table 1 General characteristics of the subjects

参数 Parameters	均数 ±标准差 Mean ± S. D.	范围 Range
年龄(岁) Age (years)	61.3 ±7.1	48.8 ~82.6
YSM (years) 绝经年数(年)	11.3 ±7.9	0.2 ~33.8
Height (cm) 身高 (cm)	157.7 ±6.7	138.0 ~175.0
Body weight (kg) 体重 (kg)	59.2 ±10.6	33.9 ~97.8
Lean mass (kg) 瘦组织量 (kg)	37.28 ±5.50	25.78 ~57.51
Fat mass (kg) 体脂量 (kg)	19.94 ±5.98	5.12 ~37.32
Fat mass (%) 体脂百分比 (%g)	33.1 ±5.7	14.4 ~46.0
FN_BMD (g/cm^2) 股骨颈骨密度 (g/cm^2)	0.645 ±0.120	0.359 ~1.054
TH_BMD (g/cm^2) 全髋骨密度 (g/cm^2)	0.829 ±0.134	0.469 ~1.172
CT (mm) 股骨颈皮质厚度 (mm)	3.9 ±1.5	2.0 ~7.9
CSA (mm^2) 横截面惯性距 (mm^2)	111.2 ±19.5	61.7 ~176.6
SM (mm^3) 截面模数 (mm^3)	438.5 ±110.6	168.3 ~932.2
SI (unitless) 强度指数	1.29 ±0.31	0.72 ~2.33

2.3 Multivariate analysis

When hip BMD and geometric indices of hip bone strength were entered as a dependent variable respectively, and age, height, years since menopause and LM as independent variables in a forward stepwise regression model (model 1), LM was significant predictor of bone mass of the hip BMD and hip geometric strength. LM explained 15.7% to 15.8% (Adjusted $R^2 = 0.157 - 0.158$, $P < 0.01$), explained 20.6% to 33.5% (Adjusted $R^2 = 0.206 - 0.335$, $P < 0.05$ for all) of the variability of hip BMD and hip geometric parameters, respectively. However, when both LM and FM were included in the multivariate

表 2 人体测量指标、体成分与髋骨强度参数相关性分析

Table 2 Correlational analysis between anthropometrics, body composition and geometric indices of the hip bone strength

项目 Item	股骨颈 骨密度（g/cm²） FN_BM （g/cm²）	全髋骨 密度（g/cm²） TH_BMD （g/cm²）	股骨颈 皮质厚度（mm） CT（mm）	横截面 惯性距（mm²） CSA（mm²）	截面模数 （mm³） SM（mm³）	强度指数 SI（unitless）
年龄（岁） Age（years）	-0.197[a]	-0.310[b]	-0.231[a]	-0.265[b]	-0.151	-0.349[c]
绝经年数（年） YSM（years）	-0.204[a]	-0.298[b]	-0.311[b]	-0.285[b]	-0.189[a]	-0.306[c]
身高（cm） Height（cm）	0.289[b]	0.243[a]	0.378[c]	0.502[c]	0.554[c]	0.306[b]
体重（kg） Weight（kg）	0.441[c]	0.315[b]	0.482[c]	0.491[c]	0.517[c]	0.370[c]
瘦组织量（kg） Lean mass（kg）	0.351[c]	0.261[b]	0.382[c]	0.460[c]	0.502[c]	0.297[b]
体脂量（kg） Fat mass（kg）	0.409[c]	0.270[b]	0.469[c]	0.393[c]	0.408[c]	0.353[b]

注：[a] $P<0.05$，[b] $P<0.01$，[c] $P<0.001$ 表示相关系数统计学差异的显著性

表 3 骨密度及髋骨强度指数逐步多元回归分析结果

Table 3 Results of multiple linear regression analysis of bone mass and the hip bone strength indices

	股骨颈骨密度（g/cm²） FN_BMD（g/cm²）			全髋骨密度（g/cm²） TH_BMD（g/cm²）			股骨颈皮质厚度（mm） CT（mm）		
	标准化回归系数 Sβ	P 值 P-value	调整决定系数 Adjusted R^2	标准化回归系数 Sβ	P 值 P-value	调整决定系数 Adjusted R^2	标准化回归系数 Sβ	P 值 P-value	调整决定系数 Adjusted R^2
模型 1 瘦组织量（kg） Model 1 LM（kg）	0.365	<0.001	0.158	0.278	0.003	0.157	0.404	<0.001	0.244
模型 2 瘦组织量（kg） 体脂量（kg） Model 2 FM（kg）	0.416	<0.001	0.199	0.285	0.002	0.161	0.480	<0.001	0.313
LM（kg）	0.173	0.132		0.164	0.162		0.171	0.108	

	横截面惯性距（mm²） CSA（mm²）			截面模数（mm³） SM（mm³）			股骨近端强度指数 SI（unitless）		
	标准化回归系数 Sβ	P 值 P-value	调整决定系数 Adjusted R^2	标准化回归系数 Sβ	P 值 P-value	调整决定系数 Adjusted R^2	标准化回归系数 Sβ	P 值 P-value	调整决定系数 Adjusted R^2
模型 1 瘦组织量（kg） Model 1 LM（kg）	0.346	0.003	0.312	0.259	0.014	0.335	0.316	0.001	0.206
模型 2 瘦组织量（kg） 体脂量（kg） Model 2 FM（kg）	0.272	0.004	0.309	0.234	0.009	0.340	0.370	<0.001	0.244
LM（kg）	0.233	0.078		0.156	0.203		0.140	0.210	

注：模型 1 包括的协变量为年龄、绝经年数、身高；模型 1 包括的协变量为年龄、绝经年数、身高、体脂量

Note: Covariates included in the regression model were age, height, and years since menopause (model 1), additional controlling for FM (model 2) regression model (additional adjustment for LM) (model 2), the relationships between LM and bone data were not retained, only FM was an independent predictor for bone mass and hip strength. Variation explained by FM for FN_BMD, TH_BMD, and hip strength parameters (CT, CSA, SM, and SI) was, respectively, 19.9%, 16.1%, 31.3%, 30.3%, 34.0% and 24.4% (Table 3). Increasing age was associated with decreases in FN_BMD [standardised β (Sβ) −0.218, $P = 0.017$], TH_BMD (Sβ −0.324, $P = 0.001$), SI (Sβ −0.367, $P < 0.001$). Years since menopause was related to decreased CT (Sβ −0.327, $P < 0.001$), CSA (Sβ −0.181, $P = 0.047$).

3 Discussion

In this study, we evaluated the relationships between body composition and hip geometric strength assessed by HSA. As expected, we found hip BMD was strongly related to CT, CSA, SM and SI. This study indicated thinning of the cortical shell and deterioration of the resistance to bending and SI with aging in femoral neck. These results are in conformity with those reported by Reider et al.[14-15]. Estrogen deficiency, which represents the most common cause of osteoporosis, is a high turnover state in which both bone formation and resorption are accelerated, but the relative activity of the osteoclast is greater than that of the osteoblast. Rapid bone turnover and resorption of bone in the endosteal surface are accelerated during the postmenopausal period, no doubt the femoral neck cross-sections exhibit cortical thinning with aging[16], which leads to bone mass loss and structural deterioration of bone.

Several studies have investigated the connection between body weight and longitudinal changes in HSA indices. Although Dongmei et al.[10] reported that maintaining weight may help retain hip geometric strength and reduce the risk of hip fracture, they did not measure body composition to determine which body component exerted a stronger effect on HSA indices. Body mass is composed of three compartments: FM, LM and bone mass, of which the first two represent 95% of body weight. Changes in body composition may occur with aging: in the elderly water content and LM decrease, while amount of FM increases. The relative role of LM and FM on bone mass remains a contentious issue. Low BMD of the proximal femur is a valuable predictor for hip fracture risk, however, age-related loss of bone mass in the hip does not necessarily imply reduced mechanical strength[17]. Bone strength is determined by bone mass and quality. Strength of bone is governed by structural dimensions and tissue materials properties, neither of which is directly measured by a conventional BMD measurement. The degree and distribution of primary abnormality in one will often lead to changes in others. BMD alone does not always reliably predict osteoporosis and osteoporotic fracture. The preventive or adverse effect of LM and FM on bone may be associated with bone geometry. Thus, it was considered worth evaluating the change patterns in body composition and hip structural geometric properties.

The main finding from our study data is that FM but not LM was the strongest determinant of hip bone strength. The findings challenge the view that it was an importantly detrimental role for FM in negatively influencing bone mass and density[5,18] or LM was the most significant variable affecting bone strength[19]. The possible causes of drawing different conclusions may be that, firstly, LM, FM, and body weight are highly collinear variables, and linear models including all three would be nonsensical and its inclusion might lead to misinterpretations to the results. Newly published studies by Kim et al.[5,20] demonstrated that FM is negatively associated with bone mineral content in postmenopausal women after controlling for age and body weight. Yoo et al.[21] found percentage fat mass had a negatively decisive factor on BMD after adjusting for risk factors including age and body weight only in premenopausal women but not in men or postmenopausal women. These findings[5,20-21] are in contrast to the results observed in our study. Actually, it is not appropriate to treat body weight as independent variable in their study, and therefore produced misleading results. The association of body composition and bone mass is age-dependent and sex-dependent[20-22]. Sahin et al.[17] have evaluated body composition, BMD and circulating leptin levels and found LM is a better predictor of BMD. Nevertheless, they did not make an adjustment for confounders (age, YSM and height, ect.). Lu et al.[23] examined ethnic difference in the association of body fat and trunk fat with BMD among Chinese, white, and black subjects and found that, with greater body and trunk fat, both white and black subjects were more likely to have a lower BMD than Chinese subjects. Therefore, differences in different research ethnicity, population structure, gender with different genetic backgrounds, lifestyles and living environments should be taken into account.

The BMI is the currently accepted measure for classifying weight-related risk. Zillikens et al.[24] investigated the role of fat distribution in BMD and found that positive associations between android fat distribution and BMD are explained by higher BMI and not by higher insulin levels and/or lower adiponectin levels. Negative associations after adjustment for BMI suggest that android fat deposition and android-to-gynoid fat ratio is not beneficial and possibly even deleterious for bone.

LM explained 15.7% to 15.8%, 20.6% to 33.5% of the variability of hip BMD and hip geometric parameters, respectively. There is evidence of a complex interaction between LM and bone strength. Several explanations have been proposed for this relationship. LM is predominantly muscle and that femur geometry scales in proportion to lean mass is consistent with the mechanostat theory hypothesizes that the increasing muscle forces that occur during growth influence the size and strength of the bone, and that the largest forces on the skeleton are primarily from dynamic (muscle mass), rather than static (fat mass) loads[25].

Higher mechanical loading has been shown to stimulates osteocytes, dendritic resident cells, which transduce the signal into anabolic responses[5]. Although the weight-bearing may partly explain the effect of FM on bone strength, FM approximately accounts for only 16 - 25% of total body weight in normal-weight men and women and the remaining is LM[26]. There is substantial evidence that both bone remodeling and the distribution of adipose tissue are regulated through the hypothalamus and sympathetic nervous system. Therefore, weight-associated gravitational forces may be insufficient to explain the impact of FM on bone. Several mechanisms may be helpful to explain the association between the non-weight-bearing effect of FM and bone strength. Firstly, in postmenopausal women, adipocytes are important sources of estrogen production, and estrogen is known to inhibit bone resorption by inducing osteoclasts apoptosis[27]. Furthermore, overweight / obesity has been associated with insulin resistance, which may contribute to androgen and estrogen overproduction and reduce sex-hormone binding proteins. As a result, the elevated sex hormone levels leads to increased bone mass due to reduced osteoclast activity and, possibly, increased osteoblast activity. Secondly, adipose tissue can release adipocytokines (such an leptin, adiponectin and Visfatin), which appear to influence bone mass through alternative mechanisms such as adipocyte-dependent hormonal factors[28-29]. Leptin inhibits osteoclastogenesis, increases proliferation and differentiation of osteoblasts and promotes bone formation directly or indirect[29].

Nevertheless, limitations of this study must be acknowledged. Firstly, The study design was cross-sectional in nature, and it is not possible to establish any cause-and-effect inference on the relationship between body composition and geometric indices of hip bone strength. Secondly, there are inherent limitations in trying to describe 3-dimensional measures of hip geometry based on 2-dimensional data in an image plane generated by DXA. Lastly, It is indispensable to emphasize that results from our studies cannot be assumed to apply to the general population because we evaluated only the healthy postmenopausal Chinese women.

In summary, Our data has demonstrated that FM is the most significant determinant of hip BMD and geometric indices of hip bone strength at the proximal femur, and LM does not have an decisive impact on bone strength when FM was taken into account in healthy postmenopausal Chinese women. It must be pointed out that the associations of body weight and bone mass, hip geometric parameters are based on FM rather than LM, and the influence of FM on bone strength is likely as a result of the non-weight-bearing effects.

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体脂量是绝经后女性股骨近端骨强度的决定因素

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