Relationship of Muscle and Adipose Tissue with Bone Mineral Density in Pre- and Post-menopausal Women Undergoing Health Check-ups: Postprint

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Abstract

Background: The relationship between muscle and adipose tissue and bone mineral density (BMD) in menopausal women has been studied, but due to differences in regional distribution, the effects of muscle and fat on BMD remain unclear. Objective: To analyze the relationship between lumbar spine, femoral neck, and total hip BMD with fat and muscle tissue in pre- and post-menopausal women, and to identify predictors of BMD, providing a theoretical basis for improving the quality of life in middle-aged and elderly individuals and for the prevention and treatment of osteoporosis. Methods: A retrospective analysis was conducted on 2355 women aged 40-60 years who underwent physical examinations at the Health Management Center of the Affiliated Hospital of Guizhou Medical University from January 2018 to October 2021. BMD and body composition (fat and muscle tissue) were measured using dual-energy X-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA). Pearson correlation and linear regression analyses were used to determine the relationship between fat and muscle tissue and BMD. ROC curve analysis was performed to validate the predictive value of appendicular lean mass (ALM) for osteoporosis. Results: Both pre- and post-menopausal fat mass, visceral fat area (VFA), and skeletal muscle mass of the whole body, trunk, and limbs were positively correlated with BMD at all sites. Pre-menopausal VFA was not correlated with lumbar spine BMD. Multiple linear regression analysis controlling for covariates showed that VFA was negatively correlated with BMD at all sites both pre- and post-menopause (β=-0.003, -0.002, -0.001 and β=-0.002, -0.002, -0.001, $P<0.05$); ALM remained positively correlated with BMD at all sites post-menopause (β=0.017, 0.013, 0.012, $P<0.05$), but was not correlated with BMD pre-menopause. ROC curve analysis showed that at the

BMI$ 18.5 $threshold, the area under the curve (AUC) for ALM in predicting post-menopausal and whole-population OP of the total hip, lumbar spine, and femoral neck was > 0.6, with the best predictive site being the total hip for ALM > 16.24 kg (AUC = 0.825 > 0.760 > 0.641 and AUC = 0.834 > 0.780 > 0.664, P < 0.05). Conclusion : ALM is positively correlated with lumbar spine, femoral neck, and total hip BMD in post-menopausal women and the entire population; the positive correlation between ALM > 16.24 kg and bone density is observed in populations with BMI $18.5, representing an independent protective factor against osteoporosis.

Full Text

Relationship Between Muscle and Adipose Tissue and Bone Mineral Density in Perimenopausal Women Undergoing Health Examinations

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Abstract

Background: The relationship between muscle and adipose tissue and bone mineral density (BMD) in menopausal women has been investigated, but site-specific distribution differences have left the impact of muscle and fat on BMD unclear. **Objective:** To analyze the relationship between BMD at the lumbar spine, femoral neck, and total hip and fat/muscle tissue in pre- and post-menopausal women, and to identify predictors of BMD, thereby providing a theoretical basis for improving quality of life and preventing osteoporosis in middle-aged and elderly individuals. **Methods:** A retrospective analysis was conducted on 2,355 women aged 40-60 years who underwent health examinations at the Health Management Center of the Affiliated Hospital of Guizhou Medical University from January 2018 to October 2021. BMD and body composition were measured using dual-energy X-ray absorptiometry (DXA) and bioelectrical impedance analysis (BIA). Pearson correlation and linear regression analyses determined the associations between adipose/muscle tissue and BMD. ROC curve analysis validated the predictive value of appendicular lean mass (ALM) for osteoporosis. **Results:** Fat mass, visceral fat area (VFA), and total body, trunk, and appendicular muscle mass were positively correlated with BMD at all sites both before and after menopause. Premenopausal VFA was not associated with lumbar spine BMD. Multiple linear regression controlling for covariates revealed that VFA was negatively correlated with BMD at vari-

ous sites before and after menopause (β = -0.003, -0.002, -0.001 and β = -0.002, -0.002, -0.001, respectively; $P < 0.05$). ALM remained positively correlated with postmenopausal BMD (β = 0.017, 0.013, 0.012; $P < 0.05$) but not with premenopausal BMD. ROC curve analysis showed that at BMI $\geq$ 18.5, the area under the curve (AUC) for ALM predicting OP at the total hip, lumbar spine, and femoral neck exceeded 0.6 in postmenopausal and total populations, with the optimal predictive site for ALM > 16.24 kg being the total hip (AUC = 0.825 > 0.760 > 0.641 and AUC = 0.834 > 0.780 > 0.664, respectively; $P < 0.05$). **Conclusion:** ALM is positively correlated with lumbar spine, femoral neck, and total hip BMD in postmenopausal and total populations. ALM > 16.24 kg demonstrates a positive correlation with BMD in individuals with BMI $\geq$ 18.5 and serves as an independent protective factor against osteoporosis.

Keywords: menopause; bone mineral density; adipose tissue; muscle tissue; physical examination

Introduction

Although modern living conditions and medical care have gradually improved, the proportion of elderly individuals continues to increase, making the prevalence of osteoporosis (OP) and related complications more widespread. Statistics indicate that bone diseases account for approximately 7.5% of the disease burden in individuals over 60 years old, imposing a substantial burden on families and society [1]. Aging typically leads to decreased bone mass and muscle mass while increasing adipose tissue. Body weight, BMI, fat mass, and muscle mass are all important determinants of OP or fragility fractures. However, due to differences in body composition, BMI is not an accurate indicator of body fat, as it cannot reflect body shape, fat, and muscle mass components, though it can indicate excess weight [2].

Fat and muscle mass are independent influencing factors of body weight and important components, together accounting for 95% of total body weight. Muscle, fat, and bone interact in complex ways. Therefore, studying OP from the perspective of muscle, fat, and bone is both urgent and important, requiring a better understanding of how age-related changes in fat and muscle mass are interrelated and affect OP. Previous studies have shown that muscle and adipose tissue influence BMD differently at various sites, lacking simultaneous analysis of the relationship between muscle/fat mass and BMD. Therefore, this study measured BMD at various sites using DXA, the gold standard for diagnosing OP, and employed bioelectrical impedance analysis (BIA), which offers relatively high availability, low cost, and portability, to measure fat and muscle mass. This study aims to explore the relationship between BMD at the lumbar spine, femoral neck, and total hip and fat/muscle mass in pre- and postmenopausal women, and to identify predictors of BMD, providing a theoretical basis for improving quality of life and preventing osteoporosis in middle-aged and elderly individuals.

Methods

1.1 Study Subjects

A retrospective study design was employed, randomly selecting 2,355 women undergoing health examinations at the Health Management Center of the Affiliated Hospital of Guizhou Medical University from January 2018 to October 2021 as study subjects. Inclusion criteria: women aged 40-60 years undergoing health examinations; no myopathy, malignant tumors, or infectious diseases; no bone metabolic diseases or long-term use of bone metabolism medications. Exclusion criteria: individuals with metal implants; history of bilateral oophorectomy; use of fat-reducing or hormone therapy drugs within the past six months; abnormal liver/kidney function, diabetes, etc. This study was approved by the Medical Ethics Committee of the Affiliated Hospital of Guizhou Medical University (approval number: 2021150k), and all participants provided informed consent.

1.2 Measurements

1.2.1 Fat and Muscle Content Height, body weight, and waist circumference were measured by licensed nurses, and body mass index (BMI) was calculated using the formula BMI = weight/height^2. A Korean InBody IOI305 bioelectrical impedance analyzer (BIA) [3,4] was used to measure fat mass, visceral fat area (VFA), appendicular lean mass (ALM), and trunk and total body muscle mass.

1.2.2 Bone Mineral Density Measurement BMD values were measured using dual-energy X-ray absorptiometry (DXA) with a GE Healthcare LUNAR Prodigy system. Prior to examination, professional medical staff entered participant information into the system, and daily calibration was performed before measurements to ensure the instrument's coefficient of variation remained within a reasonable range.

1.2.3 Diagnostic Criteria and Grouping Premenopausal women with Z-score <-2.5 SD were diagnosed with osteoporosis; postmenopausal women were categorized as osteoporosis (T-score $\leq$ -2.5), osteopenia (-2.5 $<$ T-score $\leq$ -1), or normal bone mass (T-score $>$ -1) [5]. BMI was classified according to the Chinese Working Group on Obesity [6]: 18.5 $\leq$ BMI $<$ 23.9 kg/m^2 as normal, 24.0 $\leq$ BMI $<$ 27.9 kg/m^2 as overweight, and $\geq$ 28 kg/m^2 as obese.

1.4 Statistical Methods

Statistical analysis was performed using SPSS 26.0 software, with GraphPad Prism 8.0.2 used for figure generation. Normally distributed continuous variables were expressed as mean $\pm$ standard deviation ($\bar{x} \pm s$) and analyzed using independent samples t-test. Pearson correlation analysis examined the relationship between fat/muscle tissue variables and BMD at various sites. Multiple

linear regression analysis assessed the relationship between fat/muscle tissue variables and BMD at different sites. The area under the receiver operating characteristic (ROC) curve evaluated the predictive ability of appendicular skeletal muscle mass for OP and determined cutoff values. Statistical significance was set at $\alpha = 0.05$ for two-tailed tests.

Results

The study included 2,355 participants, with 1,261 premenopausal and 1,094 postmenopausal women. The mean age was 45.98 $\pm$ 3.66 years for premenopausal women and 54.12 $\pm$ 3.25 years for postmenopausal women. Comparisons of BMI, fat mass, VFA, and appendicular, trunk, and total body muscle mass with BMD at various sites between pre- and postmenopausal women showed statistically significant differences ($P < 0.05$). Details are provided in Table 1 .

2.2 Correlation Between Fat and Muscle Tissue and Bone Mineral Density at Various Sites

Except for visceral fat area (VFA), which showed no correlation with lumbar spine BMD in premenopausal and total population women ($P > 0.05$), BMI, fat mass, VFA, and total body, appendicular, and trunk muscle mass were all positively correlated with BMD at various sites ($P < 0.05$). Details are presented in Table 2 .

2.3 Multiple Linear Regression Analysis of Fat and Muscle Tissue Components and Bone Mineral Density

Model 1: Using lumbar spine, femoral neck, and total hip BMD as dependent variables and age and BMI as independent variables, the analysis showed that age and BMI were influencing factors for BMD at all sites in both pre- and postmenopausal women ($P < 0.05$).

Model 2: Using BMD at the three sites as dependent variables and age, BMI, fat mass, and visceral fat area as independent variables, the analysis revealed that fat mass and visceral fat area were influencing factors for BMD at all sites in both pre- and postmenopausal women ($P < 0.05$).

Model 3: Using BMD at the three sites as dependent variables and age, BMI, total body muscle mass, appendicular muscle mass, and trunk muscle mass as independent variables, the results showed that in the total population, total body muscle mass was an influencing factor for femoral neck BMD; appendicular skeletal muscle mass was an influencing factor for lumbar spine, femoral neck, and total hip BMD; and trunk muscle mass was an influencing factor for femoral neck BMD. In premenopausal women, total body muscle mass influenced lumbar spine and femoral neck BMD, while appendicular skeletal muscle mass influenced total hip BMD. In postmenopausal women, total body muscle mass influenced femoral neck and total hip BMD; appendicular skeletal mus-

cle mass influenced lumbar spine, femoral neck, and total hip BMD; and trunk muscle mass influenced femoral neck and total hip BMD ($P < 0.05$).

Model 4: Using BMD at the three sites as dependent variables and age, BMI, fat mass, visceral fat area, and total body, appendicular, and trunk muscle mass as independent variables, the analysis demonstrated that in the total population, total body and trunk muscle mass were influencing factors for femoral neck BMD, while ALM was an influencing factor for lumbar spine, femoral neck, and total hip BMD. In premenopausal women, muscle mass at all sites was not associated with BMD. In postmenopausal women, total body muscle mass influenced femoral neck and total hip BMD; ALM influenced lumbar spine, femoral neck, and total hip BMD; and trunk muscle mass influenced femoral neck BMD ($P < 0.05$). Details are provided in Table 3 .

2.4 Relationship Between Appendicular Skeletal Muscle Mass and Bone Mineral Density Across Different BMI Thresholds

Correlation analysis showed that at BMI $\geq$ 18.5, the relationship between appendicular skeletal muscle mass and BMD at all three sites remained positively correlated ($P < 0.05$). Details are presented in Table 4 .

2.5 Predictive Value of Appendicular Skeletal Muscle Mass for Osteoporosis

At the BMI $\geq$ 18.5 threshold, the area under the curve (AUC) for ALM in predicting OP at all sites exceeded 0.6 in both postmenopausal and total populations, with the highest predictive value observed for the total hip site (AUC $= 0.825 > 0.760 > 0.641$ and AUC $= 0.834 > 0.780 > 0.664$, respectively; $P < 0.05$).

Figure 1 [Figure 1: see original paper]. ROC curve analysis of ALM predicting OP at three skeletal sites across study populations using BMI as the cutoff point.

Discussion

The decline in muscle mass and BMD in menopausal women indicates that skeletal muscle and bone are highly sensitive to hormonal changes during the menopausal transition. Our results showed that premenopausal women had lower adipose tissue but higher muscle mass and BMD compared to postmenopausal women, consistent with the findings of Sipilä S [7]. Postmenopausal women exhibited higher fat mass and visceral fat area but lower trunk, appendicular, and total body muscle mass than premenopausal women, aligning with the results of Ye Zhenzhen [8]. However, Ye Zhenzhen concluded that ALM was a protective factor for BMD in pre- and postmenopausal women and the total population, which differs from our finding that ALM was not a protective factor for BMD in premenopausal women. This discrepancy may be

attributed to differences in body composition analyzers and BMD measurement sites (calcaneus in their study versus the WHO-recommended osteoporosis diagnostic sites of lumbar spine, femoral neck, and total hip in our study).

Muscle tissue promotes bone growth and development and increases bone mass through mechanical effects (gravity from muscle weight and stress from muscle contraction) and through chemical regulation via paracrine mechanisms acting on mesenchymal, osteogenic, osteoclastic, and bone cells, thereby regulating bone metabolism and promoting bone formation and/or inhibiting bone resorption. Our study demonstrated that appendicular skeletal muscle mass (ALM) was positively correlated with BMD at all sites, consistent with the findings of Siddique N [9], Fan Jie [10], and Li Y [11], but inconsistent with Kapuš O [12]. After controlling for confounders, ALM remained positively correlated with lumbar spine, femoral neck, and total hip BMD in postmenopausal and total populations, serving as an independent protective factor for BMD, whereas fat mass showed no correlation with BMD at any site. Numerous studies have identified muscle mass as a primary determinant of bone mass, though conclusions vary regarding specific sites of action. Some research indicates that muscle mass in postmenopausal women is positively correlated with BMD at all sites, while other studies suggest muscle tissue only affects BMD at specific locations. Yuan Jiayao [13] and Yin Tongtong [14] reported that ALM was positively correlated with BMD after controlling for confounders. Soare I [15] found muscle mass was positively correlated with lumbar spine BMD. Li Yan [16] observed that only trunk muscle mass was significantly correlated with BMD, while Sheng [17] found muscle mass was more determinant for total hip BMD.

Our study demonstrated that muscle tissue indeed has different effects on BMD at various sites. After controlling for confounders such as adipose tissue and age, only ALM remained positively correlated with lumbar spine BMD; total body muscle mass and ALM remained positively correlated with total hip BMD; and appendicular, trunk, and total body muscle mass all remained positively correlated with femoral neck BMD, while the correlation between fat mass and BMD disappeared. These findings corroborate the conclusions of Xiang [18], though Xiang did not analyze muscle mass at different sites. The differences may be attributed to variations in participant age, body composition and BMD measurement tools, and incomplete site coverage. The positive mechanical effects of muscle mass on BMD are well-established, and the decline in BMD in postmenopausal women is often associated with decreased muscle mass. Therefore, appropriate exercise to maintain muscle mass and BMD at certain levels may delay OP progression and reduce fracture risk.

Increased body weight adds load to bone tissue, stimulates bone formation, reduces bone resorption, and partially offsets age-related bone loss. Adipose tissue itself can also serve as an endocrine marker of bone-enhancing growth factors, facilitating BMD increase and reducing OP occurrence. Our study showed that BMI was positively correlated with BMD at all sites, consistent with Gandham, A [19], but partially differing from Zhang Y [20], who reported BMI was posi-

tively correlated with femoral neck BMD but not with lumbar spine BMD. Body weight/BMI cannot fully explain the protective effect of fat mass on bone. Postmenopausal women experience ovarian endocrine dysfunction and decline, with decreased estrogen levels leading to bone resorption exceeding bone formation and imbalanced bone turnover—key pathogenic mechanisms of postmenopausal OP. Adipose tissue can convert androstenedione into metabolically active estrogen, representing a major source of estrogen secretion and explaining the protective effect of adipose tissue on bone. Abdominal fat can also inhibit osteoclast activation and induce osteoclast apoptosis through secretion of inflammatory factors, thereby reducing bone resorption. The effect of adipose tissue is related to its distribution, necessitating in-depth research on how fat content at different sites affects BMD. Our study demonstrated that fat mass and visceral fat area (VFA) were positively correlated with BMD, consistent with Yuan Jiayao [1]. However, after controlling for age, BMI, and muscle mass, fat mass and VFA were not correlated with BMD, differing from the results of Siddique N [2], Tang, H [21], and [22]. VFA was negatively correlated with BMD, consistent with the findings of Qin Qian and Tan Fan [23]. VFA is a negative predictor of BMD because estrogen derived from the aromatase pathway in adipose tissue is the main source for preventing postmenopausal OP. We hypothesize that low aromatase expression in visceral adipose tissue affects estrogen synthesis, leading to decreased BMD. Excessive visceral fat is a potential pathogenic factor for bone metabolic diseases requiring early clinical intervention.

The positive correlation between fat and BMD can be explained by the relationship between fat and estrogen effects. The relationship between BMD and muscle may also be influenced by estrogen, as muscle contains estrogen receptors that play important roles in muscle cell apoptosis. Previous studies have not clearly established the predictive value of muscle and fat mass for BMD, with conflicting conclusions regarding predicted skeletal sites. Epidemiological surveys in some regions [23] have found that BMD begins to decline with age after age 40, accelerates around age 50, and becomes significantly osteoporotic around age 60—a pattern likely related to estrogen level changes before and after menopause. Starting at age 60, hip BMD becomes significantly lower than lumbar spine BMD in the same age group, making hip BMD diagnosis more accurate than lumbar spine BMD for elderly individuals. Our study analyzed the prediction of BMD at various sites by fat and muscle tissue in pre- and postmenopausal women aged 40-60, finding that both muscle mass and fat mass were positively correlated with BMD. After adjusting for confounders, appendicular skeletal muscle mass was a predictor of lumbar spine, femoral neck, and total hip BMD in postmenopausal and total populations, with the total hip being the best predictive site. In contrast, Kapuš O [8] showed that body fat mass was a predictor of femoral neck BMD in postmenopausal women, with no correlation found between muscle mass and BMD at any site after controlling for confounders. Aedo S [24] demonstrated that body fat mass was a predictor of hip BMD. Qin Qian [25] showed that visceral fat area was a predictor of BMD, but this correlation disappeared after controlling for age. These discrepancies

may be attributed to differences in study design, study populations, menopausal status, and confounding factors.

In summary, visceral fat area is negatively associated with BMD at all sites, while fat mass and total body, trunk, and appendicular skeletal muscle mass (ALM) are positively associated with BMD at all sites. ALM is positively associated with lumbar spine, femoral neck, and total hip BMD in postmenopausal and total populations, with AUC values >0.6. However, ALM >16.24 kg best predicts OP risk at the hip site in both postmenopausal and total populations.

Author Contributions

Xu Haina and Ran Limei conceptualized and designed the study; Xu Haina and Zhu Yan implemented the research; Xu Haina, An Miaomiao, and Wu Chunyan collected data; Xu Haina performed data analysis and interpretation and drafted the manuscript; Ran Limei was responsible for quality control and revision, acquisition of funding, and guidance on manuscript writing, and takes overall responsibility for the article.

Conflicts of Interest

This article has no conflicts of interest.

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Note: Figure translations are in progress. See original paper for figures.