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Association between high levels of gynoid fat and the increase of bone mineral density in women

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ABSTRACT

Objectives: This study aimed to assess whether an increase of gynoid fat is associated with high BMD independent of age and ASMM.

Methods: An observational study was performed in women aged between 20 and 79 years. Fat mass, ASMM, and BMD were measured with dual-energy X-ray absorptiometry. The binned scatterplots and multivariate linear regression models were used to study the relationship between hip BMD and age, height, android fat, gynoid fat, and ASMM.

Results: Of 673 women invited, 596 accepted to participate. Their mean age was 55.4 ± 12.8 years, weight 63.4 ± 9.4 kg, height 1.61 ± 0.06 m, body mass index 24.54 ± 3.59 kg/m², average hip BMD 0.914 ± 0.122 g/cm², android fat 2.12 ± 0.83 kg, gynoid fat 4.54 ± 1.07 kg, and ASMM 15.15 ± 1.97 kg. The final regression model included age (linear coefficient −0.004; 95% confidence interval [CI]: −0.005 to −0.003; p < 0.001), ASMM (linear coefficient 0.013; 95% CI: 0.009 to 0.018; p < 0.001), and gynoid fat (linear coefficient 0.013; 95% CI: 0.005 to 0.022; p < 0.002).

Conclusion: Gynoid fat is associated with BMD in the hip independently of age and ASMM.

Introduction

In women, bone mineral density (BMD) is related to age, estrogenic action, and appendicular skeletal muscle mass (ASMM). The gynoid fat distribution is linked to estrogenic action.

Methods and subjects

Study participants

This retrospective observational study included women aged 20–79 years. Participants, who attended a preventive health control in Santiago, Chile between January 2015 and October 2016, were randomly selected.

Exclusion criteria included: women who used medications likely to have an effect on muscle mass or bone (e.g. levothyroxine, corticosteroids, hormone replacement therapy, and oral contraceptives); women who were on dedicated dietary or exercise programs; and women with non-communicable diseases, such as polycystic ovarian syndrome, and chronic pulmonary, cardiac, hepatic, or renal diseases. Furthermore, women with limb deformities and disorders on the effect of the distribution of body fat on BMD

Conclusion:

Gynoid fat is associated with BMD in the hip independently of age and ASMM.
of the nervous and musculoskeletal systems were also excluded.

**Instruments**

Questionnaires and clinical examination were conducted following standardized procedures and by trained clinicians to measure: age (years), weight (kg), height (m), average hip BMD (includes the average BMD between the right and left hips; g/cm²), android fat (kg), gynoid fat (kg), and ASMM (kg).

Dual-energy X-ray absorptiometry (Lunar Corporation, Madison, WI, USA) was performed on all study participants to measure whole and regional body composition. Percentage of fat mass, lean mass, and bone mineral content were measured. In addition, the BMD in both femoral necks was recorded. Determination of BMD in the vertebral spine was not used, to avoid any interference caused by osteoarthritis in the spine. The information retrieved included bone mineral content, mineral density, T-score, and Z-score, and was analyzed with the software provided by the manufacturer (version 4.7e). We calculated the appendicular lean mass as the sum of lean mass in the arms and legs. Calibration for the measurement of BMD was performed using a phantom spine made of calcium hydroxyapatite and embedded in a lucite block. Scans of the phantom spine occurred every other day according to the manufacturer’s guidelines. The BMD values obtained from the calibration were stable over the entire study period (mean 0.991 g/cm²; coefficient of variation 0.08%).

The android and gynoid regions were defined using the software provided by the manufacturer. The ‘android region’ has a lower boundary at the pelvis cut and an upper boundary above the pelvis cut at 20% of the distance between the pelvis and the neck cuts. The lateral boundaries are the arm cuts. The ‘gynoid region’ has an upper boundary between the upper part of the greater trochanters and a lower boundary defined at a distance equal to twice the height of the android region. The lateral boundaries are the outer leg cuts. All scans were performed by the same operator while the subjects were wearing light indoor clothing and no removable metal objects.

**Statistical analysis**

The analysis was conducted with Stata/SE 16.0 for Windows (StataCorp LLC, College Station, TX, USA). Quantitative variables were described according to their distribution and the corresponding central tendency and dispersion estimates were computed.

Binned scatterplots are a non-parametric method of plotting the conditional expectation function (which describes the average dependent value for each independent value). Therefore, binned scatterplots inform about the functional form of variables and their standard errors. The binned scatterplots were used to study the relationship between average hip BMD and the variables of age, height, weight, android fat, gynoid fat, and ASMM, and the corresponding Pearson’s correlation coefficients were also computed.

A preliminary linear regression model was fitted including age, height, android fat, gynoid fat, and ASMM as predictors; the dependent variable (predicted or outcome) was average hip BMD. A stepwise backward-selection approach was followed to select the final predictors in the regression model. The final model included predictors for which linear coefficients showed $p < 0.05$.

The following information was estimated from the final model: log likelihood, Akaike Information Criterion, Bayesian Information Criterion, and adjusted-$R^2$. Also, for each predictor in the final model, the linear coefficients and standardized linear coefficients were computed. In addition, the adequate compliance of the following assumptions for ordinary least squares regression was assessed: normality of residuals, homoscedasticity, multicollinearity, functional form (linearity), model specification, and independence. The normality of residuals was evaluated with graphic methods (p-norm, q-norm, and kernel density estimation on histogram) and tests for normality of a random variable based on the quantile-mean covariance. The error variance constant (homoscedasticity) was assessed by plotting the residuals versus fitted (predicted) values and the Breusch–Pagan test (null hypothesis: variance of the residuals is homogeneous). The variance inflation factor for each predictor in the final model was studied to avoid multicollinearity. When we estimate linear regressions, we assume that the relationship between the response variable and the predictors is linear. The linearity assumption of the regression between the response and the predictors was established through an augmented component-plus-residual plot. A model specification error can occur when one or more relevant variables are omitted from the model or one or more irrelevant variables are included in the model. The link test and the Ramsey reset test were using to assess the specification error. Finally, the assumption of independent errors was evaluated with the Durbin–Watson test and Durbin’s alternative test.

**Ethical considerations**

The study was approved by the CEGEP (Centro de Estudios Ginecológicos y Preventivos, Santiago, Chile) and is in complete agreement with the Declaration of Helsinki. All patients provided written informed consent.

**Results**

For this study, 673 women were invited, and 596 (88.5%) accepted to participate. All variables were symmetrically distributed. The mean ± standard deviation of the variables of interest was: age 55.36 ± 12.77 years, weight 63.36 ± 9.41 kg, height 1.61 ± 0.06 m, body mass index 24.54 ± 3.59 kg/m², average hip BMD 0.914 ± 0.122 g/cm², android fat 2.12 ± 0.83 kg, gynoid fat 4.54 ± 1.07 kg, and ASMM 15.15 ± 1.97 kg.

The binned scatterplots between average hip BMD and the variables of age, height, weight, android fat, gynoid fat, and ASMM suggested that there is a linear relationship among these variables (Figure 1). Pearson’s correlation...
coefficients are presented in Table 1. Of note, the correlation between average hip BMD and age, height, weight, android fat, gynoid fat, and ASMM was highly significant ($p < 0.01$).

Weight is not suitable for incorporation into a linear regression model\textsuperscript{15,16} because gynoid fat and android fat are a linear combination for weight (Pearson coefficient $>0.8$).

The stepwise backward-selection approach yielded a final linear regression model including age (linear coefficient $-0.004$; 95% confidence interval [CI]: $-0.005$ to $-0.003$; $p < 0.001$), ASMM (linear coefficient 0.013; 95% CI: 0.009 to 0.018; $p < 0.001$), and gynoid fat (linear coefficient 0.013; 95% CI: 0.005 to 0.022; $p = 0.002$). Android fat showed a very close positive correlation with gynoid fat and was automatically excluded from the final model. The linear coefficient of the intercept in the final model was 0.880 (95% CI: 0.800 to 0.959; $p < 0.01$). The final model had the following

Figure 1. Binned scatterplots between average hip bone mineral density and the variables of age, weight, height, android fat, gynoid fat, and appendicular skeletal muscle mass in 596 women who attended a preventive health control in Santiago, Chile, during January 2015 and October 2016. $y =$ predictor for simple linear regression using ordinary least squares.
Table 1. Pearson's correlation coefficient between average hip bone mineral density and the variables of age, height, android fat, gynoid fat, appendicular skeletal muscle mass, and weight in 596 women who attended a preventive health control in Santiago, Chile, during January 2015 and October 2016.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Pearson's correlation coefficient</th>
</tr>
</thead>
<tbody>
<tr>
<td>Average hip bone mineral density</td>
<td></td>
</tr>
<tr>
<td>Age</td>
<td>$-0.46^*$</td>
</tr>
<tr>
<td>Height</td>
<td>$0.11^*$</td>
</tr>
<tr>
<td>Android fat</td>
<td>$0.16^*$</td>
</tr>
<tr>
<td>Gynoid fat</td>
<td>$0.18^*$</td>
</tr>
<tr>
<td>Appendicular skeletal muscle mass</td>
<td>$0.30^*$</td>
</tr>
<tr>
<td>Weight</td>
<td>$0.27^*$</td>
</tr>
<tr>
<td>Age</td>
<td>$-0.11^*$</td>
</tr>
<tr>
<td>Height</td>
<td>$0.17^*$</td>
</tr>
<tr>
<td>Android fat</td>
<td>$0.01$</td>
</tr>
<tr>
<td>Gynoid fat</td>
<td>$0.12^*$</td>
</tr>
<tr>
<td>Appendicular skeletal muscle mass</td>
<td>$0.07$</td>
</tr>
<tr>
<td>Height</td>
<td></td>
</tr>
<tr>
<td>Android fat</td>
<td>$0.03$</td>
</tr>
<tr>
<td>Gynoid fat</td>
<td>$0.19^*$</td>
</tr>
<tr>
<td>Appendicular skeletal muscle mass</td>
<td>$0.55^*$</td>
</tr>
<tr>
<td>Weight</td>
<td>$0.30^*$</td>
</tr>
<tr>
<td>Android fat</td>
<td>$0.74^*$</td>
</tr>
<tr>
<td>Gynoid fat</td>
<td>$0.28^*$</td>
</tr>
<tr>
<td>Appendicular skeletal muscle mass</td>
<td>$0.85^*$</td>
</tr>
<tr>
<td>Weight</td>
<td></td>
</tr>
<tr>
<td>Android fat</td>
<td>$0.32^*$</td>
</tr>
<tr>
<td>Gynoid fat</td>
<td>$0.82^*$</td>
</tr>
</tbody>
</table>

$p < 0.01$.

Discussion

The results of univariate analysis (binned scatter plots and Pearson’s correlation coefficients) support that BMD is related to age, gynoid fat, and ASMM. However, significant correlation was found between BMD of the hip and height and android fat. This could be a product of confounding factors, among which are highlighted gynoid fat, ASMM, and other factors not considered but mentioned in the study limitations.

The final regression model indicates that ASMM is associated with better bone density, which could be explained by the cross-talk between muscle and bone. Numerous studies support the concept of a bone–muscle unit, where constant cross-talk between the two tissues takes place, involving molecules released by the skeletal muscle secretome, which affect bone, and osteokines secreted by the osteoblasts and osteocytes, which, in turn, impact muscle cells. Also, the association between BMD and muscle can be influenced by estrogen, since the muscle has estrogen receptors that seem to play a significant role in the apoptosis of muscle cells.

Another result is the negative effect of age on BMD. Aging progressively triggers greater cellular senescence, a process that is expressed in bone as osteoporosis. Estradiol attenuates this process by increasing osteogenic differentiation through promoting increased expression of SATB2, a protein that regulates cellular transcription and which is crucial for osteogenic differentiation of bone stem cells and therefore for bone quality.

In the absence of detailed information about menopause status, some epidemiologic studies consider age alone as a crude proxy for menopausal status. In this study with age incorporated, aging and the menopausal status were linked to hypoestrogenism. Although several of the factors associated with low bone mass in women are linked to hypoestrogenism, we cannot consider it the most relevant factor in bone metabolism and in the risk of osteoporosis, since many other conditions can modify bone mass. Proof of this is the broad list of diseases that can cause secondary osteoporosis. However, hypoestrogenism is another factor to consider when assessing the risks of osteoporosis in a woman, and the important thing is that it is a modifiable factor and there is solid evidence that shows the positive results of menopausal hormone therapy in the prevention of osteoporotic fractures.

The principal result indicates that gynoid fat, independent of age and ASMM, predicts BMD of the hip. This result supports gynoid fat being associated with better BMD, consistent with the evidence observed. BMD has been described as associated, inter alia, with ethnicity, sex, age, body phenotype, estrogen, calcium, and lifestyle factors. The positive association between gynoid fat and bone mineral density can be explained not only by the positive relationship between gynoid fat and estrogenic effect, but also other factors related to greater gynoid fat such as lifestyle and physical exercise.

The results of this study have limitations due to the lack of incorporation of variables that could have influenced bone mass, such as physical activity, menopause status, age at menopause, smoking, alcohol consumption, parity, lifetime duration of lactation, level of physical activity, personal history of fracture, family history of fracture osteoporosis, vitamin D status, and intake of supplements. This study is an initial contribution to a causal model of the factors that affect BMD in women, and therefore further studies should be performed to establish causal relations.
Conclusion
Greater gynoid fat is associated with better BMD in the hip; therefore, there could be lower risk of osteoporosis. It would be interesting to study whether this association could be due to some action of the gynoid fat on the bone, or an effect on hypoeostrogenism, or an indirect effect of lifestyle and physical exercise.

Potential conflict of interest The authors report no conflicts of interest and are responsible only for the content and writing of this article.

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