BRIEF REPORT

Adiposity in Relation to Vitamin D Status and Parathyroid Hormone Levels: A Population-Based Study in Older Men and Women

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Objective: In small case-control studies, obesity was associated with worse vitamin D status. Our aim was to assess the association of adiposity (anthropometric measures as well as dual energy x-ray absorptiometry) with serum 25-hydroxyvitamin D (25-OH-D) and serum PTH levels in a large population-based study including older men and women.

Methods: Subjects were participants of the Longitudinal Aging Study Amsterdam and were aged 65 yr and older. In 458 participants, serum 25-OH-D and PTH were determined, and body mass index, waist circumference, waist to hip ratio, sum of skin folds, and total body fat percentage by dual energy x-ray absorptiometry were measured.

Results: After adjustment for potential confounders, higher body mass index, waist circumference, and sum of skin folds were statistically significantly associated with lower 25-OH-D (standardized β values were –0.136, –0.137, and –0.140, respectively; all P < 0.05) and with higher PTH (0.166, 0.113, and 0.114, respectively; all P < 0.05). Total body fat percentage was more strongly associated with 25-OH-D and PTH (−0.261 and 0.287, respectively; both P < 0.001) compared with anthropometric measures. Total body fat percentage remained associated with 25-OH-D after adjustment for PTH, and with PTH after adjustment for 25-OH-D.

Conclusion: Precisely measured total body fat is inversely associated with 25-OH-D levels and is positively associated with PTH levels. The associations were weaker if anthropometric measures were used, indicating a specific role of adipose tissue. Regardless of the possible underlying mechanisms, it may be relevant to take adiposity into account when assessing vitamin D requirements. (J Clin Endocrinol Metab 90: 4119–4123, 2005)

VITAMIN D IS well known for its essential role in bone metabolism and calcium homeostasis (1). However, it has become increasingly clear that the vitamin D endocrine system has additional physiological functions (2).

Evidence is increasing that the vitamin D endocrine system is related to obesity. Obesity has been found to be associated with lower levels of serum 25-hydroxyvitamin D (25-OH-D) (3–11) and higher levels of serum PTH (3, 8, 9, 12, 13). Underlying causes that have been suggested are less sun exposure in obese subjects due to limited mobility or clothing habits and a higher storage of vitamin D in adipose tissue (4, 11). However, overweight may also be the consequence of poor vitamin D status. Vitamin D is an important determinant of serum PTH levels, and increased PTH promotes calcium influx into the adipocytes. In these cells, intracellular calcium enhances lipogenesis, and therefore, PTH excess may promote weight gain (14, 15).

The relation between body fat content and serum 25-OH-D or PTH has usually been investigated in relatively small (case-control) studies (3–5, 7–9, 11). Furthermore, not many studies used direct measures of body fatness. The aim of the present study was to assess the association of adiposity with serum 25-OH-D and PTH levels in a large population-based study including older men and women.

Subjects and Methods

Study sample

The Longitudinal Aging Study Amsterdam is an ongoing cohort study of the predictors and consequences of changes in autonomy and well-being in an aging population in The Netherlands. The sampling and data collection procedures have been described in detail previously (16). Briefly, a random sample of older men and women (aged 55–85 yr), stratified by age, sex, urbanization, and expected 5-yr mortality, was drawn from the population registers of 11 municipalities in areas in the west, northeast, and south of The Netherlands. In total, 3107 subjects participated in the baseline examination (1992/1993).

In 1995/1996, a second examination took place; participants were then aged 65 yr and older. After an interview at home, participants were invited for a medical interview at one of the research centers, where blood samples were obtained. Respondents living in the west (n = 685) were also invited for a whole body dual energy x-ray absorptiometry (DXA) scan, which was obtained for 518 respondents. The study sample for the present study included subjects in whom a DXA scan was per-
formed and serum 25-OH-D and PTH levels were available (n = 514). Subjects with missing anthropometric information (n = 61) were excluded. Therefore, our final study sample consisted of 453 subjects who were predominantly Caucasian (99%). Informed consent was obtained from all respondents. The study was approved by the medical ethics committee of the Vrije University Medical Center.

**Measurements**

Blood samples were obtained and centrifuged in the morning. Subjects were allowed to have tea and toast, but no dairy products. The serum samples were stored at −70°C. Serum PTH was measured by an immunoradiometric assay (Incastar Corp., Stillwater, MN), and serum 25-OH-D was determined according to a competitive binding protein assay (Nichols Diagnostics, San Juan Capistrano, CA). The interassay coefficients of variation were 12 and 10%, respectively. The analyses were performed using SPSS for Windows (version 11.0.1, SPSS, Inc., Chicago, IL). Multiple linear regression analyses were performed after adding them to the regression models. Effect modification by sex was tested using chi-square tests. All analyses included. Therefore, our final study sample consisted of 453 subjects who were predominantly Caucasian (99%). Informed consent was obtained from all respondents. The study was approved by the medical ethics committee of the Vrije University Medical Center.

The assessments of body mass index (BMI; kilograms per meter squared), waist circumference (centimeters), and hip to waist circumference ratio (WHR) have been described previously (17). The thicknesses of skin folds (millimeters) at the triceps, biceps, suprailiac, and subscapular were measured in triplicate, and the sum of the mean thicknesses of each skin fold was used in the analyses.

Total body fat (kilograms) was measured by whole body DXA (software version V5.67A, QDR 2000, Hologic, Inc., Waltham, MA). The total body fat percentage (percentage) was calculated as (total body fat/total body weight)

**Statistical analyses**

All analyses were performed using SPSS for Windows (version 11.0.1, SPSS, Inc., Chicago, IL). Multiple linear regression analyses were performed to study the associations between body composition variables (independent variables) and serum 25-OH-D or PTH levels (dependent variables). Because the distribution of serum PTH was skewed, we used the logarithmic transformation. We adjusted for potential confounders by adding them to the regression models. Effect modification by sex was evaluated by stratified analyses and tested by adding product terms of body composition variables × sex to the regression models. To facilitate direct comparisons of the strengths of the associations, the results of the regression models are reported as standardized β values. A standardized β of 0.2 indicates that if the independent variable increases by 1 sd, the dependent variable increases by 0.2 sd.

**Results**

Table 1 shows the characteristics of the study participants according to sex-specific quartiles of total body fat percentage. Total body fat was inversely associated with serum 25-OH-D and positively with serum PTH levels in both sexes (all P < 0.05). In 8.0% of the men and 14.4% of the women, the serum 25-OH-D level was less than 10 ng/ml (25 nmol/liter; deficient status), and 44.7% of the men and 56.1% of the women had serum 25-OH-D levels below 20 ng/ml (50 nmol/liter; insufficient status). Anthropometric measures were also inversely related to 25-OH-D, but this crude association was only statistically significant for BMI and waist circumference in women (P < 0.05). BMI, waist circumference,

<table>
<thead>
<tr>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Quartile 1</strong></td>
<td><strong>Quartile 2</strong></td>
</tr>
<tr>
<td>Range in TBF%</td>
<td>8.5–25.9</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>22.6 ± 3.0</td>
</tr>
<tr>
<td>25-OH-D (ng/ml)</td>
<td>13.1 ± 4.5</td>
</tr>
<tr>
<td>PTH (pmol/liter)</td>
<td>6.0 ± 2.0</td>
</tr>
<tr>
<td><strong>Adiposity measures</strong></td>
<td></td>
</tr>
<tr>
<td>Total body fat (kg)</td>
<td>12.8 ± 3.4</td>
</tr>
<tr>
<td>TBF% (percentage)</td>
<td>19.2 ± 4.1</td>
</tr>
<tr>
<td>Sum of skin folds (mm)</td>
<td>37.9 ± 22.8</td>
</tr>
<tr>
<td>Age (yr)</td>
<td>65.4 (59.0, 72.8)</td>
</tr>
<tr>
<td>Alcohol use (%)</td>
<td>35.2</td>
</tr>
<tr>
<td>Smoking (%)</td>
<td>30.5</td>
</tr>
</tbody>
</table>

**Data are the mean ± sd, median (interquartile range), or percentage. To convert to SI units multiply by 2.496 for 25-OH-D (nanomoles per liter) and by 0.105 for PTH (picomoles per liter).**
ence, and sum of skin folds were statistically significantly and positively associated with serum PTH in women only (all \( P < 0.05 \)).

After adjustment for age, season, sex, and smoking, higher BMI, waist circumference, and sum of skin folds were statistically significantly associated with lower 25-OH-D and higher PTH concentrations (Table 2, model 1). The associations of DXA total body fat (either in kilograms or as a percentage) with serum 25-OH-D and PTH levels were stronger than the associations of the anthropometric measures and were statistically significant for both men and women (Table 2 and Fig. 1).

When analyses were performed for men and women separately, the associations of body composition variables with serum PTH tended to be stronger in women than in men, except for WHR. When interaction by sex was tested, it was not statistically significant for 25-OH-D, and it was only borderline statistically significant for sum of skin folds and PTH \(( P = 0.062)\). However, when comparing associations between men and women, substantial differences were observed (Table 2).

Additional adjustment of the associations for serum creatinine, alcohol intake, or physical activity level (total activity or outdoor activities only) did not appreciably change the associations (data not shown). After adjustment for smoking, the associations became stronger (change of >10%); therefore, we presented the associations after adjustment for smoking. The Pearson correlation coefficient between serum 25-OH-D and ln-PTH was \(-0.30\). Additional adjustment for PTH considerably weakened the associations between measures of body fatness and 25-OH-D, and additional adjustment for 25-OH-D considerably weakened the associations between measures of body fatness and PTH (Table 2, model 2). Most associations with DXA-measured total body fat, however, remained statistically significant.

When we distinguished trunk fat from leg fat and added them simultaneously to the regression models as two separate independent variables, leg fat was a strong determinant of 25-OH-D, whereas trunk fat was not significantly associated with 25-OH-D [standardized \( \beta \) value, \(-0.161 (P = 0.017)\) and \(-0.054 (P = 0.341)\), respectively]. In contrast, trunk fat was a strong determinant of PTH levels, whereas leg fat was not significantly associated with PTH [standardized \( \beta \) value, 0.155 \((P = 0.013)\) and 0.055 \((P = 0.457)\), respectively].

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**TABLE 2.** Associations [standardized \( \beta \) values (sB)] of body composition variables (continuous, independent variable) in relation to 25-OH-D (continuous, dependent variable) and in relation to PTH, for both sexes combined and for men and women separately

<table>
<thead>
<tr>
<th></th>
<th>Both sexes</th>
<th>Model 1</th>
<th>Women</th>
<th>Model 2</th>
<th>Men</th>
<th>Women</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>sB</td>
<td>P</td>
<td>sB</td>
<td>P</td>
<td>sB</td>
<td>P</td>
</tr>
<tr>
<td>25-OH-D</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>BMI</td>
<td>-0.136</td>
<td>0.001</td>
<td>-0.080</td>
<td>0.182</td>
<td>-0.181</td>
<td>0.003</td>
</tr>
<tr>
<td>PTH</td>
<td>-0.096</td>
<td>0.020</td>
<td>-0.075</td>
<td>0.203</td>
<td>-0.093</td>
<td>0.122</td>
</tr>
<tr>
<td>WHR</td>
<td>-0.051</td>
<td>0.317</td>
<td>-0.081</td>
<td>0.176</td>
<td>-0.002</td>
<td>0.969</td>
</tr>
<tr>
<td>WC</td>
<td>-0.137</td>
<td>0.002</td>
<td>-0.125</td>
<td>0.036</td>
<td>-0.138</td>
<td>0.025</td>
</tr>
<tr>
<td>Sum of skin folds</td>
<td>-0.140</td>
<td>0.004</td>
<td>-0.129</td>
<td>0.033</td>
<td>-0.119</td>
<td>0.054</td>
</tr>
<tr>
<td>TBF</td>
<td>-0.185</td>
<td>0.000</td>
<td>-0.152</td>
<td>0.012</td>
<td>-0.186</td>
<td>0.002</td>
</tr>
<tr>
<td>TBF%</td>
<td>-0.261</td>
<td>0.000</td>
<td>-0.170</td>
<td>0.004</td>
<td>-0.197</td>
<td>0.001</td>
</tr>
<tr>
<td>BMI</td>
<td>0.166</td>
<td>0.000</td>
<td>0.026</td>
<td>0.685</td>
<td>0.298</td>
<td>0.000</td>
</tr>
<tr>
<td>PTH</td>
<td>0.126</td>
<td>0.005</td>
<td>0.006</td>
<td>0.921</td>
<td>0.235</td>
<td>0.000</td>
</tr>
<tr>
<td>WHR</td>
<td>0.055</td>
<td>0.325</td>
<td>0.039</td>
<td>0.543</td>
<td>0.066</td>
<td>0.352</td>
</tr>
<tr>
<td>WC</td>
<td>0.113</td>
<td>0.019</td>
<td>0.038</td>
<td>0.553</td>
<td>0.193</td>
<td>0.005</td>
</tr>
<tr>
<td>Sum of skin folds</td>
<td>0.114</td>
<td>0.031</td>
<td>0.002</td>
<td>0.972</td>
<td>0.201</td>
<td>0.003</td>
</tr>
<tr>
<td>TBF</td>
<td>0.199</td>
<td>0.000</td>
<td>0.108</td>
<td>0.096</td>
<td>0.255</td>
<td>0.000</td>
</tr>
<tr>
<td>TBF%</td>
<td>0.287</td>
<td>0.000</td>
<td>0.147</td>
<td>0.021</td>
<td>0.256</td>
<td>0.000</td>
</tr>
</tbody>
</table>

TBF, Total body fat; WC, waist circumference. Model 1, Adjusted for age, season, smoking, and also for sex if men and women were combined. Model 2, Model 1 additionally adjusted for PTH or 25-OH-D.
Discussion

This report shows a strong inverse association between total body fatness and serum 25-OH-D levels and a strong positive association between body fatness and serum PTH levels in older men and women, independent of age, sex, season, study region, and smoking. The associations were weaker if anthropometric estimates were used compared with DXA total body fat percentage.

In the 1980s, small case-control studies showed that serum 25-OH-D levels were lower in obese subjects compared with nonobese individuals (3, 4, 20), and serum PTH levels were higher (3), which was confirmed in more recent studies (5, 9, 11). In observational studies, similar associations of BMI with 25-OH-D or PTH were shown (7, 8, 12, 13), but these were not always statistically significant (6, 10, 21). In our sample we found statistically significant associations between BMI and 25-OH-D and between BMI and PTH levels. However, the associations of these hormones with total body fat percentage by DXA were even stronger, which was also found in younger women (mean age, 47 yr) (10). These results indicate that it is adiposity, and not simply body weight or BMI, that is associated with serum 25-OH-D and PTH concentrations. Previous studies have probably underestimated the associations by using anthropometric measures.

In reports from the 1970s (22, 23), it was suggested that the association between serum 25-OH-D and obesity could be explained by an increased storage of 25-OH-D in adipose tissue in obese subjects. Rosenstreich et al. (22) supplemented rats with radiolabeled vitamin D, and adipose tissue was found to be the major storage site. Mawer et al. (23) found similar results in human tissues after injection of radioactive cholecalciferol. In a more recent study by Wortsman et al. (11), the capacity of the skin to produce vitamin D was not altered in obesity. However, the increase in serum vitamin D after sun exposure was 57% less in obese compared with nonobese subjects. This increase in serum vitamin D after sun supplementation was similar in obese and nonobese subjects. This supports the hypothesis of a decreased release of endogenously produced vitamin D into the circulation due to more storage in subcutaneous fat in obese subjects (11). The fact that in our study leg fat was more strongly related to 25-OH-D levels compared with trunk fat supports the idea that endogenously produced vitamin D is particularly stored in the subcutaneous fat depot (11).

Recently, evidence has been accumulating that obesity can also be the consequence of a low vitamin D status. Increased PTH levels, of which serum 25-OH-D is an important determinant, promote calcium influx into the adipocytes. In these cells intracellular calcium enhances lipogenesis; therefore, PTH excess may promote weight gain (14, 15). The fact that PTH was also associated with adiposity after adjustment for 25-OH-D could suggest that PTH, also independently of 25-OH-D, contributes to the development of adiposity. The observation that a higher dietary intake of calcium, which is related to lower PTH levels, is related to lower body weight (24) and less weight gain (25) also fits the hypothesis of high PTH levels as a cause of obesity. Subjects with primary hyperparathyroidism, who have increased PTH levels, were also markedly heavier than age-matched controls (26, 27). In addition, calcium supplementation, which also decreases PTH levels, resulted in a greater weight loss compared with placebo treatment (25, 28). These intervention studies suggest a modest, but causal, relation between serum PTH and weight change. Serum 25-OH-D is an important determinant of PTH levels, and interventions have shown that supplementation with α-calcidol resulted in modest, but significant, weight loss (29, 30). In our study, however, the 25-OH-D level was also related to adiposity independently of PTH levels.

In conclusion, in a large population-based study, including both men and women, we found that total body fat percentage measured by DXA is strongly associated with serum 25-OH-D and PTH levels, independently of age, sex, season, or smoking. The associations were weaker if anthropometric measures were used, indicating a specific role of adipose tissue. Long-term longitudinal studies with repeated measures of vitamin D and PTH should be performed to explore the direction of effects underlying our observations. Considering the possible role of vitamin D and PTH in the development of cancer, muscle weakness, insulin resistance, diabetes, and cardiovascular disease (31–33), it may be relevant to take adiposity into account when assessing vitamin D requirements.

Acknowledgments

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