Serum parathyroid hormone level is associated with body mass index. The 5th Tromso study

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Abstract

Objective: To study whether serum parathyroid hormone (PTH) and serum calcium are associated with body mass index (BMI), and their predicting role in obesity.

Design: Population based, cross-sectional study.

Methods: In 2001 a population-based health survey was held in Tromsø, North Norway. Questionnaires on medical history and lifestyle factors were completed and anthropometric data were collected. Calcium and vitamin D intakes and a physical activity score were calculated. Serum calcium and PTH were measured in a subset of 3447 men and 4507 women. Pearson correlation and linear regression were used to evaluate associations between BMI, PTH and serum calcium, and logistic regression was used to test PTH and serum calcium as predictors of obesity and to calculate odds ratio. Relative risk was calculated using frequency tables.

Results: For serum calcium and PTH there was a significant positive relation to BMI in both genders (P < 0.001), which to our knowledge has not previously been reported on the basis of a large epidemiological study. Age, low calcium and vitamin D intakes were explanatory variables for serum PTH. The highest quartile of serum PTH (>4.20 pmol/l) was a significant predictor for obesity (P < 0.001) in both genders, adjusted for age, physical activity and serum calcium. Obesity rates were higher in those with PTH levels in the highest quartile compared with those in the lower quartiles, which resulted in a relative risk of 1.40 (95% confidence interval (C.I.) 1.20–1.60) for men and 1.48 (95% C.I. 1.31–1.67) for women.

Conclusions: Serum PTH, adjusted for age, physical activity and serum calcium, is positively associated with BMI in both sexes, and serum PTH is an independent predictor of obesity in our statistical model.

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Introduction

Obesity is a predisposing factor for cardiovascular morbidity (1), diabetes mellitus type II (2), and all cause mortality (3). Prevalence of overweight is approaching epidemic proportions (4) and in North Norway there has been an elevation in mean body mass index (BMI) of about 1 kg/m² from 1974 to 1994/95 (5).

The cause of obesity is multifactorial with sedentary lifestyle and excessive energy intake as the most important contributors (6). Abnormal calcium metabolism has also been linked to weight gain (7), and a high calcium intake may prevent obesity (8). Furthermore, a low vitamin D intake is associated with increased BMI at least in the population of North Norway (9).

Parathyroid hormone (PTH) is a calcium regulating hormone which is secreted in response to a low serum calcium level. If a low calcium and/or vitamin D intake are related to obesity, one would expect the same to be true for serum PTH.

In 2001, a general health survey with emphasis on lifestyle factors and cardiovascular diseases was performed in Tromsø, and included more than 8000 subjects. Measurement of serum PTH was performed in 7954 subjects, thus providing a large database for testing the hypothesis of a relationship between PTH and BMI.

Subjects and methods

Study population

In 2001, all men and women older than 29 years, living in the municipality of Tromsø, and who either had participated in the second phase of the 4th Tromsø study (9) or became 30, 40, 45, 60 or 75 years of age during 2001, were invited to participate in the 5th Tromsø study. The present 5th Tromsø study was conducted in a similar manner to the previous ones (10, 11).
**Questionnaires**

Questionnaires including questions about medical history, life-style factors and dietary habits were obtained from all participants. A physical activity score was calculated by adding together hours of moderate and hard physical activity, giving the hours of hard physical activity double value. The questionnaire on dietary habits included questions on the type of milk and number of glasses drunk daily and how often fatty fish (e.g. mackerel or salmon) or different types of cheese were eaten. Furthermore, the subjects were asked about their use of vitamin D and calcium supplementation. Each glass of milk was assumed to be 200 ml, each topping with cheese 10 g, and the amount of fatty fish in a dinner portion 200 g. These portions are usual Norwegian servings (12). Each vitamin D capsule or cod liver oil supplementation was assumed to contain 10 \( \mu g \) vitamin D, and each calcium tablet 500 mg calcium. Daily intake of calcium from dairy products and intake of vitamin D were calculated on the basis of a Norwegian food table (13). The questionnaire was not designed to calculate calorie intake.

**Measurements**

Height and weight were measured while the subjects wore light clothing and no shoes. BMI was defined as weight (kg) divided by height squared (m\(^2\)). In all subjects blood samples were drawn for later hormone analyses. Serum PTH and calcium were analysed as previously described (14). Our reference range for serum calcium is 2.20 – 2.60 mmol/l, and for serum PTH it is 1.1 – 6.8 pmol/l for those aged < 51 years and 1.1 – 7.5 pmol/l for those aged > 50 years.

**Statistical analysis**

Statistical analyses were carried out using the SPSS for Windows, version 11.0 (SPSS, Chicago, IL, USA). We applied linear regression with enter method with BMI as a dependent variable and age, physical activity, serum PTH, serum calcium, calcium supplementation, calcium from dairy products, and vitamin D intake as explanatory covariates (15). The frequency distribution of BMI was normal on visual inspection and had a skewness of 0.77 and a kurtosis of 0.7. All variables except calcium supplementation were continuous. Calcium supplementation was coded as: never used, sporadic use and daily use, and was treated as a categorical variable in the regression analysis. The validity of the regression model was tested by visual inspection of the residuals.

Interaction between PTH quartiles and gender in relation to BMI was investigated with the use of univariate analysis of variance. Differences between groups were evaluated with one-way ANOVA. Linear regression with enter method was used to find relations between PTH and age, serum calcium, calcium supplementation, calcium from dairy products and vitamin D intakes. Serum PTH had a skewed distribution. This variable was therefore log transformed and entered in this form as a dependent variable in the latter regression model.

Obesity was defined as BMI \( \geq 30 \text{ kg/m}^2 \) (16). Logistic regression was used to test the following potential predictors of obesity for independence: age, physical activity, serum PTH quartiles and serum calcium quartiles. Serum PTH quartiles (< 2.30, 2.30 – 3.20, 3.21 – 4.20 and > 4.20 pmol/l in both sexes) and serum calcium quartiles (< 2.30, 2.30 – 2.35, 2.36 – 2.41 and > 2.41 in both sexes) were entered as categorical variables to evaluate the odds ratio with the lowest quartile as a reference category. We used analysis of frequency tables to calculate relative risks. Differences with \( P < 0.05 \) were considered to be statistically significant. All tests were carried out two-sided. Unless otherwise stated, the values are means ± S.D.

**Ethics**

The Regional Ethics Committee approved the study, and all participants gave their written informed consent.

**Results**

A total of 8128 men and women were examined in the 5th Tromso study, which constituted 78% of those invited. PTH was successfully measured in 3447 men and 4507 women aged 30 to 89 years. There was no significant difference in age, BMI and gender distribution between those who underwent hormone analyses and those who were initially enrolled (data not shown). There was a significant interaction between gender and serum PTH (\( P < 0.01 \)) in relation to BMI, and we therefore analysed men and women separately. All variables had a linear relation to BMI.

The demographics of the study population are given in Table 1 along with standardised regression coefficients and correlation coefficients with BMI as a dependent variable. In both sexes serum PTH was the strongest explanatory variable for BMI and the elevation of PTH by 1 pmol/l led to a BMI increment of 0.17 kg/m\(^2\) in men and 0.26 kg/m\(^2\) in women. Physical activity was the second strongest predictor for BMI, which resulted in a decrement of BMI by 0.07 kg/m\(^2\) in men and 0.15 kg/m\(^2\) in women when increasing moderate physical activity by 1 h per week. When entering the intake of calcium in the model as that from dairy products and that from supplementation, the former had a positive relation to BMI (\( P < 0.05 \) in both genders), while the latter had a negative relation to BMI (\( P < 0.05 \) in women, not significant in men).
Standardized β coefficients from the linear regression model with serum PTH as a dependent variable are presented in Table 2. Low calcium intake from dairy products and old age in both genders, and low vitamin D intake in women, were significant explanatory factors for serum PTH. However, neither low calcium intake nor low vitamin D intake appeared to be explanatory variables for serum calcium when adjusted for age, BMI and serum PTH (data not shown).

Among those studied, 627 men and 939 women were obese. Obesity rates were higher in those with PTH levels in the fourth quartile (serum PTH > 4.20 pmol/l) compared with those in lower quartiles, which resulted in a relative risk of 1.40 (95% confidence interval (C.I.) 1.20–1.60) for men and 1.48 (95% C.I. 1.31–1.67) for women.

Only the strongest explanatory variables for BMI such as age, physical activity, serum PTH and serum calcium were entered in the logistic regression model as predictors of obesity (Table 3). The highest quartile of serum PTH turned out to be a significant predictor for obesity in both genders after adjusting for age, physical activity and serum calcium. In addition, the two highest quartiles of serum calcium were significant predictors for obesity in women, adjusted for age, physical activity and serum PTH.

**Discussion**

In the present population-based cross-sectional study we found a significant positive relation between serum PTH and BMI, which to our knowledge has not been reported before on the basis of a large epidemiological study. Those within the highest PTH quartile had approximately a 50% greater risk of being obese. In addition, the highest quartile of serum PTH in both genders was an independent and significant predictor of obesity when adjusted for age, physical activity and serum calcium.

Previous studies on the relationship between PTH and BMI were based on smaller studies that yielded inconclusive results (17, 18). Thus, Landin-Wilhelmsen et al. studied 181 men and 166 women and found a positive correlation between PTH and BMI. In men, PTH remained significant after correction for age, smoking, hypertension, low calcium intake in men, low vitamin D intake, and years of education.
coffee consumption, and 25-hydroxyvitamin D (17). However, they did not adjust for serum calcium, and in the multivariate analysis age lost its significance as an explanatory variable for PTH. In our study, age was the most significant explanatory variable for serum PTH, which is in accordance with another population-based epidemiological study (19). Lind et al. (18) studied 143 hypertensive and 51 normotensive subjects and measured serum PTH in a random subgroup of 76 subjects. They found no relation between BMI and PTH, but demonstrated a significant negative correlation between ionised calcium and BMI. Since PTH is one of the crucial factors up-regulating ionised calcium (20), the absence of an association between PTH and BMI in the presence of a negative association between the latter and ionised calcium is surprising. On the other hand, the authors found a positive relation between the ratio of total to ionised calcium and BMI.

Since total serum calcium is the sum of calcium bound to albumin and globulins and the free calcium fraction, this may confirm a positive relation between serum albumin and BMI (21). Furthermore, low levels of ionised calcium were found in 44 morbidly obese subjects in a study by Andersen et al. (22). In the same study, serum PTH levels were higher in the obese, but adjustment for age and physical activity was not performed. A large population-based study on almost 6000 urinary stone patients by Powell et al. demonstrated significantly elevated serum PTH levels in obese subjects compared with non-obese, but their analysis was not adjusted for age and other explanatory factors for BMI (23). Finally, Stein et al. (24) studied 143 nursing home and hostel residents and found those with secondary hyperparathyroidism and a low serum 25-hydroxyvitamin D level to be approximately 8 kg heavier that those in the control group.

Overweight as a consequence of elevated serum PTH may be explained by several mechanisms. Thus, PTH stimulates the renal hydroxylation of 25-hydroxyvitamin D to its active form, 1,25-dihydroxyvitamin D (25), which in turn elevates the calcium influx into adipocytes (7). Increased intracellular calcium enhances lipid storage (26) and possibly also activates phosphodiesterase 3B, which subsequently reduces catecholamine-induced lipolysis (27). Both these effects would promote lipid storage in fat tissue.

On the other hand, the elevated serum PTH in obesity might be the result and not the cause of obesity. Thus, in obesity a deranged renal handling of calcium, leading to negative calcium balance and thus elevated serum PTH levels, has been reported (28). The increased excretion of calcium is in parallel with sodium excretion (29), and the elevation of the latter may be a result of a higher salt intake in obese subjects (30). Furthermore, serum PTH decreases with weight loss in obese subjects both on a low-calorie diet (28) and after laparoscopic gastric banding (31).

Low calcium (32) and vitamin D (9) intakes have recently been linked to obesity. In the present study this was seen for vitamin D intake for men, but not significantly so for women. For calcium intake we have previously found a positive relation to BMI (9) which was also seen in the present study regarding calcium obtained from dairy products. On the other hand, calcium supplementation had a negative association to BMI. It is therefore likely that there are weight gain promoting components in milk that override the effect of calcium. As there was a negative association between dairy calcium intake and PTH, a positive association between dairy calcium and BMI, and a positive association between PTH and BMI, this weakens, but does not rule out, a causal role for PTH in the development of obesity.

However, in this respect it must be strongly emphasised that we have only demonstrated a statistical association between serum PTH and BMI, which does not necessarily imply a cause-and-effect relationship. Accordingly, serum PTH may simply be a pathophysiologically unrelated marker of obesity.

### Table 3

<table>
<thead>
<tr>
<th>Quartiles of serum PTH (pmol/l)</th>
<th>Odds ratio in men</th>
<th>Odds ratio in women</th>
</tr>
</thead>
<tbody>
<tr>
<td>Serum PTH (pmol/l)</td>
<td>Unadjusted</td>
<td>Adjusted*</td>
</tr>
<tr>
<td>&lt; 2.30</td>
<td>1.0</td>
<td>1.0</td>
</tr>
<tr>
<td>2.30–3.20</td>
<td>0.9 (0.8–1.2)</td>
<td>1.0 (0.8–1.3)</td>
</tr>
<tr>
<td>3.21–4.20</td>
<td>0.9 (0.7–1.2)</td>
<td>1.0 (0.8–1.3)</td>
</tr>
<tr>
<td>&gt; 4.20</td>
<td>1.4 (1.1–1.8)*</td>
<td>1.6 (1.2–2.1)**</td>
</tr>
</tbody>
</table>

*Adjusted for age, physical activity and serum calcium in the case of PTH; adjusted for age, physical activity and serum PTH in the case of calcium.

*P < 0.05, **P < 0.001.
Our study has some shortcomings. First of all, the food-frequency questionnaire used by us had a limited number of questions regarding calcium intake, and the calculated intake is obviously an underestimation. Furthermore, calcium supplementation was coded as a categorical variable and thus the difference between codes was assumed to be similar, which probably was not the case for all subjects. In addition, we did not have the opportunity to adjust our data for total caloric intake, and the effects of calcium and vitamin D intake on BMI should therefore be treated with caution.

In conclusion, we have found serum PTH to be a highly significant predictor of obesity in our statistical model. In order to infer cause-and-effect relations, intervention studies with calcium and/or vitamin D supplementation to lower serum PTH in obese subjects, with weight loss as the primary end point, should be undertaken.

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References


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