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# Fat mass is an important predictor of parathyroid hormone levels in postmenopausal women

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**Abstract**

Previously, we reported that people with elevated parathyroid hormone (PTH) levels due to primary hyperparathyroidism have increased body weight compared to eucalcemic controls. We sought to determine whether the same relationship between PTH and body weight exists in eucalcemic healthy postmenopausal women, and to investigate the relationships between components of body weight, PTH, vitamin D metabolites, and metabolic indices.

We performed a cross-sectional analysis of 116 healthy community-dwelling postmenopausal women. Pearson correlation analysis was used to test for univariate linear relationships between variables, and stepwise multiple regression analysis to assess for multivariate relationships.

We found that PTH was significantly positively correlated with body weight, regional and total fat mass, and percent body fat, and negatively correlated with activity levels, 25 hydroxyvitamin D (25OHD), dietary calcium intake, and serum phosphate. On multivariate analysis, PTH was positively related to percent body fat ($P = 0.020$; partial $r^2 = 0.10$) and negatively related to dietary calcium intake ($P = 0.041$; partial $r^2 = 0.03$) and serum phosphate ($P = 0.026$; partial $r^2 = 0.04$). Adjusting for vitamin D insufficiency or 25OHD levels did not affect the relationship between PTH and fat mass. For 25OHD, there were significant positive correlations with lumbar spine BMD and serum albumin, and significant negative correlations with PTH, total fat mass, trunk fat, and pelvic fat. On multivariate analysis, 25OHD was positively related to serum albumin ($P = 0.008$; partial $r^2 = 0.07$) and negatively related to pelvic fat mass ($P = 0.014$; partial $r^2 = 0.05$). Adjusting for PTH levels did not change the relationship between 25OHD and pelvic fat mass.

We conclude that fat mass is a significant independent determinant of serum PTH levels, and that this relationship is independent of the inverse relationship between 25OHD and fat mass. This association between fat mass and PTH might contribute to the association between primary hyperparathyroidism and increased body weight.


*Keywords:* Parathyroid hormone; 25 hydroxyvitamin D; Body weight; Fat mass; Vitamin D metabolites

## Introduction

Previously, we reported that postmenopausal women who had elevated parathyroid hormone (PTH) levels due to primary hyperparathyroidism (PHPT) were 9.2 kg heavier than healthy aged-matched controls [1]. The majority of this weight difference was due to increased fat mass (7.2 kg of 9.2 kg). Recently, we extended this observation in a meta-analysis of 17 studies that reported body weight in PHPT, in which we found that patients with PHPT were on average 3.3 kg heavier than age- and gender-comparable eucalcemic controls [2]. The reason for this finding is not clear, and could theoretically operate in either direction: obesity could cause PHPT or vice versa. Our previous work suggested that higher body weight precedes the development of PHPT [3]. A growing body of evidence suggests that body weight and/or fat mass are inversely related to levels of serum 25-hydroxyvitamin D (25OHD) [4–10], which in turn are important determinants of circulating levels of PTH [11,12]. We therefore hypothesized that body weight/fat mass would be positively correlated with serum PTH levels in eucalcemic subjects, and that this relationship would be mediated by vitamin D status.

Accordingly, we performed a cross-sectional analysis of data obtained in a cohort of healthy postmenopausal women, to

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determine the relationships among body weight, body composition, PTH, and vitamin D metabolites. We measured regional body composition to determine whether visceral fat (trunk and pelvic fat) was more predictive than total body fat. The results of these analyses suggest that fat mass is an important determinant of PTH and 25OHD but not 1,25-dihydroxyvitamin D [1,25$(OH)_2$D]. The relationship between fat mass and PTH appeared to be independent of the inverse association between fat mass and levels of 25OHD, and was not mediated by hypovitaminosis D.

## Methods

116 healthy postmenopausal women who were recruited for a study of the effects of hydrochlorothiazide on rates of bone mineral density (BMD) loss had a measurement of serum 25OHD. Full details of the study protocol have been published previously [13]. In brief, postmenopausal women who had not had a menstrual period in the last 5 years were recruited. Women who had undergone hysterectomy and were over the age of 55 with hormonally-confirmed postmenopausal status were also eligible. Exclusion criteria included disorders of calcium metabolism (including PHPT, Paget's disease, previously treated osteoporosis); renal, thyroid, or hepatic dysfunction; other major systemic illnesses; the use of drugs known to affect calcium metabolism including the use of calcium supplements >500 mg/day; and the use of hormone replacement therapy in the previous 12 months. Participants were not excluded if they were vitamin D deficient or used vitamin D supplements.

Approximately 1200 women responded by telephone to initial advertisements and 301 completed screening questionnaires. 199 women were eligible to participate, but 14 elected not to proceed further. Thus, 185 women consented to enter the study. A random subset of 116 of these women had serum 25OHD measured, and data from this subgroup are included in the current analyses. The study was approved by the Auckland Ethics Committee.

Height was measured at baseline using a Harpenden stadiometer, and weight was recorded using electronic scales. Activity levels were recorded using a standardized questionnaire [14]. All women supplied a fasting blood sample and second-voided urine sample. Body composition and BMD of the lumbar spine, proximal femur, and total body were measured with a dual-energy X-ray absorptiometer (DXA) (Lunar DPX-L, Madison, WI, software version 1.3y). Serum 25OHD was measured by radioimmunoassay (Incstar Corporation, Stillwater, MN). Serum 1,25$(OH)_2$D was measured by radioimmunoassay (Nichols Institute, San Juan Capistrano, CA) in a randomly selected subgroup of 54 women. Serum PTH was measured using an Allegro assay (Nichols Institute, San Juan Capistrano, CA). Fasting insulin levels were measured using an in-house radioimmunoassay, with an intraassay CV of 3.9%, and an interassay CV of 7.8%.

Insulin levels were logarithmically transformed because they were not normally distributed. Pearson correlation analysis was used to test for significant linear correlations between variables. Multivariate analysis was performed to determine the significant independent predictors of PTH, and 25OHD. Multivariate analysis was not performed for 1,25$(OH)_2$D because of the small sample size ($n$ = 54). Significance level was set at $P < 0.05$, all tests were two-tailed. Stepwise forward selection and backward elimination multiple regression analyses were performed to analyze the factors contributing most significantly to the variable of interest. Variables from Table 1 with $P < 0.25$ in univariate analysis were included in the stepwise models with PTH, or 25OHD as the dependent variables. Variables with $P < 0.05$ were retained in the model. Residuals were inspected. Models were chosen on the basis of biological plausibility and parsimony. Multiple linear regression was also used to determine the consequences of adjusting for vitamin D insufficiency and 25OHD levels. All statistical analyses were obtained using SPSS for Windows (SPSS Inc., Chicago, IL version 12.0.1) or the SAS software package (SAS Institute, Cary, NC version 9).

## Results

Descriptive and biochemical characteristics of the study population are summarized in Table 1. The subgroup of 54 women who had 1,25$(OH)_2$D measurements had similar baseline characteristics to the group as a whole (data not shown). We identified those variables that demonstrated significant correlations with PTH, 25OHD, and 1,25$(OH)_2$D using Pearson correlation analysis. These correlations are presented in Table 2.

Table 1
Descriptive and biochemical characteristics of the study population

| $n$ = 116 | Mean (SD) | Range |
|---|---|---|
| Age (years) | 62.6 (5.9) | 46–89 |
| Height (cm) | 162 (5.4) | 150–177 |
| Weight (kg) | 67.4 (11.5) | 44–110 |
| Fat mass (kg) | 27.3 (9.0) | 8.0–56.1 |
| Lean mass (kg) | 36.7 (3.6) | 29.9–46.2 |
| Percent body fat (%) | 41.7 (7.3) | 18–59 |
| Albumin-adjusted serum calcium (mmol/L) | 2.27 (0.07) | 2.11–2.47 |
| Serum PTH (pmol/L) | 2.7 (1.2) | 1.0–7.6 |
| Serum 25OHD (nmol/L) | 54 (22) | 12–115 |
| 25OHD < 25 nmol/L | 7% | |
| 25OHD < 50 nmol/L | 47% | |
| Serum 1,25$(OH)_2$D (pg/mL) [a] | 36 (9) | 10–60 |
| Dietary calcium intake (mg/24 h) | 1050 (540) | 248–2948 |
| Fasting serum insulin (mU/L) | 7.7 (6.4) | 0.8–51 |
| Fasting serum glucose (mmol/L) | 5.0 (1.1) | 3.3–13.5 |
| Serum albumin (g/L) | 44 (2) | 37–49 |
| Alkaline phosphatase (U/L) | 79 (18) | 40–137 |
| Total body bone mineral content (kg) | 2.2 (0.29) | 1.47–2.95 |
| *Bone mineral density (g/cm$^2$)* | | |
| L2–L4 | 1.06 (0.15) | 0.66–1.63 |
| Femoral neck | 0.85 (0.12) | 0.55–1.21 |
| Total body | 1.05 (0.08) | 0.91–1.21 |

[a] Serum 1,25-dihydroxyvitamin D was measured in a random subset of 54 women.

PTH was significantly positively correlated with body weight, regional and total fat mass, and percent body fat. The relationship between PTH and total fat mass is shown in Fig. 1. There were significant negative correlations of PTH with activity levels, 25OHD, dietary calcium intake, and serum phosphate. For 25OHD, there were significant positive correlations with lumbar spine BMD and serum albumin, and significant negative correlations with PTH, total fat mass, trunk fat, and pelvic fat. For 1,25$(OH)_2$D, significant positive correlations were observed with 24-h urine calcium and alkaline phosphatase, and a significant negative correlation with height. There were no significant correlations with PTH ($r$ = 0.14, $P$ = 0.31) or serum phosphate ($r$ = −0.18, $P$ = 0.20).

In order to determine whether the relationship between PTH and fat mass is dependent on the presence of vitamin D insufficiency (25OHD < 50 nmol/L as recommended by a recent WHO report [15]), we created a model with PTH as the dependent variable, and fat mass and a coded variable representing the presence or absence of vitamin D insufficiency as the explanatory variables. Using this model, there was no change in the relationship between PTH and fat mass after adjusting for the presence of vitamin D insufficiency (for model of PTH and fat mass, $r^2$ = 0.06, $P$ = 0.007; for model of PTH, fat mass, and vitamin D insufficiency, $r^2$ = 0.07, fat mass, $P$ = 0.015; vitamin D insufficiency, $P$ = 0.36). We used a similar