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ORIGINAL ARTICLE

The association of adiposity with parathyroid hormone in healthy older adults

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Abstract Elevated parathyroid hormone (PTH) is a risk factor for increased morbidity and mortality. PTH levels increase with adiposity in older adults but the basis for this association is unclear. The objective of this study was to examine the association of percent body fat (%Fat) with serum PTH in 307 older men and women and to determine the extent to which it may be explained by vitamin D status, bone turnover, calcium metabolism, and glucose homeostasis. The data are from the baseline visit of a clinical trial of calcium and vitamin D to prevent bone loss. %Fat was measured by dual-energy X-ray absorptiometry and fasting blood and urine samples were collected. Serum PTH levels increased by about 0.4 pmol/l per 10 unit increase in percent body fat ($P = 0.003$). The variables that we examined, including plasma 25-hydroxyvitamin D and serum osteocalcin, calcium, phosphorus, and insulin explained only a small proportion of this association (18%). Further work is needed to identify the mediators of the higher PTH levels in subjects with greater adiposity. This is important in view of worldwide increases in overweight and obesity and the potential contribution of elevated PTH to morbidity and mortality.

Keywords Body fat · Parathyroid hormone · Bone turnover · Calcium binding · Insulin · Glucose

Introduction

Elevated parathyroid hormone (PTH) is a major risk factor for cardiovascular disease [1–5] and mortality [6–8] in patients with chronic kidney disease. Higher PTH levels may also increase the risks for hypertension [9], metabolic syndrome [10], and mortality [11] in healthy older adults. Recent results from the Health Professionals Follow-Up Study suggest that, even within the normal range, higher PTH values are predictive of incident hypertension over a ten-year period [12]. Many factors including parathyroid gland disease, dietary calcium, and vitamin D status influence PTH secretion, and increased body fat may also do so. Body size and adiposity have been positively associated with PTH in generally healthy older adults [13–17], and fat tissue appears to be the compartment of weight that is most closely related to PTH in this group [14]. This association has been interpreted by some as an indicator that elevated PTH causes weight gain [18] and by others that obesity raises PTH [13]; these two possibilities are not mutually exclusive. Elevated PTH may promote weight gain by inhibiting lipolysis [19] and promoting insulin resistance [20]. At the same time, higher adiposity may increase PTH by lowering 25-hydroxyvitamin D [25(OH)D], perhaps through sequestration of vitamin D in fat tissue [21]. The best evidence that obesity *can* influence PTH comes from weight loss studies in which children [22] and adults [23] who lost weight through diet and exercise had decreases in PTH that were correlated with the amount of weight lost. Weight loss resulting from bariatric surgery has been associated with *increased* PTH but this can be attributed to

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the reduced absorption of calcium and vitamin D that result from the procedure [24].

Although poor vitamin D status may explain some of the association between obesity and PTH, it appears not to be the only factor to do so because the association persists after adjustment for 25(OH)D [13, 14]. The objective of this analysis is to examine additional factors that may explain the association of adiposity with PTH in generally healthy older adults. One potential explanatory factor is reduced bone turnover. In many [25–27] though not all [17] studies, subjects with more fat mass have lower levels of biochemical markers of bone turnover including carboxy-terminal propeptide of type I procollagen and osteocalcin. In the setting of an adiposity-mediated reduction in bone turnover, the influx of calcium from bone into the circulation would be reduced, and a higher ambient PTH concentration might be required to maintain a given circulating ionized calcium concentration. A second way that adiposity could increase PTH is by altering calcium complexing and/or protein binding. Andersen et al. [28] reported that morbid obesity was associated with alterations in calcium complexing anions that resulted in reduced tubular reabsorption of calcium and reduced serum ionized calcium. Adiposity may also influence PTH via effects of free fatty acids on protein binding of calcium [29]. In support of this, Lind et al. [30] observed a positive association of the ratio of total to ionized calcium with body mass index in healthy older adults. Finally, adiposity could increase PTH by increasing serum insulin, fasting glucose, or insulin resistance. Among patients with type 2 diabetes, hyperglycemia causes increased excretion of calcium and phosphorus and an increase in PTH [31]. Furthermore, experimental decreases in serum phosphorus have been shown to decrease PTH secretion independently of the serum calcium concentration [32].

An understanding of intermediary variables in the association of adiposity with PTH would suggest potential approaches to preventing or treating elevated PTH and resulting morbidity among overweight and obese individuals. In this study, we investigate the association between percent body fat (%Fat) and serum PTH in generally healthy older adults and seek to determine the extent to which it is mediated by indicators of vitamin D status (25-hydroxyvitamin D), bone turnover [serum osteocalcin and urinary N-telopeptide cross-links (NTx)], mineral homeostasis (total and ionized serum calcium and their ratio and serum phosphorus), and glucose homeostasis (insulin, glucose and HOMA-IR).

Results

In preliminary analyses, we investigated the possibility that the association of %Fat with PTH might differ by sex. We did this by including a %Fat by sex interaction term in analysis of covariance (ANCOVA) models run for the pooled sample of men and women. The interaction term was not close to being statistically significant ($P = 0.760$), and subsequent analyses were therefore conducted in the pooled sample. However, given the expected and observed lower %Fat of men compared with women (27.4 ± 6.4 in men compared with 38.7 ± 6.9 in women, $P < 0.001$), all analyses in the pooled sample were adjusted for sex.

Demographic and physical characteristics of the 307 subjects are shown by %Fat tertiles in Table 1. Mean body mass index (BMI) across the tertiles (25, 26, and 29 kg/m^2, respectively) illustrate that a majority of the study participants were overweight (BMI 25.0–29.9) rather than normal-weight or obese (Table 1). Age and calcium intake did not differ significantly across the %Fat tertiles but were adjusted for in subsequent analyses because of their associations with PTH ($r = 0.17$, $P = 0.003$ for age; $r = -0.16$, $P = 0.006$ for calcium intake).

Mean laboratory values are shown by %Fat tertiles in Table 2 and their correlations with %Fat as a continuous variable and with PTH are shown in Table 3. Mean PTH in the highest tertile of %Fat (4.4 ± 0.2) was about 18% higher than that in the lowest tertile and well within the normal range (1.1–6.9 pmol/l). Although the differences in PTH across %Fat tertiles were only marginally significant

Table 1 Demographic and physical characteristics (mean ± SD or %) of the 307 subjects by tertiles of percent body fat

	% Body fat tertile			
	Lowest	Middle	Highest	*P*
N	103	102	102	
Female (%)	16.5	50.0	97.1	<0.001
Body fat (%)	24.0 ± 4.5	33.8 ± 2.3	43.2 ± 3.7	<0.001
BMI (kg/m^2)	24.8 ± 2.8	26.2 ± 3.5	29.2 ± 4.1	<0.001
Height (cm)	170 ± 9	168 ± 10	159 ± 7	<0.001
Weight (kg)	72.6 ± 12.4	74.5 ± 16.9	73.6 ± 11.3	0.572
Age (year)	71.5 ± 5.3	71.0 ± 4.3	70.4 ± 3.9	0.204
Calcium intake (mg per day)	760 ± 361	767 ± 366	737 ± 351	0.222

Table 2 Laboratory values (mean ± SEM) in the 307 subjects by tertiles of percent body fat, adjusted for sex, age, and calcium intake

	% Body fat tertile			
	Lowest	Middle	Highest	*P*
Serum intact PTH (pmol/l)	3.69 ± 0.18	3.99 ± 0.16	4.36 ± 0.20	0.099
Plasma 25(OH)D (nmol/l)	79.9 ± 3.7	81.2 ± 3.3	68.5 ± 4.1	0.054
Serum osteocalcin (nmol/l)	1.16 ± 0.04	1.10 ± 0.03	0.98 ± 0.04	0.011
Urine NTX (nmol BCE/24 h)	219 ± 15	221 ± 13	212 ± 16	0.909
Serum insulin (pmol/l)	28.0 ± 3.1	51.4 ± 2.8	63.3 ± 3.5	<0.001
Plasma glucose (mmol/l)	5.19 ± 0.08	5.57 ± 0.07	5.68 ± 0.08	<0.001
HOMA-IR	0.88 ± 0.13	1.84 ± 0.11	2.31 ± 0.14	<0.001
Serum phosphorus	1.04 ± 0.01	1.02 ± 0.01	0.98 ± 0.02	0.036
Serum total calcium (mmol/l)	2.27 ± 0.01	2.26 ± 0.01	2.24 ± 0.01	0.129
Serum ionized calcium (mmol/l)	1.264 ± 0.004	1.259 ± 0.004	1.246 ± 0.005	0.036
Ratio of total to ionized calcium	1.797 ± 0.005	1.798 ± 0.004	1.801 ± 0.005	0.894
Urine calcium (mmol/24 h)	3.24 ± 0.19	3.13 ± 0.17	3.29 ± 0.21	0.803

Table 3 Partial correlations of laboratory variables with PTH and %Fat, adjusted for sex, age, and calcium intake in 307 subjects

	PTH		%Fat	
	r	*P*	*r*	*P*
Serum intact PTH (pmol/l)	–	–	0.17	0.003
Plasma 25(OH)D (nmol/l)	−0.25[a]	<0.001	−0.10	0.082
Serum osteocalcin (nmol/l)	0.12	0.037	−0.21	<0.001
Urine NTX (nmol BCE/24 h)	−0.04	0.530	−0.02	0.761
Serum insulin (pmol/l)	0.09	0.121	0.41	<0.001
Plasma glucose (mmol/l)	0.08	0.184	0.24	<0.001
HOMA-IR	0.09	0.125	0.41	<0.001
Serum phosphorus (mmol/l)	−0.17	0.003	−0.17	0.003
Serum total calcium (mmol/l)	−0.07	0.239	−0.13	0.023
Serum ionized calcium (mmol/l)	−0.08	0.151	−0.15	0.009
Ratio of total to ionized calcium	0.02	0.784	0.01	0.809
Urine calcium (mmol/24 hr)	−0.10	0.091	−0.02	0.794

[a] After log–log transformation, $r = -0.27$, $P = 0.019$

($P = 0.099$), the correlation of PTH with %Fat as a continuous variable was highly significant (Table 3). The inverse correlation of 25(OH)D with PTH was highly significant both before and after log–log transformation (Table 3) but 25(OH)D was only marginally correlated with %Fat. Serum osteocalcin, a marker of bone formation, was positively correlated with PTH and inversely correlated with %Fat, but urinary NTx, a marker of bone resorption, was not correlated with either %Fat or PTH. Serum phosphorus was inversely correlated with both PTH and %Fat. Except for urinary calcium excretion and the ratio of total to ionized serum calcium, which were not correlated with PTH or %Fat, the remaining potential explanatory variables were positively (insulin, glucose, and HOMA-IR) or inversely (serum total calcium) correlated only with %Fat. In further analyses, we noted that serum osteocalcin was positively correlated with both total ($r = 0.18$, $P = 0.001$) and ionized ($r = 0.13$, $P = 0.029$) serum calcium after adjustment for age, sex, and calcium intake.

Whether or not selected laboratory variables "explained" the association of PTH with %Fat was examined by including them as covariates in ANCOVA models in which PTH was the dependent variable, %Fat was the primary independent variable, and sex, age, and calcium intake were adjusted for (Table 4). The potential explanatory variables that we examined included those that had at least a small correlation with both PTH and %Fat (i.e., $r = 0.08$–0.09), regardless of the statistical significance of the association. For groups of highly collinear variables (osteocalcin and NTX; insulin, glucose, and

Table 4 Regression coefficients (*B*) for body fat (%) as a predictor of PTH (pmol/l), *P* for the coefficients and R^2 for the models in 307 subjects

	B	*P*	R^2
Unadjusted	0.026	0.016	0.016
Adjusted for:			
Age, sex, calcium intake	0.043	0.003	0.078
Age, sex, calcium intake, 25(OH)D[a]	0.037	0.009	0.129
Age, sex, calcium intake, osteocalcin	0.052	<0.001	0.102
Age, sex, calcium intake, serum Ca++	0.041	0.005	0.081
Age, sex, calcium intake, serum phosphorus	0.037	0.011	0.097
Age, sex, calcium intake, insulin	0.041	0.011	0.078
All the above[b]	0.035	0.025	0.178

[a] After log–log transformation, $P = 0.012$, $R^2 = 0.140$

[b] In men only, $B = 0.042$, $P = 0.112$, $R^2 = 0.211$; in women only, $B = 0.0.021$, $P = 0.284$, $R^2 = 0.175$

HOMA-IR; total and ionized calcium), we selected the one variable that was most highly correlated with PTH and %Fat. The inclusion of each potential explanatory variable changed the coefficients for %Fat modestly, but these variables, even when included together, explained only a small amount of the variability in PTH ($R^2 = 0.18$ for fully adjusted model). The R^2 values were also low in men (0.21) and women (0.18) when these groups were examined separately (Table 4 footnote b).

Discussion

In this study of predominantly overweight but generally healthy older adults, a 10 unit higher percent body fat was associated with about a 0.4 pmol/l higher serum PTH level after adjustment for age, sex, and calcium intake. Given a normal range for PTH of about 1–7 pmol/l, this difference may be clinically meaningful. The size of this association is comparable to that reported by Snijder in a large cohort of generally healthy older Swedish adults who also had %Fat measured by dual energy X-ray absorptiometry (DXA) [16] and in whom modestly higher PTH was associated with an increased prevalence of hypertension [9].

As has also been reported by others [13, 14], the association of PTH with %Fat was largely independent of the plasma 25(OH)D level. These findings make it unlikely that current low vitamin D status in more adipose individuals is the sole explanation for their higher PTH levels. We cannot rule out the possibility that effects of long-term adiposity on vitamin D status may have had persistent effects on PTH levels. Chronic vitamin D deficiency contributes to parathyroid gland enlargement and commensurate increases in PTH secretion [33], and the gland may remain enlarged even after correction of vitamin D deficiency [34]. Modestly increased bone turnover also does not appear to explain the association of %Fat with PTH. Although, higher serum osteocalcin was associated with somewhat higher serum calcium, neither higher osteocalcin nor higher serum calcium explained the higher PTH in more adipose subjects. Higher PTH among more adipose subjects also does not appear to be explained by a difference in calcium binding since serum total and ionized calcium and their ratio were not correlated with PTH. In agreement with Lind et al. who studied generally healthy Swedish adults, ionized calcium was inversely correlated with adiposity, but in contrast to their findings, the ratio of total to ionized calcium was not associated with adiposity [30]. Finally, although we observed expected associations of adiposity with increased glucose and insulin, these measures did not explain the association of adiposity with PTH either via effects on serum calcium and phosphorus or independently of them.

In conclusion, this study demonstrates a positive association of increased adiposity with serum PTH in a generally healthy cohort of older American adults. Our study examined several potential mechanisms that might explain this association but failed to identify any of them as important. These negative findings are unlikely to result from inadequate statistical power because partial correlations as small as 0.12 were statistically significant in this data set. Although each of the variables we examined may play a small role in the association of adiposity with PTH, the association remains largely unexplained. Thus further work is needed to identify the mediators of higher PTH levels in subjects with greater adiposity. This will be important in view of worldwide increases in overweight and obesity and the potential contribution of elevated PTH to morbidity and mortality.

Materials and methods

Study design and subjects

The data used in this analysis are from the baseline visit of a 3-year randomized, controlled trial that investigated the effect of supplementation with calcium and vitamin D on bone mineral density and fracture incidence in predominantly Caucasian older men and women (STOP/IT) [35]. Subjects stopped taking their own calcium supplements at least 3 weeks before the baseline measurements. A total of 445 healthy men and women age 65 and older were enrolled in the study. The study was approved by the Institutional Review Board at Tufts University and all subjects provided written informed consent to participate. Exclusion criteria included hyperparathyroidism, 24-h urine calcium >7.49 mmol for women and >8.73 mmol for men, current cancer, kidney or liver disease, low bone mineral density (>2 standard deviations below the age-matched reference mean), dietary calcium intake greater than 37.4 mmol per day, and use of medications known to affect calcium metabolism. Subjects were excluded from the present analysis if they used diuretics ($n = 53$), were missing measurements of insulin and glucose which were measured only in subjects who completed the trial ($n = 74$), were missing another key laboratory measurement ($n = 7$), or had extreme outlying values for key laboratory measurements ($n = 4$, see "Statistical analysis" section below).

Measurements

Blood was drawn between 0700 and 0930 after an overnight fast, and urine measurements were made in 24-h collections. Serum PTH was measured by immunometric

assay (Nichols Institute, San Juan Capistrano, CA) and has a normal range of 1.05 to 7.27 pmol/l. PTH values in pmol/l can be converted to pg/ml by multiplying the former by 0.1053. Serum total calcium and serum phosphorus were measured on a clinical chemistry analyzer (Cobas Mira, Roche Diagnostic Systems, Inc., Montclair, NJ) according to the company's standard operating procedures. Serum ionized calcium was measured with a Nova 7 Analyzer (Nova Biomedical, Newton, MA). Urine calcium was measured by direct current plasma emission spectroscopy with the Specta Span 6 Emission Spectrometer (Beckman Instruments, Fullerton, CA). Plasma 25(OH)D was measured by the method of Chen et al. [36]. Serum osteocalcin was measured by immunoradiometric assay (Nichols Institute). Urinary N-telopeptide cross-links (NTx) was measured by enzyme-linked immunosorbent assay (Ostex International, Seattle, WA). Serum insulin was measured by radioimmunoassay commercial kit [DPC Coat-A-Count Insulin assay (Diagnostic Products, Los Angeles, CA)]. Plasma glucose was measured by an oxygen rate method using the Beckman Synchron LX System (Beckman Coulter, Fullerton, CA). The homeostasis model assessment of insulin resistance (HOMA-IR) was calculated as glucose (mmol/l) × insulin (mU/l)/22.5 [37]. Height was measured with a wall-mounted Harpenden stadiometer and weight was measured with a digital scale. %Fat was calculated from total body scans made by dual-energy X-ray absorptiometry on a DPX-L scanner (Lunar Radiation, Madison, WI). The coefficient of variation of fat mass in our laboratory is 0.94 [38]. Calcium intake was estimated with a food frequency questionnaire [39].

Statistical analysis

Analyses were conducted with SPSS version 15.0 (Chicago, IL). Data were reviewed graphically for evidence of outliers, non-normality, and non-linearity. As a result of this review, data for four individuals with extreme values of PTH ($N = 1$), glucose ($N = 2$), and NTx ($N = 1$) were set aside resulting in a final sample size of 307 subjects. Also as a result of the graphical review, we performed log–log transformations to correct mild nonlinearity in the association of PTH with 25(OH)D. We investigated %Fat as a continuous variable and also created tertiles of %Fat in order to illustrate subject characteristics and PTH levels with increasing adiposity. Partial correlations and analysis of covariance (ANCOVA) were used to describe linear associations between continuous variables and to compute adjusted means across %Fat tertiles. ANCOVA examines the effect of certain variables (e.g. %Fat as a continuous variable and tertiles of %Fat) on continuous outcome variables (e.g., PTH) after removing the variance for which quantitative predictors (e.g. sex, age, and calcium intake) account. Two-tailed P-values < 0.05 were considered to indicate statistical significance.

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