ORIGINAL ARTICLE

Parathyroid hormone reflects adiposity and cardiometabolic indices but not bone density in normal men

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Hyperparathyroidism may be associated with skeletal and cardiovascular abnormalities, but it is unclear whether these associations exist for high-normal levels of parathyroid hormone (PTH). We assessed relationships between PTH and anthropometric, skeletal and cardiometabolic indices in normal men. Body composition, blood pressure, biochemistry and bone mineral density (BMD) were evaluated in 151 healthy men. BMD was reassessed at 2 years, and coronary artery calcium (CAC) was measured at 3.5 years. Relationships between PTH and other baseline characteristics, CAC scores and change in BMD were evaluated. PTH correlated positively with baseline body mass index, fat mass, diastolic blood pressure, triglycerides, total and low-density lipoprotein (LDL) cholesterol, ($r = 0.19\text{--}0.25$, $P = 0.02\text{--}0.002$), and with category of CAC score. Relationships between PTH and cardiometabolic indices remained significant after adjustment for age, 25-hydroxyvitamin D and estimated glomerular filtration rate. Men in the top PTH tertile ($\geq 4.4 \text{ pmol l}^{-1}$, $n = 51$) were more likely to have LDL cholesterol $\geq 3.5 \text{ mmol l}^{-1}$, diastolic blood pressure $\geq 85 \text{ mm Hg}$, and CAC score > 0 than men in lower tertiles. PTH was not associated with history of fracture, baseline BMD, or change in BMD over 2 years. In summary, in this cohort of healthy men, PTH levels are linearly related to adiposity and to cardiometabolic indices, but not to BMD or bone loss. These findings suggest that adiposity should be considered as an independent cause of secondary hyperparathyroidism, and they may be relevant to patients with normocalcemic hyperparathyroidism, in whom high PTH levels may be a marker of adiposity and cardiometabolic risk rather than always indicating parathyroid autonomy.

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Introduction

Hyperparathyroidism, resulting from either autonomous parathyroid hyperfunction or a secondary stimulus of parathyroid hormone (PTH) production, is a common endocrine problem. Potential consequences of PTH excess include accelerated bone loss and fragility fracture, nephrolithiasis, renal impairment, increased cardiovascular risk, and in the setting of primary hyperparathyroidism, symptomatic hypercalcemia.¹ Vitamin D deficiency, renal dysfunction, hypercalciuria, malabsorption and the use of medications (for example, lithium) are recognized causes of secondary hyperparathyroidism.² Although not typically considered causes of secondary hyperparathyroidism, characteristics such as age, fat mass and blood pressure have previously been

shown to be independently associated with circulating PTH concentrations.^{3–5} These variables may have a role in determining an individual's PTH level.

The determinants of PTH become particularly important when considering the entity of normocalcemic hyperparathyroidism.^{6–8} This condition is characterized by persistent PTH elevation in the absence of hypercalcemia or recognized causes of secondary hyperparathyroidism. It is unusual to define a disease in terms of levels of a single analyte, and doing so implies that up to 2.5% of the population might have this condition. Furthermore, there is disagreement about where the upper limit of the PTH reference range should lie, particularly in individuals without vitamin D deficiency or renal dysfunction.⁹ It has been suggested that normocalcemic

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hyperparathyroidism represents an early, subclinical form of primary hyperparathyroidism, and that affected individuals are at risk of developing skeletal, cardiovascular and renal consequences, and of becoming hypercalcemic.^{6,8} This notion is supported by some case series, in which up to 50% of patients have osteoporosis, ~10% have nephrolithiasis, and up to 40% demonstrate disease progression.^{6–8,10} Cardiovascular outcomes in normocalcemic hyperparathyroidism have not been well studied, but some reports suggest that these individuals have an elevated risk of hypertension and cardiovascular disease, similar to what has been observed in primary hyperparathyroidism.^{11,12} Several patients from these cohorts have undergone parathyroidectomy and have been found to have either parathyroid adenomas or hyperplasia.^{6–8,10} However, many of these individuals came to attention following referral for investigation of problems such as osteoporosis, raising the possibility that referral bias may account for the high prevalence of pathology reported.^{6–8} Conversely, in other reports, no association between normocalcemic hyperparathyroidism and adverse skeletal or renal outcomes has been identified, and there has been no evidence of progression to hypercalcemic hyperparathyroidism.^{13–15} Thus, it is unclear whether normocalcemic hyperparathyroidism is a discrete pathological entity with real associated morbidity, and there is currently no consensus regarding its management.¹

It is not clear whether the deleterious associations of PTH that have been documented in some cohorts with normocalcemic hyperparathyroidism manifest because PTH exceeds a certain 'cut point', or whether the disease associations are linear. In the present investigation, we have identified a cohort of healthy men, free of referral bias and assessed relationships between serum PTH and specific pathologies (skeletal and cardiometabolic), with a view to determine whether these pathologies are associated with high-normal PTH levels.

Results

Baseline characteristics and PTH correlations

Table 1 sets out the baseline characteristics of the study population and their correlations with PTH. PTH was positively related to body mass index (BMI), fat mass, diastolic blood pressure, triglycerides, total and low-density lipoprotein (LDL) cholesterol, and was inversely associated with dietary calcium intake, 25-hydroxyvitamin D and urinary calcium excretion. The significant correlations between PTH and baseline cardiometabolic indices are illustrated in **Figure 1**. After adjustment for age, 25-hydroxyvitamin D and estimated glomerular filtration rate (eGFR) in a linear regression model with PTH as the dependent variable, PTH remained significantly

Table 1 Baseline characteristics of men ($n = 151$) and Pearson's correlation with parathyroid hormone (PTH) levels

Characteristic	Mean (s.d.)/n (%)	Range	Correlation with PTH (r)	P-value for correlation
Age (y)	58.0 (10.2)	41.6–88.0	0.13	0.12
Height (cm)	176.6 (6.6)	159.8–191.6	–0.15	0.07
Weight (kg)	82.3 (10.7)	62.6–123.3	0.12	0.14
BMI (kg m^{-2})	26.4 (2.9)	19.8–38.2	0.24	0.004
Total body fat mass (kg)	19.3 (6.9)	4.9–42.4	0.23	0.005
Total body lean mass (kg)	59.0 (6.6)	45.5–76.1	–0.05	0.57
Systolic blood pressure (mm Hg)	132 (14)	98–169	0.16	0.05
Diastolic blood pressure (mm Hg)	79 (8)	58–106	0.22	0.006
Dietary calcium intake (mg per day)	854 (413)	179–2338	– 0.19	0.02
Physical activity (MJ per day)	32.2 (5.5)	25.9–56.6	–0.14	0.11
History of smoking (n, %)	69 (46%)			
Current smoker (n, %)	6 (4%)			
Previous fractures ≥ 40 years (n, %)	12 (8%)			
Anti-hypertensive medication (n, %)	14 (9%)			
PTH (pmol l^{-1})	4.1 (1.3)	1.8–8.5		
Albumin-adjusted calcium (mmol l^{-1})	2.33 (0.09)	2.10–2.59	0.11	0.18
25-hydroxyvitamin D (nmol l^{-1})	91.3 (33.6)	33.0–256.0	– 0.23	0.004
Phosphate (mmol l^{-1})	1.01 (0.13)	0.70–1.40	–0.08	0.31
eGFR ($\text{ml min}^{-1} 1.73 \text{ m}^{-2}$)	73.3 (11.3)	51.7–111.9	–0.09	0.25
P1NP ($\mu\text{g l}^{-1}$)	39.1 (15.2)	14.0–140.0	–0.10	0.23
Urinary calcium excretion (mmol l^{-1})	2.05 (1.80)	0.10–9.80	– 0.18	0.03
Fasting blood glucose (mmol l^{-1})	5.0 (0.5)	4.1–6.9	0.13	0.11
Triglycerides (mmol l^{-1})	1.31 (0.66)	0.50–3.60	0.19	0.02
Total cholesterol (mmol l^{-1})	5.61 (0.82)	3.40–7.50	0.25	0.002
HDL cholesterol (mmol l^{-1})	1.46 (0.35)	0.80–2.70	–0.05	0.54
LDL cholesterol (mmol l^{-1})	3.55 (0.72)	1.60–5.30	0.23	0.005
Total body BMD (g cm^{-2})	1.26 (0.08)	1.08–1.51	0.05	0.58
Lumbar spine BMD (g cm^{-2})	1.26 (0.15)	0.92–1.69	0.10	0.24
Total hip BMD (g cm^{-2})	1.08 (0.13)	0.83–1.36	0.07	0.37
Femoral neck BMD (g cm^{-2})	1.01 (0.13)	0.72–1.35	0.00	0.97
Bilateral arm BMD (g cm^{-2})	0.99 (0.07)	0.83–1.22	0.06	0.44
Bilateral leg BMD (g cm^{-2})	1.45 (0.11)	1.14–1.80	–0.05	0.54

Abbreviations: BMI, body mass index; BMD, bone mineral density; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low-density lipoprotein; P1NP, procollagen type 1 N-terminal propeptide.

Laboratory reference ranges for biochemical parameters: PTH 1.7–7.3 pmol l^{-1} , total calcium 2.10–2.55 mmol l^{-1} , 25-hydroxyvitamin D 50–150 nmol l^{-1} , phosphate 0.7–1.5 mmol l^{-1} , P1NP 20–85 $\mu\text{g l}^{-1}$, urinary calcium excretion 2.5–7.5 mmol per day , fasting blood glucose 3.5–5.4 mmol l^{-1} , triglycerides <2.0 mmol l^{-1} , total cholesterol <5.0 mmol l^{-1} , HDL cholesterol >1.0 mmol l^{-1} , LDL cholesterol <3.4 mmol l^{-1} .

Bolded entries indicate statistically significant correlations with PTH.

Figure 1 Correlations between serum parathyroid hormone (PTH) and cardiometabolic risk factors. *r*, Pearson correlation coefficient; BMI, body mass index.

associated with BMI ($P = 0.005$), fat mass ($P = 0.004$) diastolic blood pressure ($P = 0.006$), triglycerides ($P = 0.03$), LDL cholesterol ($P = 0.004$), and dietary calcium intake ($P = 0.02$). Because adiposity is known to influence blood pressure and lipid levels, we further adjusted the relationships between PTH and diastolic blood pressure, triglycerides, total and LDL cholesterol for fat mass. Following this adjustment, PTH remained significantly associated with LDL ($P = 0.01$) and total cholesterol ($P = 0.004$), the relationship with diastolic blood pressure was attenuated ($P = 0.04$), and the association with triglycerides was no longer significant ($P = 0.23$).

Relationship between PTH and coronary artery calcium

The 86 patients who had CAC scores assessed were divided into clinically relevant categories based on whether their CAC score was 0 ($n = 22$), 1–100 ($n = 38$) or > 100 ($n = 26$). Mean PTH, by CAC score category, is shown in **Figure 2**. There were significant differences in mean PTH between CAC score groups ($P = 0.002$, analysis of covariance (ANCOVA) adjusted for treatment group). Men with CAC score > 100 had significantly higher baseline PTH levels than men with a CAC score of 0 (4.4 pmol l^{-1} vs 3.2 pmol l^{-1} ; $P = 0.001$, *post hoc* Tukey's test). PTH and CAC score category were linearly related ($P = 0.0005$, linear contrasts). These results remained significant after adjustment for fat mass, age, 25-hydroxyvitamin D and eGFR ($P = 0.02$ for difference between CAC score categories and $P = 0.008$ for linear contrasts).

Figure 2 Relationship between serum parathyroid hormone (PTH) level and coronary artery calcium (CAC) score. CAC score categories are shown on the x-axis, where a score of 0 indicates low cardiovascular risk. PTH values are means and error bars represent 95% confidence intervals. $P = 0.0005$ for linear trend (ANOVA, linear contrasts).

Comparison of cohort characteristics among PTH tertiles

Anthropometric and cardiometabolic indices are compared across PTH tertiles in **Table 2**. BMI, fat mass, blood pressure, fasting blood glucose and total cholesterol levels were significantly increased in the top PTH tertile. After adjusting for age, 25-hydroxyvitamin D and eGFR, systolic blood pressure and

Table 2 Comparison of cardiometabolic indices and bone mineral density according to parathyroid hormone (PTH) tertile

Variable	Lowest tertile (n=51)	Middle tertile (n=49)	Highest Tertile (n=51)	Unadjusted P-value ^a	Adjusted P-value ^b
PTH range (pmol l ⁻¹)	1.8–3.3	3.4–4.3	4.4–8.5	—	—
Age (years)	56.2 (10.3)	57.3 (9.8)	60.4 (10.3)	0.11	—
25-OHD (nmol l ⁻¹)	98.3 (33.0)	95.0 (38.5)	80.7 (26.5)	0.02	—
BMI (kg m ⁻²)	26.0 (2.6)	25.7 (2.7)	27.4 (3.2)	0.01^c	0.002^{c,d}
Fat mass (kg)	18.7 (6.7)	17.9 (6.1)	21.4 (7.4)	0.02^c	0.03^c
SBP (mm Hg)	131 (12)	129 (14)	136 (14)	0.04^c	0.16
DBP (mm Hg)	77 (7)	78 (7)	81 (10)	0.02^d	0.02^d
eGFR (ml min ⁻¹ 1.73 m ⁻²)	74.9 (12.0)	74.4 (12.0)	70.5 (9.5)	0.10	—
Blood glucose (mmol l ⁻¹)	4.98 (0.43)	4.94 (0.42)	5.19 (0.56)	0.02^c	0.04^c
Triglycerides (mmol l ⁻¹)	1.22 (0.67)	1.35 (0.71)	1.37 (0.59)	0.47	0.57
Total cholesterol (mmol l ⁻¹)	5.36 (0.79)	5.51 (0.80)	5.85 (0.82)	0.03^d	0.05
LDL cholesterol (mmol l ⁻¹)	3.43 (0.72)	3.48 (0.67)	3.74 (0.74)	0.07	0.09
HDL cholesterol (mmol l ⁻¹)	1.46 (0.36)	1.42 (0.30)	1.49 (0.39)	0.66	0.67
CAC score > 0 (n/N, %)	21/35 (60%)	22/29 (76%)	21/22 (95%)	0.01^d	—
Total body BMD (g cm ⁻²)	1.25 (0.08)	1.25 (0.09)	1.26 (0.08)	0.96	0.40
Lumbar spine BMD (g cm ⁻²)	1.25 (0.15)	1.25 (0.15)	1.27 (0.14)	0.69	0.41
Total hip BMD (g cm ⁻²)	1.08 (0.13)	1.07 (0.13)	1.09 (0.13)	0.78	0.31
Femoral neck BMD (g cm ⁻²)	1.01 (0.13)	1.01 (0.14)	1.00 (0.13)	0.92	0.69
Bilateral arm BMD (g cm ⁻²)	0.99 (0.06)	0.99 (0.07)	0.99 (0.07)	0.98	0.36
Bilateral leg BMD (g cm ⁻²)	1.47 (0.11)	1.44 (0.12)	1.45 (0.11)	0.46	0.51

Abbreviations: BMI, body mass index; BMD, bone mineral density; CAC, coronary artery calcium; DBP, diastolic blood pressure; eGFR, estimated glomerular filtration rate; HDL, high density lipoprotein; LDL, low-density lipoprotein; SBP, systolic blood pressure; 25-OHD, 25-hydroxyvitamin D.

Variables are reported as mean (s.d.), with the exception of CAC score, which is reported as the number (percentage) of men with CAC score > 0.

^aIn unadjusted analyses, continuous variables were compared using analysis of variance (ANOVA), and CAC scores were compared using χ^2 analysis.

^bIn adjusted analyses, continuous variables were compared using analysis of covariance (ANCOVA), with age, 25-hydroxyvitamin D and estimated glomerular filtration rate included as covariates.

^cSignificant difference between top tertile and middle tertile identified using the method of Tukey's test.

^dSignificant difference between top tertile and bottom tertile identified using the method of Tukey's test.

Bold entries indicate *P*-values < 0.05.

Figure 3 Proportion of men (*n* = 151) with cardiometabolic risk factors, stratified by parathyroid hormone (PTH) level. *Denotes a significant difference between tertiles, *P* < 0.05 (Chi squared). BMI, body mass index; CAC, coronary artery calcium; DBP, diastolic blood pressure; FBG, fasting blood glucose; HDL, high-density lipoprotein cholesterol; LDL, low-density lipoprotein cholesterol; SBP, systolic blood pressure.

total cholesterol no longer differed significantly across tertiles. The prevalence of cardiometabolic risk factors was assessed using established cutoffs.^{16,17} A higher proportion of men in the top tertile had LDL cholesterol levels ≥ 3.5 mmol l⁻¹, diastolic blood pressure ≥ 85 mmol l⁻¹ and coronary artery calcium scores > 0 (Figure 3). Of the 86 men who had CAC scores assessed, CAC score was > 0 in 60% of men in the lowest PTH

tertile, 76% in the middle PTH tertile and 95% in the top PTH tertile. Of the 16 men taking anti-hypertensive medication, 1 had a PTH level in the lowest tertile, 5 had PTH levels in the middle tertile and 8 had PTH in the highest tertile (*P* = 0.06 for difference).

BMD was comparable across tertiles of PTH at all sites (Table 2). The proportion of men who had a prior fracture as age 40 was not different between tertiles (10% in the lowest tertile, 6% in the middle tertile, 8% in the highest tertile, *P* = 0.79).

Relationship between PTH and change in BMD

Correlation between baseline PTH level and change in BMD over 2 years was assessed in 50 men who had been randomized to the placebo arm of the trial. There was no association between PTH and change in BMD at the total body (*r* = -0.04, *P* = 0.79), the total hip (*r* = 0.00, *P* = 0.98), the femoral neck (*r* = 0.10, *P* = 0.49) or the spine (*r* = 0.19, *P* = 0.20).

Multivariable regression

Using stepwise multivariable linear regression, a model was constructed to examine independent determinants of PTH concentration. An *a priori* decision was made to include the following established predictors of PTH in one model: age, 25-hydroxyvitamin D, eGFR, urinary calcium excretion, dietary calcium intake. The model created using this forced selection method is shown in Table 3 and also includes BMI, total cholesterol and diastolic blood pressure as meeting the *P* < 0.15 inclusion criterion. Although eGFR was included in the model, it did not reach the *P* < 0.15 inclusion criterion. This model accounts for 26% of variation in PTH concentrations.

Stepwise regression was then repeated without mandating the inclusion of specific variables. The final model was chosen

Table 3 Multivariate regression models showing the strongest predictors of parathyroid hormone (PTH) concentration

Independent Variable	Forced variable selection ^a		Stepwise selection ^b	
	Standardized β -coefficient	P-value	Standardized β Coefficient	P-value
25-hydroxy vitamin D	−0.19	0.01	−0.24	0.002
Dietary calcium intake	0.14	0.03	−0.19	0.02
Urinary calcium excretion	−0.17	0.03	−0.17	0.03
Total cholesterol	0.23	0.003	0.19	0.02
BMI	0.21	0.009	0.14	0.08
Diastolic blood pressure	0.14	0.08	0.15	0.07
Age	0.17	0.04	—	—
eGFR	0.12	0.16	—	—

Abbreviations: BMI, body mass index; eGFR, estimated glomerular filtration rate.
^aEstablished predictors of PTH were forced *a priori* into the model. R^2 for model = 0.26, P -value for model < 0.0001.
^bThis model was determined using stepwise selection, with no variables forced into the model. R^2 for model = 0.26, P -value for model < 0.0001.

on the basis of goodness of fit and parsimony and comprised six variables: 25-hydroxyvitamin D, urinary calcium excretion, dietary calcium intake, BMI, total cholesterol and diastolic blood pressure (**Table 3**). This model also accounts for 26% of variation in PTH concentrations. There was no indication of multicollinearity on formal testing in either model. Calcium score was not included in regression analyses, as only 86 participants underwent CAC assessment.

Discussion

Results of this study, carried out in a non-referral cohort of community-dwelling men, indicate that PTH levels are not associated with BMD, and that within a healthy population, the individuals with the highest PTH levels do not experience excess bone loss over 2 years. However, our evaluation highlights important associations between PTH and BMI, fat mass, blood pressure, lipid levels and coronary artery calcification. These associations are not limited to men with the highest PTH levels. Rather, the results of this study demonstrate a continuous relationship of PTH with adiposity and cardiometabolic risk factors, indicating that adiposity should be considered as a cause of secondary hyperparathyroidism and implying that high or high-normal PTH levels might represent a marker of underlying cardiometabolic disease in some individuals.

It is possible that adiposity or related metabolic abnormalities stimulate PTH production. A number of studies have reported associations between PTH and adiposity,^{5,18} as well as other cardiovascular risk factors and mortality.^{19,20} Individuals with normocalcemic hyperparathyroidism have been shown to have increased BMI, triglycerides, LDL cholesterol and blood glucose.²¹ Our findings confirm the relationships between PTH and BMI, fat mass, blood pressure and lipid levels, and also highlight an association between PTH and coronary artery calcification that has not, to our knowledge, been previously reported. Associations between PTH and cardiometabolic risk factors were present throughout the entire cohort, indicating

that this relationship is not unique to those with the highest PTH levels. Total cholesterol, BMI and diastolic blood pressure proved to be important predictors of PTH concentration in multivariate models. Although obese individuals often have vitamin D deficiency, which drives PTH production, this has been unable to fully explain PTH variance in previous studies,²² and the associations of PTH with fat mass/BMI were independent of 25-hydroxyvitamin D in the present study.

The mechanism(s) linking these cardiometabolic indices and PTH remains uncertain. Similar to other studies that have assessed the determinants of PTH,^{4,5,23} our models were only able to explain part of the variance, pointing to other possible influences. PTH has been shown to be related to serum leptin.²² PTH levels are increased in obesity,²² and leptin levels are higher in patients with primary hyperparathyroidism,²⁴ but are not reduced by parathyroidectomy,²⁴ suggesting that PTH is not driving leptin secretion, but that possibly the reverse may be the case. PTH increases secretion of interleukin-6 and tumour necrosis factor- α ,²⁵ which are pro-inflammatory and likely to increase vascular disease. The administration of leptin to leptin-deficient mice results in three- to fivefold increases in circulating parathyroid hormone levels,^{26,27} though similar changes have not been seen in limited human studies.^{28,29} Thus, a possible pathogenic pathway would be that higher body weight, itself independently associated with hypertension and hyperlipidaemia, results in increases in PTH levels. Another potential mediator of the relationship between adiposity and PTH is fibroblast growth factor 23 (FGF23). Levels of this hormone correlate with measures of adiposity,³⁰ and there is evidence indicating that FGF23 has a complex relationship with PTH (reviewed in Blau and Collins³¹). In preclinical studies, PTH has been shown to stimulate FGF23 expression via activation of nuclear receptor-associated protein-1 (Nurr1) and also potentially through Wnt signalling. There is also evidence to suggest that FGF23 exerts an effect on PTH. Although some preclinical data suggest that FGF23 may suppress PTH production, treatment of mouse parathyroid tissue with FGF23 has been shown to increase cell proliferation and PTH secretion.³² In addition, clinical conditions of FGF23 excess, such as renal failure and tumor-induced osteomalacia, are associated with elevated circulating PTH concentration.³¹ Furthermore, in a patient with a translocation causing elevated FGF23 and increased α -klotho, hyperparathyroidism was observed, suggesting a possible stimulatory influence of FGF23 on PTH in certain clinical scenarios.³¹

With respect to the relationships that we observed between PTH and blood pressure, lipid levels and coronary artery calcification in the present study, it is possible that these associations are simply products of the relationship between PTH and adiposity. However, recent data indicate an independent and potentially bidirectional relationship between PTH and the renin-angiotensin-aldosterone system, which may explain associations between PTH and blood pressure (reviewed in ref. 33). In patients with primary hyperparathyroidism, circulating aldosterone concentrations have been observed to decrease following parathyroidectomy. On the other hand, PTH levels are elevated in persons with primary hyperaldosteronism, and have been shown to normalize following surgical or medical treatment of the hyperaldosteronism. Taken together, these data indicate the possibility of a positive feedback loop between PTH and aldosterone.³³

The direction of effect in the relationship between PTH and cardiometabolic risk factors cannot be established from these cross-sectional analyses. The existing literature is also unable to provide a definitive answer to this question, and raises the possibility of bidirectional effects. If high PTH influences the development of cardiometabolic risk, then risk factors may be expected to improve following normalization of PTH. Some prospective studies of individuals undergoing parathyroidectomy for primary hyperparathyroidism have reported improvements in blood pressure, lipids, endothelial function and left ventricular mass,^{34,35} while others have failed to demonstrate a change.^{36,37} To our knowledge, no studies have documented reductions in weight, cardiovascular events or mortality following parathyroidectomy for primary hyperparathyroidism.²¹ On the other hand, if cardiometabolic risk influences PTH, then PTH concentrations would be expected to mimic fluctuations in cardiovascular and metabolic parameters. Previous work by our group suggests that weight gain predates PTH elevation in women with primary hyperparathyroidism,³⁸ and a study in obese adolescents found that PTH decreased significantly following weight loss.³⁹ PTH levels have also been found to decrease when individuals with diabetes are treated with a thiazolidinedione or metformin, although it is not clear whether this is the direct result of improved glycemic control or mediated by the effect of the medication on bone turnover.⁴⁰ In a large longitudinal cohort study of female nurses who did not have primary hyperparathyroidism at baseline, those with hypertension were ~1.5 times more likely to develop primary hyperparathyroidism than normotensive women.⁴¹ Our findings highlight the important need for further research examining the relationship between PTH and cardiometabolic risk, and characterizing the phenotype associated with normocalcemic hyperparathyroidism.

We did not find an association between PTH and BMD or fracture history in the present cohort. Furthermore, changes in BMD over two years were unrelated to PTH. These findings are in contrast with some previous reports of people with PTH levels in the upper normal range, and persons with normocalcemic hyperparathyroidism. The prevalence of osteoporosis is high amongst individuals with normocalcemic hyperparathyroidism who were identified following referral to a metabolic bone disease clinic, exceeding 50% in some reports.^{6–8} In a non-referral population, Berger and colleagues found that community-dwelling individuals in the upper PTH reference range ($\text{PTH} \geq 5.6 \text{ pmol/l}^{-1}$) had reduced BMD at the femoral neck and total hip compared with those with lower PTH levels.⁴² In a longitudinal assessment of the Mr Os-Sweden cohort, men with baseline $\text{PTH} \geq 4.2 \text{ pmol/l}^{-1}$ experienced greater annual bone loss at the hip than men with lower PTH levels.⁴³ However, our findings corroborate the results of several other large studies, carried out in unselected populations. In another analysis of the Mr Os-Sweden cohort, BMD was comparable among men with normocalcemic hyperparathyroidism and normal controls.¹⁵ In a subgroup of the WHO MONICA study, men and women with normocalcemic hyperparathyroidism were no more likely to have had a fracture than normal individuals, and calcaneal ultrasound showed similar attenuation in both groups.¹⁴ In a cohort of women presenting for osteoporosis screening, normocalcemic hyperparathyroidism was not associated with lower BMD or increased risk of fracture.⁴⁴ The reason for these inconsistencies is unclear.

One possible explanation is that the entity of normocalcemic hyperparathyroidism actually encompasses a heterogeneous group of individuals who have the same biochemical profile but different causes and consequences.¹⁵ This group may include: (1) normal individuals whose PTH levels are within the top 2.5% of the population and therefore fall outside of the reference range, (2) individuals with parathyroid autonomy (that is, a *forme fruste* of primary hyperparathyroidism) and (3) individuals with a secondary elevation in PTH due to an unknown (but possibly cardiometabolic) stimulus.

Similar to previous reports,^{4,23} we found significant inverse associations between PTH and 25-hydroxyvitamin D, dietary calcium intake and urinary calcium excretion. Age is another established determinant of PTH,²³ and although we did not identify a significant correlation between age and PTH in bivariate analyses, the two parameters were significantly associated in our multivariate regression model, suggesting that the relationship between PTH and age is influenced by other determinants of PTH. Serum calcium concentration and renal function directly influence PTH secretion. PTH concentrations are often correlated with serum calcium and with GFR,^{4,23} although the relationship with GFR tends to be attenuated in cohorts with normal renal function.⁴ We did not identify significant associations between PTH and either of these parameters, which may be because our cohort lacked men with significant calcium aberrations or renal dysfunction. The men assessed in this study were a homogeneous and relatively healthy group. This has the advantage of limiting referral bias, which might have resulted in overestimation of skeletal consequences of high and high-normal PTH in other studies.^{6–8} However, our results are not necessarily generalizable to men with renal dysfunction, vitamin D deficiency or known vascular disease.

Conclusions

In healthy, community-dwelling men PTH levels are related to adiposity and cardiometabolic risk factors, but not associated with low BMD or rates of bone loss. These findings support the notion of PTH as a marker of cardiovascular risk, and suggest that cardiovascular risk may be elevated in normocalcemic hyperparathyroidism. While correlation does not imply causation, cardiovascular risk evaluation may be prudent in individuals with high or high-normal PTH. Further study is required to elucidate the directions of the relationships between PTH, adiposity and cardiometabolic indices, and to assess long-term outcomes in individuals who are found to have an isolated high or high-normal PTH level.

Materials and Methods

This analysis uses data from 151 community-dwelling men who participated in a clinical trial at our centre. The original study has been described previously.⁴⁵ In brief, men aged 40 years or older were randomized to receive calcium supplements (600 or 1200 mg per day) or placebo for a 2-year period. PTH was measured at baseline in 50 subjects per group, providing the cohort for this report. Exclusion criteria included major active disease (including coronary heart disease, hypertension, diabetes mellitus, untreated thyroid disease, liver disease, malignancy, or known metabolic bone disease), current lipid-lowering therapy, serum creatinine $> 0.002 \text{ mg dl}^{-1}$, severe vitamin D deficiency ($25\text{-hydroxyvitamin D} < 25 \text{ nmol/l}^{-1}$) and BMD Z-score

< -2.0 at the spine or total hip. The study was approved by the local ethics committee, and informed consent was obtained.

Data acquisition

Height was measured with a Harpenden stadiometer, and weight was determined using electronic scales. Blood pressure was measured using a Dynamap automatic monitor. The protocol involved a 5-min rest period followed by three blood pressure measurements, taken 3 min apart. Results were averaged. Dietary calcium intake was assessed with a validated food frequency questionnaire.

BMD and body composition was measured at baseline and again every six months for two years, using a Prodigy dual-energy X-ray absorptiometer (DEXA, GE-Lunar, WI, USA). BMD was assessed at the spine, hip and the total body.

Fasting blood samples were collected at baseline. 25-hydroxyvitamin D was measured using either a radioimmunoassay (DiaSorin, Stillwater, MN, USA) or a chemiluminiscence assay (Nichols, San Juan Capistrano, CA, USA), both assays meeting the performance targets for the Vitamin D External Quality Assessment Scheme. Results using the Nichols assay were converted to Diasorin results. Serum procollagen type 1 N-terminal propeptide (P1NP) and PTH were measured using Roche autoanalyzers (Roche Diagnostics, Indianapolis, IN, USA). Total cholesterol, HDL cholesterol and triglycerides were measured using a Roche-Hitachi 747 autoanalyzer (Roche Diagnostics, Mannheim, Germany). LDL cholesterol was calculated using the Friedewald formula.

Eighty-six men from this cohort (80 men from the placebo group and 83 who received calcium 1200 mg per day throughout the 2-year study period) underwent coronary computed tomography using a 64-slice scanner (LightSpeed VCT, General Electric, Milwaukee, WI, USA), an average of 3.5 years after study entry. Scans were analyzed using the Agatston system with manufacturer-supplied software, and CAC scores were determined.

Statistical analysis

Associations between PTH and baseline parameters, and between PTH and change in BMD (in the placebo group only) were assessed using Pearson's correlation since these variables satisfied the criteria for normality. Interactions with age and estimated glomerular filtration rate (eGFR) were evaluated. Parameters that were correlated with PTH in bivariate analysis (P -value < 0.15) were included, along with established predictors of PTH, in a stepwise multivariate regression analysis to obtain a parsimonious model that reflects the strongest determinants of PTH. This approach relies more on external clinical/scientific judgement for model selection than the typical automated stepwise procedure which has a tendency to overfit models which subsequently lack generalisability, may include spurious predictors and exclude known important predictors. Variance inflation factor (VIF) and tolerance (1/VIF) were calculated for each model to assess multicollinearity. VIF > 10 was considered indicative of multicollinearity.

Participants were stratified into tertiles of PTH concentration. Differences between tertiles were assessed using the chi-squared test for categorical variables and analysis of variance (ANOVA) for continuous variables. Significant main or interaction effects were further explored using Tukey's *post hoc* test, to preserve the overall pairwise error rate. Tests for linear or quadratic trend were conducted using orthogonal contrasts. Continuous variables that differed significantly between PTH tertiles were also assessed using ANCOVA, with age, 25-hydroxyvitamin D and eGFR included as covariates.

All data analysis was done with SAS v9.4 (SAS Institute, Cary, NC, USA), and figures were created using Prism v6.0 (GraphPad Software, Inc., La Jolla, CA, USA). The threshold for statistical significance was P < 0.05, with no adjustment for multiple testing in these hypothesis-generating analyses, beyond that of *post hoc* analyses in the context of a significant main effect.

Conflict of Interest

The authors declare no conflict of interest.

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