CLINICAL STUDY

The association between serum parathyroid hormone and bone mineral density, and the impact of smoking: the Tromsø Study

Monica Sneve¹, Nina Emaus², Ragnar Martin Joakimsen^{3,4} and Rolf Jorde^{1,4}

¹Department of Internal Medicine, University Hospital of North Norway, 9038 Tromsø, Norway, ²Institute of Community Medicine, University of Tromsø, 9037 Tromsø, Norway, ³Department of Nephrology, University Hospital of North Norway, 9038 Tromsø, Norway and ⁴Institute of Clinical Medicine, University of Tromsø, 9037 Tromsø, Norway

(Correspondence should be addressed to M Sneve who is now at Medical Department B, Post box 101, University Hospital of North Norway, 9038 Tromsø, Norway; Email: monica.sneve@unn.no)

Abstract

Objective: To explore the relation between serum parathyroid hormone (PTH) and bone mineral density (BMD), adjusted for lifestyle factors including smoking.

Design: Cross-sectional study.

Methods: The Tromsø Study is a population-based study performed for the fifth time in 2001. Serum PTH was measured and the subjects filled in a questionnaire covering lifestyle factors. BMD at the hip, distal and ultradistal forearm was measured.

Results: Complete datasets were available in 1442 men and 1368 women. Age, body mass index and serum PTH were strong predictors of BMD level at the hip in both genders. No significant relation was seen between serum PTH and BMD at the distal or ultradistal forearm. When smokers and non-smokers were analysed separately, the relation between PTH and BMD at the hip was significant in current non-smokers only. In males, current non-smokers had significantly higher BMD at all three measurement sites compared with current smokers. Male former smokers had values in between current and never smokers. There was a significant and negative relation between number of years smoked and BMD at the hip. In male former smokers, there was an increase in BMD with increasing years since smoking cessation.

Conclusion: Serum PTH is negatively associated with BMD at the hip, and the relation seems to be masked, or diminished, by smoking. Smoking reduces BMD at the hip, distal and ultradistal forearm in males, and the effect appears to be mainly time and not dose dependent.

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Introduction

Bone mass is affected by several factors, with gender, age, physical activity, genes and intake of calcium and vitamin D among the most important (1, 2).

Parathyroid hormone (PTH) is a main regulator of the calcium homeostasis (3). Secretion of PTH is stimulated by hypocalcaemia and suppressed by hypercalcaemia. As PTH rises in response to hypocalcaemia, it will tend to restore eucalcaemia by causing bone resorption, reduced renal calcium excretion, and, by its stimulation of renal conversion of 25-hydroxyvitamin D to 1,25-dihydroxyvitamin D, increased intestinal calcium absorption (4, 5). Even minor changes in the extracellular ionized calcium concentration cause large changes in PTH release, and the serum level of PTH may be considered a marker of the body's calcium status. Considering the importance of calcium metabolism for bone health, one would therefore expect a negative association between serum PTH and bone mineral density (BMD). In accordance with this, a reduced BMD has been

demonstrated both in subjects with primary (6, 7) and secondary (8, 9) hyperparathyroidism.

However, in epidemiological studies, the association between PTH and BMD is more uncertain. In the Rancho Bernardo Study, there was a significant negative association between serum PTH and BMD at the hip in older men and women (10, 11), which was not found by Garnero *et al.* in a study on postmenopausal women (12). In the MINOS study, the relation between PTH and BMD was significant in older men only (13). In several of these studies, adjustment for smoking status, which may affect both serum PTH and BMD (14, 15), was not performed (12, 13). This could be of considerable importance as even a modest number of cigarettes smoked per day cause a significant reduction of the serum PTH level (16), and smoking is strongly associated with osteoporosis (14, 17, 18). The effect of smoking on bone appears to be more pronounced in men and in the elderly (14, 19). However, the effect of number of cigarettes smoked per day and the effect of smoking cessation are uncertain (20–22).

In the fifth Tromsø Study, BMD was measured at the hip and the forearm, smoking status was recorded, and serum PTH measured in 2810 subjects. A large database was therefore available for evaluating the relation between BMD, serum PTH and smoking.

Subjects and methods

Subjects

The Tromsø Study is a population-based multipurpose study focusing on lifestyle-related diseases, and was first performed in 1974 (23). In the fifth Tromsø Study, performed in 2001, 10 353 subjects were invited, of whom 8130 accepted to participate. Of the attendants, 6969 subjects were invited for a comprehensive examination which included BMD measurements, and 5939 subjects (2447 men and 3492 women) accepted the invitation. BMD at the hip was measured in 5300 subjects, of which 695 scans had to be excluded because of prostheses or nails, or scans where the region of interest was out of scan. Furthermore, subjects with ineligible forearm scans, those missing PTH measurements, users of hormone replacement therapy, contraceptive pills or medication for osteoporosis, cigar, cigarillo or pipe smokers, those with serum calcium >2.55 mmol/l, and those with incomplete questionnaires were excluded, leaving 2810 subjects (1442 males and 1368 females) for the final analyses. Figure 1 displays a flow chart of the study population.

Questionnaires

All subjects filled in two self-administered questionnaires, one on entering the study and the other which they filled in at home and returned by either mail or entering the comprehensive examination. The questionnaires covered general health, smoking status including number of cigarettes smoked per day, physical activity in spare time, use of vitamin D and calcium supplements, use of hormone replacement therapy and osteoporosis medications, and alcohol and coffee consumption.

The subjects were classified as current smokers or current non-smokers of cigarettes. The current non-smokers were further subclassified into former and never smokers. Pack years were calculated by multiplying the number of cigarettes smoked per day with years smoked, divided by 20. Those smoking cigars, cigarillos or pipe only, or in addition to cigarettes, were excluded as there were no questions regarding number of cigars, cigarillos or pipes smoked per day. Distinction between ordinary cigarettes and hand-rolled cigarettes was not made.

A physical activity score was calculated as the sum of hours of light and heavy physical activity in spare time per week, with heavy physical activity given double weight. Coffee consumption was calculated as the sum of cups of all types of coffee (brewed, filtered or other

type) drunk per day. Alcohol consumption was calculated as the number of glasses of alcohol (adding glasses of wine, beer and spirits) consumed in 2 weeks, assuming equal units of alcohol in each glass.

Measurements

Height and weight were measured wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight (kg) divided by squared height (m^2).

BMD was measured at the hip by dual-energy X-ray absorptiometry (DEXA) according to the manufacturer (GE Lunar Prodigy, LUNAR Corporation, Madison, WI, USA). The mean of the right and left total hip value was used in the analyses. BMD at the distal and ultradistal forearm was measured with two single X-ray absorptiometric devices (DTX-100; Osteometer Medi-Tech Inc., Hawthorne, CA, USA). The distal forearm measurement included both the radius and the ulna from the 8 mm point (the point where the radius and ulna are separated by 8 mm) and 24 mm proximally. The ultradistal forearm measurement included only the radius, from the 8 mm point and up to the endplate. The non-dominant arm was measured, except when it was ineligible. The measurements of BMD at the forearm are previously described in detail (24). All scans were performed and reviewed by specially trained technicians.

Blood samples were drawn in the non-fasting state. Serum calcium, creatinine and PTH were measured as previously described (25). Reference ranges in our laboratory are for serum calcium, 2.20–2.60 mmol/l; for serum creatinine, 70–120 $\mu\text{mol/l}$ for men and 55–100 $\mu\text{mol/l}$ for women; and for serum PTH, 1.1–6.8 pmol/l for those 50 years old and younger and 1.1–7.5 pmol/l for those older than 50 years.

Statistical analyses

Normal distribution was evaluated with visual inspection of histograms with normal curve, normality plots ($Q-Q$ -plots), and determination of skewness and kurtosis. All dependent variables were considered normally distributed.

An initial regression analysis with total hip BMD as dependent variable and PTH quartiles, gender and smoking status as factors, and age, BMI, coffee and alcohol consumption, physical activity score, serum calcium and creatinine as independent variables, revealed significant interaction between smoking status and gender. Therefore, all analyses were done separately for males and females. In the gender-specific regression models, there were no interaction between alcohol consumption and smoking status. Alcohol consumption, serum calcium and creatinine were not significant predictors of BMD at any of the measurement sites, and were therefore excluded from the final regression models.

Groups were compared with Student's *t*-test, and for the BMD measurements also with multiple linear

Figure 1 Flow chart of the study population.

regression with variables similar to the initial regression analysis. For evaluation of individual predictors of BMD, a multiple linear regression model with variables similar to the initial regression analysis was used. Linear trend across PTH quartiles and groups, in relation to number of cigarettes smoked daily, number of years smoked and number of years since quitted smoking, were evaluated with multiple linear regression with covariates as in the initial regression analysis. Analysis of covariance was used to calculate adjusted means of BMD total hip by age and BMI.

Unless otherwise stated, data are expressed as mean $\pm$ s.d. All tests were done two-sided, and P value <0.05 was considered statistically significant. The Statistical Package for Social Sciences version 14.0 was used for all statistical analyses (SPSS Inc., Chicago, IL, USA).

Ethics

The study was approved by the Regional Ethics Committee. All participants gave written informed consent prior to the study.

Table 1 Characteristics of the study subjects in relation to gender and smoking status.

	Male					Females				
	All males	Current non-smokers	Current smokers	Former smokers	Never smokers	All females	Current non-smokers	Current smokers	Former smokers	Never smokers
N	1442	1101	341	784	317	1368	1014	354	421	593
Age (years)	65.5±9.5	66.1±9.4 [‡]	63.3±9.4 [¶]	67.5±8.3	62.9±11.1 [¶]	63.6±10.0	64.5±9.8 [‡]	60.9±10.4 [¶]	64.2±9.2	64.7±10.2
BMI (kg/m ²)	26.6±3.1	26.9±3.0 [‡]	25.7±3.1 [¶]	27.1±3.1	26.6±2.8 [§]	27.0±4.4	27.6±4.3 [‡]	25.2±4.2 [¶]	27.7±4.3	27.5±4.3
S-PTH (pmol/l)	3.56±1.70	3.69±1.78 [‡]	3.12±1.32 [¶]	3.67±1.74	3.75±1.87	3.40±1.53	3.52±1.54 [‡]	3.07±1.44 [¶]	3.55±1.60	3.49±1.50
S-calcium (mmol/l)	2.35±0.08	2.34±0.08 [*]	2.36±0.07	2.34±0.08	2.35±0.08 [§]	2.37±0.08	2.37±0.08	2.37±0.08	2.37±0.08	2.37±0.08
S-creatinine (μmol/l)	98.9±17.7	100.1±18.9 [‡]	94.7±12.4 [¶]	100.4±20.6	99.5±13.8	82.9±10.3	83.5±10.2 [‡]	81.2±10.4 [§]	83.1±10.8	83.8±9.8
Physical activity score	4.3±3.2	4.4±3.2 [*]	3.9±3.2	4.2±3.2	4.8±3.2	3.6±2.8	3.6±2.7	3.4±2.9	3.5±2.6	3.7±2.8
Coffee (cups/day)	5.1±3.1	4.4±2.5 [‡]	7.1±3.7 [¶]	4.7±2.5	3.9±2.6 [¶]	4.3±2.5	3.7±2.1 [‡]	5.8±2.8 [¶]	4.1±2.2	3.5±2.0 [¶]
BMD total hip (g/cm ²)	1.012±0.133	1.023±0.131 ^{‡,c}	0.975±0.130 ^{¶,e}	1.015±0.132	1.044±0.127 ^{,e}	0.899±0.132	0.906±0.131 [†]	0.881±0.133	0.906±0.126	0.906±0.135
BMD distal forearm (g/cm ²)	0.531±0.067	0.534±0.066 ^{‡,b}	0.522±0.070	0.528±0.069	0.546±0.057 ^{¶,d}	0.397±0.069	0.395±0.068 [*]	0.403±0.072	0.397±0.065	0.393±0.070
BMD ultradistal forearm (g/cm ²)	0.436±0.068	0.439±0.068 ^{*,a}	0.428±0.068	0.434±0.069	0.450±0.064 [¶]	0.302±0.064	0.300±0.064	0.306±0.064	0.302±0.063	0.299±0.065
Cigarettes per day			11.4±5.5	12.7±8.4				9.9±4.7 [¶]	8.4±5.4	
Years smoked			42.0±11.4 [¶]	26.7±13.8				35.6±11.0 [¶]	20.9±12.5	
Alcohol (glasses/2 weeks)	6.4±6.5	6.2±6.0	7.0±7.6	6.5±6.3	5.4±5.3	3.9±4.5	3.6±4.2	4.6±5.2	4.1±4.7	3.2±3.6

**P*<0.05, †*P*<0.01, ‡*P*<0.001 versus current smokers, §*P*<0.05, ||*P*<0.01, ¶*P*<0.001 versus former smokers (Student's *t*-test). ^a*P*<0.05, ^b*P*<0.01, ^c*P*<0.001 versus current smokers, ^d*P*<0.05, ^e*P*<0.01 versus former smokers (linear regression with age, BMI, serum PTH, coffee consumption and physical activity as covariates).

Results

Relation between serum PTH and BMD

The characteristics of the subjects are shown in Table 1. In the multiple linear regression models, serum PTH was a significant negative predictor of BMD at the hip in both genders. No significant relation was found between serum PTH and BMD at the distal or ultradistal forearm. In addition to PTH, age and smoking were also strong negative predictors of BMD, whereas BMI and physical activity were strong positive predictors of BMD (Table 2).

When dividing the cohort according to PTH quartiles, with increasing PTH quartile, there was a gradual increase in BMI and age, and a decrease in BMD at the hip, in the multiple linear regression model. There was also, with increasing PTH quartile, a decrease in the number of smokers. The difference in BMD at the hip was 3% between the lowest and the highest PTH quartiles. The significant linear trend for BMD at the hip across serum PTH quartiles was also seen when analysing non-smokers separately, but not when analysing smokers separately (Table 3).

The relation between serum PTH and BMD at the hip was also statistically significant in females <55 years of age ($n=169$, $P<0.05$), whereas this did not reach statistical significance in males <55 years ($n=168$, $P=0.16$, multivariate analysis).

Supplements with calcium tablets, vitamin D or cod liver oil were taken by 12.1, 26.0 and 53.5% of the females and 1.6, 11.5 and 47.4% of the males respectively. In general, those taking supplements were older, leaner and had lower BMD at all three measurement sites, but the differences were not statistically significant in multiple linear regression analysis. Females taking calcium supplements had significantly lower serum PTH levels than those without calcium supplements (3.0 pmol/l vs 3.4 pmol/l respectively, $P<0.001$). Inclusion of taking supplements into

the multiple linear regression analysis did not alter the relation between serum PTH and BMD.

Relation between smoking status and BMD

Using Student's *t*-test, current non-smokers were significantly older, had higher BMI, serum PTH and creatinine levels, and lower coffee consumption than current smokers. In males, the BMD at the hip, distal and ultradistal forearm were significantly higher in the current non-smokers compared with the smokers, even after adjusting for differences in age, BMI, serum PTH, physical activity and coffee consumption. In females, BMD at these three sites did not differ significantly between smokers and non-smokers after adjusting for the confounders. When dividing the current non-smokers into former smokers and never smokers, male former smokers had BMD values at the three sites in between those for current smokers and never smokers (Table 1).

Relation between smoking exposure and BMD

In the multiple linear regression models with age, BMI, serum PTH, coffee consumption and physical activity as covariates, there were no statistical significant relations between numbers of cigarettes smoked daily or pack years and measurements of BMD neither in current smokers nor in former smokers. However, for BMD at the hip, in former smokers of both genders, there was a significant negative relation with numbers of years smoked, and in males a significant positive relation with number of years since smoking cessation. These relations between number of cigarettes smoked, number of years smoked, and number of years since quitting smoking and BMD at the hip, are shown in Tables 4 and 5.

The negative relation between number of years smoked and BMD was also seen in male former smokers

Table 2 Standardized regression coefficient β and *t* values from the linear regression models with bone mineral density (BMD) total hip, distal and ultradistal forearm as dependent variables in the 1442 males and 1368 females.

Independent variables	Males						Females					
	BMD hip (g/cm ²)		BMD distal forearm (g/cm ²)		BMD ultradistal forearm (g/cm ²)		BMD hip (g/cm ²)		BMD distal forearm (g/cm ²)		BMD ultradistal forearm (g/cm ²)	
	β	<i>t</i>	β	<i>t</i>	β	<i>t</i>	β	<i>t</i>	β	<i>t</i>	β	<i>t</i>
Age (years)	-0.16	-6.48	-0.34	-13.44	-0.29	-11.43	-0.42	-18.24	-0.59	-25.97	-0.51	-21.49
BMI (kg/m ²)	0.30	12.26	0.15	6.06	0.15	5.79	0.45	19.48	0.18	7.97	0.17	6.98
PTH (pmol/l)	-0.09	-3.50	0.00	0.14	-0.02	-0.71	-0.09	-4.02	-0.03	-1.42	-0.05	-1.90
Physical activity score	0.09	3.68	0.05	1.83	0.07	2.70	0.01	0.55	0.03	1.13	0.03	1.43
Coffee (cups/day)	-0.03	-1.25	-0.02	-0.65	-0.02	-0.78	-0.05	-1.98	0.00	0.15	0.00	0.11
Current smoking status ^a	0.12	4.35	0.09	3.14	0.07	2.59	0.04	1.40	-0.00	-0.08	0.00	0.29
<i>R</i> ²		0.17		0.15		0.13		0.35		0.36		0.29

^aSmoker = 1, non-smoker = 2. Values of $|t| > 1.96$, $|t| > 2.58$ and $|t| > 3.29$ corresponds to $P < 0.05$, $P < 0.01$ and $P < 0.001$ respectively.

Table 3 Age, body mass index (BMI) and bone mineral density (BMD) total hip in all subjects, and BMD total hip in current non-smokers and smokers in relation to gender and parathyroid hormone (PTH) quartile.

PTH quartile (pmol/l)	All subjects				Current non-smokers				Current smokers			
	N	Age (years)	BMI (kg/m ²)	BMD total hip (g/cm ²)	Adjusted BMD total hip (g/cm ²) ^a	N	BMD total hip (g/cm ²)	Adjusted BMD total hip (g/cm ²) ^a	N	BMD total hip (g/cm ²)	Adjusted BMD total hip (g/cm ²) ^a	N
Males												
<2.5	365	63.0 ± 10.0	26.6 ± 2.8	1.030 ± 0.124	1.027 ± 0.115	252	1.044 ± 0.122	1.039 ± 0.127	113	0.998 ± 0.121	0.987 ± 0.117	
2.5–3.2	342	64.8 ± 9.4	26.2 ± 3.3	1.006 ± 0.131	1.012 ± 0.130	241	1.027 ± 0.128	1.028 ± 0.124	101	0.954 ± 0.123	0.962 ± 0.121	
3.3–4.2	378	66.4 ± 9.0	26.6 ± 3.2	1.012 ± 0.136	1.013 ± 0.117	302	1.018 ± 0.134	1.020 ± 0.122	76	0.985 ± 0.141	0.993 ± 0.122	
>4.2	357	67.7 ± 8.9 [†]	27.0 ± 3.1 [*]	1.000 ± 0.138 [*]	0.996 ± 0.132	306	1.008 ± 0.136 [†]	1.010 ± 0.122	51	0.951 ± 0.143	0.950 ± 0.121	
Females												
<2.4	325	61.1 ± 10.8	26.3 ± 4.3	0.920 ± 0.140	0.917 ± 0.108	214	0.930 ± 0.142	0.927 ± 0.102	111	0.901 ± 0.135	0.891 ± 0.105	
2.4–3.1	360	63.5 ± 9.0	26.8 ± 4.4	0.906 ± 0.129	0.908 ± 0.114	259	0.914 ± 0.126	0.916 ± 0.113	101	0.885 ± 0.134	0.885 ± 0.100	
3.2–4.1	350	64.0 ± 10.4	27.0 ± 4.3	0.887 ± 0.130	0.889 ± 0.112	269	0.894 ± 0.130	0.895 ± 0.115	81	0.863 ± 0.130	0.871 ± 0.108	
>4.1	333	65.6 ± 9.5 [†]	27.8 ± 4.5 [†]	0.885 ± 0.127 [†]	0.884 ± 0.110	272	0.890 ± 0.127 [†]	0.890 ± 0.115	61	0.862 ± 0.127	0.870 ± 0.109	

**P* < 0.05, [†]*P* < 0.01, [‡]*P* < 0.001 (linear trend across PTH quartiles with age, BMI, coffee consumption and physical activity as covariates).^aBMD total hip (g/cm²), adjusted by age and BMI.

at the distal and ultradistal forearm (*P* < 0.05). In female former smokers, there was a significant positive association between the numbers of years since quitting smoking and BMD at the distal forearm (*P* < 0.01), data not shown.

Discussion

In the present study, we found PTH to be a significant negative predictor of BMD at the hip in both genders, whereas no association was found between PTH and BMD at the distal and ultradistal forearm. As expected, we also found age, BMI, physical activity and smoking to be strong predictors of BMD (1, 18). With increasing PTH levels, there was an increase in BMI and age, and a decrease in number of smokers, in accordance with previous reports from the fifth Tromsø Study (16, 26).

There are several studies on the relation between serum PTH and BMD. In most (8, 10, 11, 13, 27), but not all (12), serum PTH has been negatively associated with BMD at the hip. However, the relation between serum PTH and BMD appears to be related to type of bone measured. Thus, in contrast to what appears to be the case for PTH and the predominantly cortical bone at the hip (28), there seems to be no relation between serum PTH and BMD in the vertebrae (10), which are mainly composed of trabecular bone. However, in accordance with others (13), we did not find any relation between PTH and BMD at the distal forearm, which is composed of 10–20% trabecular bone, nor at the ultradistal forearm, which is composed of 50–70% trabecular bone. This implies that other factors are also of importance regarding PTH and BMD, for example, the impact of weight bearing.

In experimental studies, PTH exerts a binary action on bone as it stimulates both osteoblast and osteoclast activities (29). Intermittent injections with PTH increase osteoblast recruitment, lifespan and activity, whereas continuously elevated levels of PTH activates osteoclasts causing diminished BMD (3). PTH has emerged as an effective therapeutic agent for osteoporosis (3), and it is intriguing that the effect seems to be greater on trabecular bone than on cortical bone. Whether the effect of PTH injections in osteoporosis is a direct effect on bone, or (partially) through stimulation of 1,25 hydroxylation of vitamin D, is uncertain. In the PaTH trial, women with larger changes in 1,25-dihydroxyvitamin D during the intervention had larger gains in BMD (30). The authors suggested that some individuals are more responsive to PTH than others, and that 1,25-dihydroxyvitamin D may play a role in the increased bone density after PTH injections.

Similarly, the relation between serum PTH and BMD found in the present study may not represent a causative effect of PTH, but may reflect covariation with other factors important for bone health. In particular, the intake of calcium and vitamin D are

Table 4 Smoking status, age, body mass index (BMI) and bone mineral density (BMD) at the hip in relation to number of cigarettes smoked, number of years smoked and number of years since quitting smoking in males.

Current smokers					Former smokers				
	<i>N</i> ^a	Age (years)	BMI (kg/m ²)	BMD hip (g/cm ²)		<i>N</i> ^a	Age (years)	BMI (kg/m ²)	BMD hip (g/cm ²)
Number of cigarettes smoked daily									
1–5	42	64.8±10.3	24.8±3.7	0.964±0.164	90	68.1±6.2	26.1±3.2	0.998±0.134	
6–10	148	64.9±8.3	25.6±2.9	0.975±0.126	306	67.3±9.0	27.0±2.8	1.020±0.135	
11–15	94	62.4±8.0	26.1±3.3	0.981±0.125	143	66.7±8.4	27.2±3.1	1.038±0.124	
≥16	51	58.0±11.5	25.7±3.0	0.976±0.131	150	66.0±8.5	27.7±3.4*	1.003±0.131	
Number of years smoked									
1–10	6	58.7±15.1	27.0±3.9	1.167±0.095	107	63.0±9.8	26.7±2.8	1.050±0.118	
11–20	17	49.0±14.8	25.9±3.4	1.006±0.084	181	65.3±8.9	27.0±3.1	1.034±0.136	
21–30	23	54.8±11.5	26.2±2.6	0.993±0.120	182	67.4±7.7	27.3±3.1	1.025±0.116	
31–40	91	58.9±6.3	26.8±2.9	1.009±0.134	152	68.5±7.3	27.7±3.1	0.998±0.129	
≥41	200	67.7±5.0	25.3±3.2	0.950±0.126	122	72.2±5.2*	26.4±3.3*	0.965±0.146*	
Number of years since quitting smoking									
0–5					114	63.9±10.9	27.3±3.6	0.995±0.131	
6–10					101	65.4±8.9	27.3±3.2	1.005±0.132	
11–20					154	67.6±7.9	27.5±2.9	1.015±0.125	
≥21					391	68.9±7.1*	26.8±3.0	1.022±0.133*	

**P*<0.001 (linear trend across groups with age, BMI, coffee consumption and physical activity as covariates).^aNot all subjects answered all questions.

important determinants of both the serum PTH level (31) and bone density (1, 2). Furthermore, low serum levels of vitamin D are associated with high serum levels of PTH, and both are associated with reduced BMD (32).

Unfortunately, it was not possible to calculate the intakes of calcium and vitamin D in the present study, but the intakes of supplements were recorded. Somewhat surprisingly, those taking calcium and vitamin D supplements (including cod liver oil) had slightly lower BMD than those not taking supplements, and inclusion of taking supplements in the analyses had no effect on the relation between PTH and BMD. As the number of

subjects taking supplements was limited, and their reason for taking the supplements unknown, this observation should be interpreted with caution. However, it may indicate that the relation between PTH and BMD is not only a phenomenon parallel to a low calcium and/or vitamin D intake.

The serum PTH levels increase with age and BMI, and decrease with smoking. As age, BMI and smoking all are related to BMD, adjustment for these variables is mandatory when analysing the relation between PTH and BMD. Regarding smoking, we have previously shown that even moderate smoking (one to five

Table 5 Smoking status, age, body mass index (BMI) and bone mineral density (BMD) at the hip in relation to number of cigarettes smoked, number of years smoked and number of years since quitting smoking in the females.

Current smokers					Former smokers			
<i>N</i> ^a	Age (years)	BMI (kg/m ²)	BMD hip (g/cm ²)		<i>N</i> ^a	Age (years)	BMI (kg/m ²)	BMD hip (g/cm ²)
Number of cigarettes smoked daily								
1–5	50	61.8±12.1	25.3±3.5	0.923±0.135	135	66.7±8.1	26.9±3.9	0.872±0.122
6–10	196	62.1±10.5	25.0±4.4	0.869±0.137	179	62.4±9.7	28.1±4.5	0.928±0.119
11–15	69	57.3±9.3	25.4±4.1	0.891±0.117	40	62.4±8.6	28.3±4.2	0.922±0.147
≥16	30	58.6±8.0	25.3±3.8	0.883±0.118	27	61.0±10.7	27.4±4.3	0.911±0.105
Number of years smoked								
1–10	8	56.9±9.8	29.9±7.5	0.938±0.250	99	61.7±10.3	26.7±4.0	0.916±0.122
11–20	37	48.7±12.5	24.6±4.0	0.947±0.122	113	62.3±9.3	28.3±4.8	0.933±0.123
21–30	68	54.9±10.6	24.9±3.3	0.924±0.122	98	64.7±8.5	28.2±4.0	0.903±0.124
31–40	114	61.7±6.8	25.6±4.1	0.869±0.118	49	67.0±7.2	27.9±4.6	0.880±0.109
≥41	112	67.5±6.1	24.7±4.4	0.845±0.137	27	71.0±5.9 [†]	27.5±4.0	0.819±0.115*
Number of years since quitting smoking								
0–5					75	62.4±9.7	27.0±4.1	0.894±0.127
6–10					56	61.1±9.4	28.8±4.4	0.919±0.130
11–20					94	64.7±10.1	28.2±4.9	0.908±0.125
≥21					172	65.7±7.7 [‡]	27.4±4.0	0.908±0.125

**P*<0.05, [†]*P*<0.001, [‡]*P*<0.01 (linear trend across groups with age, BMI, coffee consumption and physical activity as covariates).^aNot all subjects answered all questions.

cigarettes per day) reduces the serum PTH level by ~15%, that there appears to be no dose–response relationship for the PTH reduction, and that within a year after smoking cessation PTH levels are restored to non-smoking levels (16). It is therefore not surprising that smoking, which is well known to reduce BMD (14, 17), may blunt or mask the apparently harmful effect of PTH on bone, as was seen in our study.

Regarding smoking and BMD, we found in smoking males significantly lower BMD at the hip and distal and ultradistal forearm compared with non-smokers, with the difference most clearly seen at the hip. The more harmful effect of smoking on trabecular bone and the gender difference is in accordance with a large meta-analysis including more than 40 000 subjects from 86 studies (14). The cause of this gender difference is uncertain. However, in women smoking has an anti-estrogenic effect (33), whereas in males several studies have found increased levels of free testosterone in smokers (20, 33). Therefore, smoking-induced changes in gonadal hormones appear as an unlikely explanation for the gender difference found in our study.

We were not able to demonstrate any significant relation between BMD at any site and number of cigarettes smoked per day or pack years, which can be attributable to information bias. However, there was a negative relation between BMD and number of years smoked, and a positive relation with years since smoking cessation. Our results indicate that the effect of smoking on bone is mainly time and not dose dependent. In line with this, former smokers had BMD values in between those of current and never smokers. The clinical implication of our study is that even moderate smoking has a harmful effect on bone, and to avoid it completely, smoking has to be stopped. Furthermore, the smoking-related bone loss is, at least partly, reversible. However, negative effects on bone by smoking-induced early menopause and vascular changes would not be reversible.

There are several mechanisms by which smoking could induce bone loss. Smoking is associated with lower body mass, earlier menopause and possibly a damage of the blood supply to the bone (14). Smoking is also associated with a more unhealthy and sedentary lifestyle that could have an adverse effect on bone (14). Another possible mechanism is that smoking has an inhibitory effect on bone formation (15, 34). On the other hand, the PTH reduction associated with smoking could have a positive effect since PTH, as shown in the present study, is associated with reduced BMD. However, the PTH reduction would also lead to an increased renal calcium loss and a reduced 1,25-hydroxylation of vitamin D. Smoking also reduces the serum levels of 25-hydroxyvitamin D (15) and 1,25-dihydroxyvitamin D (15, 34), which in addition to the depression of the PTH levels could explain the lack of linear trend for BMD across PTH quartiles in the smokers in our study.

Our study has several limitations. We used DEXA measurements at the hip and single X-ray absorptiometric measurements at the forearm, both of which only provide a two-dimensional measure, and not a volumetric BMD or size of the trabecular and cortical bone compartments, which could have given additional information. Furthermore, it was not possible to calculate the calcium and vitamin D intake, and the serum levels of vitamin D were not measured, nor were the effects of sex steroids assessed. The study was cross-sectional, which implies that causal relations cannot be drawn, and the age distribution made results in those younger than 55 years uncertain. Blood samples were drawn in the non-fasting state, and the PTH levels may have been influenced by calcium intake. The lack of significant relation between BMD and number of cigarettes smoked daily or pack years can perhaps be explained by information bias. The estimation of the number of cigarettes smoked daily over several years probably contains some inaccuracy, and smokers tend to underestimate the number of cigarettes smoked. Another limitation is the probability of selection bias as we ended up with ~40% of the invited subjects. However, as this is not a prevalence study, selection bias seems unlikely and the relation between PTH and BMD would probably not be different among those not included in the study.

However, the study also has considerable strength. It is, to our knowledge, the largest population-based study so far published on serum PTH and BMD, and a number of possible confounders were included in the analyses and strict inclusion criteria were used.

In conclusion, we have found serum PTH to be negatively associated with BMD at the hip, and this relation seems to be masked, or diminished, by smoking. Smoking reduces BMD at the hip and distal and ultradistal forearm in males, and this effect appears to be mainly time and not dose dependent. The effect of smoking diminishes after smoking cessation.

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