CLINICAL STUDY

Serum parathyroid hormone (PTH) levels in smokers and non-smokers. The fifth Tromsø study

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Abstract

Objective: Smoking is associated with reduced bone density and calcium absorption, and reduced serum levels of vitamin D. A compensatory increase in serum parathyroid hormone (PTH) would therefore be expected as a result of an altered calcium balance. However, reports on PTH levels in smokers are conflicting. As serum PTH levels give important information on the calcium balance, the PTH levels in smokers are of interest.

Subjects and methods: In the fifth Tromsø study, smoking status was recorded and serum PTH measured in 7896 subjects. Intakes of calcium and vitamin D were evaluated with a food-frequency questionnaire. In a follow-up study on 205 subjects, serum 25-hydroxyvitamin D, calcium absorption, and renal excretion of calcium were measured in addition.

Results: The serum PTH levels were significantly lower in smokers than non-smokers (3.1 ± 1.4 vs 3.6 ± 1.9 pmol/l in males; 3.1 ± 1.5 vs 3.6 ± 1.8 pmol/l in females ($P < 0.001$) after correcting for confounding variables, linear regression). In the smokers, there was no association between number of cigarettes smoked and serum PTH. One year after quitting smoking, serum PTH levels were similar to those of people who had never smoked. The smokers had significantly lower intake of vitamin D, lower serum levels of 25-hydroxyvitamin D and lower calcium absorption. The intake of calcium and the renal excretion of calcium were similar to that in non-smokers.

Conclusions: Smokers have lower serum PTH levels than non-smokers. This cannot be explained by the predictors of serum PTH measured in our study.

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Introduction

Smoking is a major health hazard, with detrimental effects on many organs, including the skeleton. Thus, several authors have reported an association between smoking and fracture risk (1) as well as low bone density (2–4), but the underlying mechanism remains to be clarified. Possible explanations might be that smokers have a low intake of calcium and/or vitamin D, a low calcium absorption, a high calcium resorption from the skeleton or an excessive excretion of calcium in the urine. This could lead to a negative calcium balance that normally would cause a compensatory increase in serum parathyroid hormone (PTH). However, both low (5–8) as well as high (2–4) PTH levels have been reported as a result of smoking.

In the fifth Tromsø study, which was performed in 2001, smoking status and other lifestyle factors were recorded, and serum PTH was measured in 7896 subjects. In 2002, a follow-up study was performed in 205 subjects; it included measurements of serum vitamin D levels and urinary calcium excretion, and a calcium

absorption test. Accordingly, a large database was available for testing the relation between smoking and serum PTH levels.

Subjects and methods

The fifth Tromsø study

All men and women older than 29 years, living in the municipality of Tromsø and that participated in the second phase of the fourth Tromsø study (9) or became 30, 40, 45, 60 or 75 years old during 2001, were invited to participate.

A questionnaire on medical history, lifestyle factors and dietary habits, including calcium and vitamin D supplementation, was obtained from all participants. A physical activity score (adding together hours of moderate and hard physical activity per week (giving hours of hard activity double weight), an alcohol consumption score (number of glasses of beer, wine and spirits drunk per 2 weeks), the number of cups of coffee drunk per day, and intakes of calcium and

vitamin D were calculated as previously described in detail (10). The questions on smoking included past and present smoking habits, and for those that had stopped smoking, the number of years since quitting.

Height and weight were measured while the subjects wore light clothing and no shoes. Body-mass index (BMI) was defined as weight (kg) divided by height squared (m^2). Non-fasting blood samples were drawn, and serum calcium, creatinine and PTH were analysed as previously described (11). In our laboratory, the reference range for serum calcium is 2.20–2.60 mmol/l; for serum PTH, 1.1–6.8 pmol/l for those under 51 years and 1.1–7.5 pmol/l for those over 50 years; and for serum creatinine, 55–100 $\mu\text{mol/l}$ for women and 70–120 $\mu\text{mol/l}$ for men.

Follow-up study

At 6–12 months after the fifth Tromsø study, 129 subjects with serum PTH of > 6.4 pmol/l and serum calcium of < 2.40 mmol/l (secondary hyperparathyroidism) and 149 subjects with serum PTH of < 6.5 pmol/l and serum calcium of 2.20–2.60 mmol/l, were invited to participate in a follow-up study. Smoking status was recorded and measurements were performed as described above. In addition, serum 25-hydroxyvitamin D (reference range 37–131 nmol/l) and 1,25-dihydroxyvitamin D (reference range 42–169 pmol/l) were measured (12). Blood samples were drawn in the fasting state. Urine was collected for 24 h and urinary calcium measured (reference range 2.0–8.0 mmol/24 h). A calcium absorption test was performed by the method described by Nordin *et al.* (13).

Statistical analysis

Normal distribution was evaluated with visual inspection of histograms and determination of skewness and kurtosis, and all variables except serum PTH, and alcohol and coffee intakes were considered normally distributed. After logarithmic transformation, serum PTH assumed normal distribution and was used as such when evaluated as a dependent variable.

To test for interactions between smoking status and gender, factor analyses with the variable in question as dependent variable, smoking status and gender as factors, and the other variables as independent variables were performed for both the fifth Tromsø study and the follow-up study. There were significant interactions between gender and smoking status regarding BMI in the fifth Tromsø study, which was therefore analysed sex-specific.

Smokers and non-smokers were compared by Student's *t*-test for independent samples and also with a general linear model with the parameter in question as dependent variable, smoking (and gender in the follow-up study) as a factor, and the other variables as independent variables. The alcohol and coffee

intakes in smokers and non-smokers were compared with the Mann–Whitney test. Correlations between serum PTH and the other variables were assessed with Pearson's correlation coefficient, except for alcohol and coffee intakes, for which Spearman's correlation coefficient was used. A sex-specific multiple linear regression model was used to assess independent predictors of serum PTH concentration. The appropriateness of the model was verified by plotting the residuals against each variable and inspecting the plot for even distribution throughout the variable range.

Unless otherwise stated, all data are expressed as mean $\pm$ s.d. All tests were done two-sided, and a value of $P < 0.05$ was considered statistically significant. Statistical analyses were performed with SPSS version 11.0 (SPSS Inc., Chicago, IL, USA).

Ethics

The regional ethics committee approved the study, and all participants gave their written informed consent.

Results

The fifth Tromsø study

A total of 10 419 men and women were invited to participate, and 8128 attended the study. Serum PTH and calcium were measured in 7954, and among them, smoking status was recorded in 7896 subjects.

The demographics of the study population are given in Table 1. Included in the study population were 16 subjects (one smoker) considered to have primary hyperparathyroidism (serum calcium of > 2.60 mmol/l and serum PTH of > 6.4 pmol/l). In both sexes, age, BMI, serum PTH, creatinine, physical activity and vitamin D intake were significantly lower in smokers, whereas alcohol and coffee consumption were significantly higher. In males, the calcium intake was significantly lower and serum calcium significantly higher in the smokers than the non-smokers when evaluated by Student's *t*-test, but not after correction for the other variables (Table 1).

To illustrate that the difference in serum PTH between smokers and non-smokers was not the result of covariation with the strong PTH predictors age, BMI and creatinine, BMI and creatinine in each gender were divided into tertiles, and the PTH levels in smokers and non-smokers showed stratified for these predictors in the age groups 40–59 years, 60–69 years and > 69 years in Figs 1 and 2. In 47 of the 54 subgroups created in this way, the serum PTH levels were lowest in the smokers.

To evaluate the relation between numbers of cigarettes smoked versus serum PTH and the strongest predictors for serum PTH, the smokers were grouped according to 1–5, 6–10, 11–20 and > 20 cigarettes smoked per

Table 1 Demographic, biochemical and lifestyle variables in male and female smokers and non-smokers. The fifth Tromsø study.

	Males		Females	
	Smokers	Non-smokers	Smokers	Non-smokers
N	969	2458	1244	3225
Age (years)	57.3±14.0	60.8±14.0 [‡]	55.9±13.8	60.7±14.0 [‡]
BMI (kg/m ²)	26.0±3.6	27.2±3.6 [¶]	25.0±4.3	27.2±4.7 [¶]
Serum PTH (pmol/l)	3.08±1.40	3.63±1.86 [¶]	3.09±1.50	3.56±1.80 [¶]
Serum calcium (mmol/l)	2.36±0.08	2.35±0.08 ^a	2.36±0.09	2.36±0.09
Serum creatinine (μmol/l)	94.5±12.2	99.6±19.5 [¶]	80.1±9.9	83.7±10.9 [¶]
Calcium intake (mg/day)	401±289	432±299 ^b	444±311	452±305
Vitamin D intake (μg/day)	7.1±6.9	8.7±7.5 [¶]	9.9±8.0	11.1±8.1 [‡]
Alcohol (units/14 days)	5.7±8.1	4.3±7.1 ^c	3.1±5.4	2.1±3.8 ^c
Coffee (cups/day)	6.9±5.0	4.4±3.0 ^c	5.6±3.3	3.5±2.3 ^c
Physical activity (h/week)	4.0±3.3	4.4±3.3 [¶]	3.3±2.8	3.6±2.9 ^b
Smoking (cigarettes/day)	11.6±5.9		10.0±5.1	

^a*P* < 0.05; ^b*P* < 0.01; ^c*P* < 0.001 versus smokers (Student's *t*-test (alcohol and coffee: Mann–Whitney test)).

[‡]*P* < 0.05; [‡]*P* < 0.01; [¶]*P* < 0.001 versus smokers (general linear model).

day. No relation was found between number of cigarettes smoked and serum PTH, serum calcium or serum creatinine. However, in the smokers, there was a positive relation with BMI (Table 2). Even among those that smoked fewer than 6 cigarettes per day, the PTH levels were low, being 3.25±1.03 pmol/l (*n*=14), 2.72±0.93 pmol/l (*n*=40), 3.38±2.18 pmol/l (*n*=49), 3.18±1.62 pmol/l (*n*=72) and 3.09±1.52 pmol/l (*n*=162) in those that smoked 1, 2, 3, 4 and 5 cigarettes per day respectively.

In those that had stopped smoking, the serum PTH levels were almost identical to those that had never

smoked (3.58±1.84 pmol/l, *n*=3138), regardless of how long since smoking cessation (after 1 year, 3.53±1.93 pmol/l (*n*=138); after 2–5 years, 3.57±1.55 pmol/l (*n*=352); and after more than 5 years, 3.65±1.84 pmol/l (*n*=2210)).

In the correlation analysis and multiple regression model with logPTH as dependent variable, age, serum creatinine, serum calcium, BMI and smoking status were significant predictors of serum PTH in both sexes. Intake of vitamin D in females and intake of calcium in males were significantly and negatively associated with serum PTH (Table 3).

Figure 1 Mean serum PTH in relation to age, BMI tertiles (<25.2, 25.2–28.1, >28.1 kg/m²) and serum creatinine tertiles (top panel <92 μmol/l, middle panel 92–101 μmol/l, bottom panel >101 μmol/l) in smoking (●) and non-smoking (○) males. The fifth Tromsø study.

Figure 2 Mean serum PTH in relation to age, BMI tertiles (<24.3, 24.3–28.1, >28.1 kg/m²), and serum creatinine tertiles (top panel <78 μmol/l, middle panel 79–86 μmol/l, bottom panel >86 μmol/l) in smoking (●) and non-smoking (○) females. The fifth Tromsø study.

Table 2 Serum PTH and its major predictors in relation to number of cigarettes smoked. The fifth Tromsø study.

	Number of cigarettes smoked per day				
	0	1–5	6–10	11–20	> 20
N*	5683	337	1016	734	39
Age (years)	60.8±14.0	57.0±15.8	57.5±13.9	54.2±12.7	55.8±11.4
BMI (kg/m ²)	27.2±4.3	25.1±4.1	25.2±4.0	26.0±4.0	25.7±3.9
Serum PTH (pmol/l)	3.59±1.82	3.11±1.59	3.06±1.38	3.07±1.46	3.16±1.45
Serum calcium (mmol/l)	2.36±0.09	2.36±0.09	2.36±0.08	2.37±0.09	2.35±0.09
Serum creatinine (μmol/l)	90.6±17.2	87.3±15.3	85.9±12.9	87.1±11.8	86.3±11.8

* Not all of the 2213 smokers answered the question on number of cigarettes smoked per day.

Table 3 Pearson's correlation coefficients, standardised β-coefficients and *t* values with logPTH as dependent variable in 3427 males and 4469 females. The fifth Tromsø study.

	Males			Females		
	<i>r</i>	β	<i>t</i>	<i>r</i>	β	<i>t</i>
Age (years)	0.22 ^c	0.15 ^c	8.02	0.18 ^c	0.17 ^c	9.00
BMI (kg/m ²)	0.07 ^c	0.06 ^c	3.36	0.12 ^c	0.08 ^c	4.70
Serum calcium (mmol/l)	–0.19 ^c	–0.17 ^c	–9.69	–0.11 ^c	–0.15 ^c	–9.42
Serum creatinine (μmol/l)	0.19 ^c	0.21 ^c	11.57	0.14 ^c	0.11 ^c	6.60
Calcium intake (mg/day)	–0.09 ^c	–0.10 ^c	–4.65	–0.05 ^b	–0.04	–1.91
Vitamin D intake (μg/day)	0.01	0.03	1.20	–0.04 ^a	–0.05 ^a	–2.52
Alcohol (units/14 days)*	–0.10 ^c	0.00	0.17	–0.12 ^c	–0.03	–1.63
Coffee (cups/day)*	–0.06 ^c	0.01	0.61	–0.01	0.05 ^b	2.94
Physical activity (h/week)	–0.04 ^a	0.02	1.26	–0.09	–0.02	–1.04
Smoking status†		0.09 ^c	4.51		0.10 ^c	5.46

^a*P* < 0.05; ^b*P* < 0.01; ^c*P* < 0.001.

* Correlations evaluated with Spearman's rho coefficient.

† Current smoker/non-smoker.

Follow-up study

One hundred of those with secondary hyperparathyroidism and 105 control subjects attended the follow-up study. Those with secondary hyperparathyroidism had similar vitamin D intake to the controls (10.6 ± 9.7 vs 10.8 ± 7.5 $\mu\text{g/day}$), non-significantly lower serum 25-hydroxyvitamin D (60.0 ± 16.7 vs 64.2 ± 18.4 nmol/l) and significantly lower fractional calcium absorption (0.82 ± 0.28 vs $0.74 \pm 0.17\%$, $P < 0.05$). The age, BMI, serum creatinine and male/female ratio were similar in the two groups (60.3 ± 13.9 and 60.8 ± 13.9 years, 28.1 ± 5.0 and 27.0 ± 4.0 kg/m^2 , 87.3 ± 20.0 and 84.8 ± 14.3 $\mu\text{mol/l}$, and 49/51 and 56/49 men/women respectively). Among these 205 subjects, 54 were smokers. The demographics of the smokers and non-smokers are shown in Table 4. As in the main study, the smokers had significantly lower age, serum PTH and serum creatinine. The serum 25-hydroxyvitamin D levels were also significantly lower, as was the calcium absorption. On the other hand, the serum calcium levels and the urinary calcium excretion were almost identical in the two groups (Table 4). The lower PTH levels in the smokers did not affect the 25-hydroxyvitamin D/1,25-dihydroxyvitamin D ratio (0.58 ± 0.26 vs 0.64 ± 0.29 in non-smokers; $P = 0.89$ after adjusting for age, gender, BMI and creatinine). One of the smokers and eight of the non-smokers used a diuretic drug. Inclusion of these subjects had no effect on the results.

Discussion

In the present study, we have found that smokers have significantly lower serum PTH levels than non-smokers, that the number of cigarettes smoked per day does not affect the serum PTH level in the smokers, and that

serum PTH levels 1 year after smoking cessation are similar to those in non-smokers.

As expected, serum calcium was the main predictor of the serum PTH level, but, in addition, we found age, BMI and serum creatinine to be strongly and positively associated with serum PTH. As a group, the smokers were younger and had lower BMI and serum creatinine than the non-smokers, and the lower PTH levels in the smokers could therefore be simple covariation with these variables. However, the negative association between smoking and serum PTH was still highly significant after correction for these variables and was also seen in analyses stratified for age, BMI and serum creatinine.

There are several previous reports on the relation between smoking and serum PTH, but the results are conflicting. Thus, Landin-Wilhelmsen *et al.* in a study on 347 men and women (5), Brot *et al.* in a study on 510 women aged 45–58 years (6), Need *et al.* in a study on 405 postmenopausal women (7) and Mellström *et al.* in a case-control study on 129 men with earlier partial gastrectomy and 216 controls (8) found serum PTH to be significantly lower in smokers. On the other hand, Rapuri *et al.* in a study on 444 elderly women (3), Szulc *et al.* in a study on 719 men aged 51–85 years (4) and Ortego-Centeno *et al.* in a study on 57 healthy males below the age of 45 (2) found serum PTH to be significantly higher in smokers than non-smokers. However, in none of these studies were all the major confounders for serum PTH taken into account, and the largest of the studies included only a tenth of the number of subjects in our study. On the other hand, in most of these studies, the blood samples were drawn in the fasting state (3–7), whereas that was not the case in our main study. However, the same effect of smoking on serum PTH was also seen in the follow-up study where the blood samples were drawn in the fasting state. We therefore find it unlikely that differences in timing of blood sampling have affected our results for smoking and PTH.

Among the smokers we were not able to demonstrate a dose-dependent relationship between number of cigarettes smoked per day and level of serum PTH. Even in those that smoked only one or two cigarettes per day, the PTH levels were almost as low as in those that smoked 20 or more cigarettes per day. However, the number of heavy smokers was rather small, and our observation therefore mainly relates to moderate smokers. On the other hand, our results are in accordance with those published by Brot *et al.* (6), and may indicate that even moderate smoking may trigger important physiological effects.

One year after smoking cessation, serum PTH resumed the level detected in non-smokers, lending support to a causal relationship between smoking and PTH levels. We have no data on shorter smoking-free periods, but this has been addressed in a previous report comprising 20 postmenopausal women that

Table 4 Demographic and biochemical variables in smokers and non-smokers from the follow-up after the fifth Tromsø study.

	Smokers	Non-smokers
Males/females	23/31	82/69
Age (years)	55.4 ± 13.2	$62.3 \pm 13.6^{b\ddagger}$
BMI (kg/m^2)	26.8 ± 4.9	$27.8 \pm 4.4^a\ddagger$
Serum PTH (pmol/l)	3.94 ± 1.76	$4.82 \pm 2.43^{b\ddagger}$
Serum calcium (mmol/l)	2.31 ± 0.09	2.31 ± 0.11
Serum creatinine ($\mu\text{mol/l}$)	79.7 ± 11.2	$88.1 \pm 18.4^{b\ddagger}$
Serum 25-hydroxyvitamin D (nmol/l)	57.4 ± 17.4	$63.6 \pm 17.9^{a\ddagger}$
Serum 1,25-dihydroxyvitamin D (nmol/l)	108.1 ± 30.5	111.1 ± 36.8
Urinary calcium excretion (mmol/24 h)	4.21 ± 2.76	4.30 ± 2.73
Calcium absorption (fraction absorbed)*	0.74 ± 0.17	$0.80 \pm 0.25\ddagger$
Smoking (cigarettes/day)	9.9 ± 5.7	

* Measured in 43 smokers (26 males) and 126 non-smokers (70 males).

^a $P < 0.05$; ^b $P < 0.01$ versus smokers (Student's *t*-test).

[†] $P < 0.05$; [‡] $P < 0.01$ versus smokers (general linear model).

discontinued smoking for 6 weeks (14). These authors were unable to demonstrate any effect on PTH levels during this period as compared with non-quitting controls. Like us, Need *et al.* (7) found that previous smokers had similar PTH levels to non-smokers, but in their study the number of years since quitting smoking was not given.

The main regulator of the PTH level is the plasma ionised calcium, where minute changes in ionised calcium level elicit rapid changes in PTH secretion and synthesis (15). In the study by Need *et al.* on 405 postmenopausal women (7), serum ionised calcium was higher in the smokers, a characteristic which is the most likely, but not the only, explanation for the lower PTH levels in smokers. Thus, several other putative regulators, such as chromogranin peptides and interleukin-8, may modulate PTH secretion (16). In addition, a direct toxic effect of smoke on the parathyroid cells cannot be excluded. Furthermore, there might be substances in smoke that could interact directly with the calcium receptor; in theory, smoking could enhance degradation of PTH in blood samples and cause low PTH levels without influencing calcium homeostasis.

However, if the low serum PTH levels in smokers are the result of slightly increased plasma ionised calcium, why should the ionised calcium level be increased in smokers? First of all, the intake of calcium was similar in the smokers and non-smokers in our study, whereas, in the INTERMAP study on macro- and micro-nutrients in 2195 subjects from the USA, intake of calcium was actually lower in the smokers (17). Furthermore, we found the intake of vitamin D and the serum levels of 25-hydroxyvitamin D to be significantly lower in the smokers. The latter has also been reported by several other studies (3–6, 8, 18), but the mechanism is not known. In addition to the lower intake of vitamin D, other explanations could be reduced dermal production of vitamin D or increased catabolism. However, there is an inverse relation between BMI and 25-hydroxyvitamin D (19) that, because the smokers were leaner than the non-smokers, should have the opposite effect on the vitamin D levels. Regardless of this, as the smokers had lower vitamin D levels, our finding of a reduced calcium absorption was to be expected, and in accordance with previous reports by Need *et al.* (7) and Krall *et al.* (20). Finally, we found an almost identical urinary calcium excretion in smokers and non-smokers.

Thus, with normal or reduced calcium intake, reduced calcium absorption, and normal calcium excretion, one would expect a negative calcium balance and a compensatory increased serum PTH. But the latter was not seen, and one explanation could be that smoking induces increased calcium resorption from the skeleton and thereby increased serum calcium level. This would inevitably lead to osteoporosis, which has been reported in smokers in numerous studies (2–4). However, it must be emphasised that

this is highly speculative, as the serum calcium levels in the smokers and non-smokers in our study were almost superimposable. One would therefore have to assume that small changes in the serum ionised calcium level existed that were masked when the total calcium level was measured. Furthermore, if excess mobilisation of calcium from the skeleton was the cause, this should, in order to raise the serum ionised calcium level, exceed the reduction in intestinal calcium absorption and lead to hypercalciuria, which was not seen. Unfortunately, resorptive bone markers that could have supported the concept of increase calcium resorption from the skeleton were not measured in the study. Accordingly, we can offer no plausible explanation for the lower PTH levels in the smokers.

Our study has several shortcomings. First of all, we used data from two different cohorts, and, ideally, all variables should have been measured in one large study. Furthermore, our data on calcium and vitamin D intakes were based on a food-frequency questionnaire, which is not an accurate measure, and the amount of sun exposure, which is important for dermal vitamin D production, was not taken into account. The intake of vitamin D was high as compared with other populations (17). This probably reflects a high consumption of fatty fish and frequent use of vitamin D supplements, as dietary fortification with vitamin D is not used in Norway. And, as expected, the 25-hydroxyvitamin D levels were high in our population, similar to those reported previously (21). Although it is unlikely that the vitamin D status in our region should be of major importance for the relation between smoking and serum PTH, our results may not necessarily apply to other populations. Finally, smoking habits were self-reported on a questionnaire and not validated by an interview.

On the other hand, the large number of subjects included in the study, and the careful adjustment for confounders, confirms that serum PTH is lower in smokers than non-smokers. However, the mechanism and possible importance of this, especially for skeletal health, remain to be elucidated.

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