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ORIGINAL ARTICLE

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Causes of secondary hyperparathyroidism in a healthy population: the Tromsø study

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Abstract Secondary hyperparathyroidism (SHPT) develops as a compensatory mechanism when the body is in calcium deficit. SHPT may be harmful and has been associated with elevated blood pressure. The cause of SHPT could be low calcium intake, reduced intestinal calcium absorption, or increased excretion. However, the relative importance of these factors for the development of SHPT is not known. During the 5th Tromsø study, serum PTH and calcium were measured in 7954 subjects. Then 96 subjects with SHPT (defined as serum PTH above 6.4 pmol/l together with serum calcium below 2.40 mmol/l) and 106 control subjects were examined at follow-up with a food frequency questionnaire, calcium absorption test, measurement of 24-h urinary calcium excretion, and serum vitamin D status. The statistical analyses showed several interactions necessitating subgroup analysis. It was found that the calcium intake was significantly lower in the SHPT group, but only in nonsmoking males; the calcium absorption was nonsignificantly higher in the SHPT group; the serum 25-hydroxyvitamin D levels were significantly lower in the SHPT group but only in nonsmokers; and the 24-h urinary calcium excretion was significantly lower in the SHPT group but only in those not on blood pressure medication. The most frequent cause of SHPT appeared to be low calcium intake (18%) and a low serum 25-hydroxyvitamin D level (18%). However, in most subjects with SHPT all tests were within the normal range, and the cause is therefore probably a combination of several factors.

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Introduction

Parathyroid hormone (PTH), a polypeptide comprising of 84 amino acids, is produced in the parathyroid glands. Secretion of PTH is mainly regulated by the serum ionized calcium level, with a low level eliciting secretion of the hormone; elevation of the ionized calcium level has the opposite effect. PTH in turn affects the serum calcium level by increasing calcium reabsorption in the renal tubules and increasing resorption of calcium from the skeleton. Furthermore, PTH increases the conversion of 25-hydroxyvitamin D to its active form 1,25-dihydroxyvitamin D in the kidneys, which again increases intestinal calcium absorption [1]. Accordingly, if the body is in calcium deficit there is a compensatory increase in PTH secretion, giving rise to secondary hyperparathyroidism (SHPT).

A low serum ionized calcium level or calcium deficit can arise from several causes, such as low calcium intake, low calcium absorption from the intestine, or increased excretion of calcium by the kidneys. SHPT, defined as a combination of a high PTH level together with a relatively low serum calcium level, is frequently found and has been associated with elevated blood pressure [2], increased body mass index (BMI) [3], and left ventricular hypertrophy [4]. Finding the causes of SHPT, which was the purpose of the present study, may therefore be of clinical importance.

In 2001 a large epidemiological study was performed in Tromsø for the fifth time. Serum PTH and calcium were measured in almost 8000 subjects, enabling us to study a large group of subjects with SHPT.

Subjects and methods

The 5th Tromsø study was performed as a general health survey in 2001 in a manner similar to the previous ones [5]. All men and women older than 29 years living in the municipality of Tromsø and who participated in the second phase of the 4th Tromsø study [6] or became 30, 40, 45, 60, or 75 years old during 2001 were invited to participate. All subjects filled out a health questionnaire; they were also asked if they would prefer not to be invited to participate in additional studies based on the results from the present one. Nonfasting blood samples were obtained and measured for serum PTH and calcium. Subjects with serum calcium <2.40 mmol/l and PTH >6.4 pmol/l were considered to have SHPT; provided they had not declined participation in further studies, they were invited to a follow-up examination. Those who reported a history of coronary infarction, angina pectoris, or stroke in the questionnaire, those participating in other follow-up studies, and those above the age of 80, were not invited. The hospital records were also controlled to exclude subjects with serious diseases not reported in the questionnaire. For each subject with SHPT an age- and sex-matched control subject was also invited.

The follow-up study took place at the Clinical Research Unit at the University Hospital of North Norway 6–12 months after the 5th Tromsø study. A medical examination was performed and the medical history recorded. The use of blood pressure medication (including diuretics) was recorded. Height and weight were measured while the subjects wore light clothing and no shoes. The BMI was defined as weight (kg) divided by the height squared (m^2). Blood pressure was measured with an automatic device (Propaq 104 S/W version 6.0; Protocol Systems, Beaverton, OR, USA). The subjects were seated for 15 min, and three recordings were made at 2-min intervals. The mean value of the two last measurements was used. A food-frequency questionnaire that included 40 food items focusing on calcium and vitamin D intake was filled out, and daily intakes were calculated [7].

On a separate day fasting blood samples were obtained and a calcium absorption test performed according to the method described by Nordin et al. [8]. Blood samples were analyzed for serum calcium, phosphate, creatinine, PTH, 25-hydroxyvitamin D, and 1,25-dihydroxyvitamin D as previously described [9]. In our laboratory the reference range for serum calcium is 2.20–2.60 mmol/l, for serum phosphate 0.75–1.55 mmol/l, for serum PTH 1.1–6.8 pmol/l for those <51 years and 1.1–7.5 pmol/l for those >50 years, serum creatinine 55–100 μmol/l for women and 70–120 μmol/l for men, and for serum 25-hydroxyvitamin D 37–131 nmol/l and for 1,25-dihydroxyvitamin D 42–169 pmol/l.

Analysis of antibodies to gliadin and tissue transglutaminase were performed with enzyme immunoassays (Varelisa Gliadin IgA, Varelisa Gliadin IgG, and Celikey Tissue Trans-glutaminase IgA Antibody Assay; Pharmacia Diagnostics, Freiburg, Germany). Testing was performed according to the recommendations of the manufacturer. Subjects with a positive anti-tissue transglutaminase test or a strongly increased anti-gliadin immunoglobulin A (IgA) or IgG level (>50 U/ml) were considered to have celiac disease.

Urine was collected for 24 h, and the urinary calcium was measured (reference range 2.0–8.0 mmol/24 h).

Statistical analysis

Normal distribution was evaluated with visual inspection of histograms and determination of skewness and kurtosis. All variables, except intake of vitamin D, were considered normally distributed. After logarithmic transformation, vitamin D intake assumed a normal distribution and was used as such when evaluated as a dependent variable.

The SHPT group and the controls were compared using Student's *t*-test for independent samples; they were also compared using a general linear model, with the parameter in question as the dependent variable, SHPT/control group, gender, smoking status, and use of blood pressure medication as factors and age and BMI as covariables. In addition, for systolic and diastolic blood pressure, the serum calcium, phosphate, and 1,25-dihydroxyvitamin D were dependent variables, and creatinine was included as a covariable; for creatinine, systolic blood pressure was added as a covariable; and for 24-h urinary calcium excretion, serum creatinine and systolic blood pressure were added as covariables. In case of interaction between the factors, subgroup analyses were performed. Comparisons between the SHPT and the control group regarding gender, smoking status, and use of blood pressure medication were done with the chi-squared test.

To evaluate the cause of the SHPT, the number of subjects in the SHPT group who had a calcium and vitamin D intake, fractional calcium absorption, and serum 25-hydroxyvitamin D level below the control group's 5th percentile, and serum creatinine and 24-h urinary calcium excretion above the control group's 95th percentile, were recorded.

Unless otherwise stated, all data are expressed as the mean ± SD. All tests were done two-sided, and $P < 0.05$ was considered statistically significant. Statistical analyses were performed with SPSS version 11.0 (SPSS, Chicago, IL, USA).

Ethical approval

The study was approved by the Regional Ethics Committee, and all subjects gave their written informed consent to participate.

Results

Subjects

A total of 10419 men and women (age 30–89 years) were invited to participate in the 5th Tromsø study; 8128

Table 1. Serum PTH levels (pmol/l) at the 5th Tromsø study and at follow-up in the 202 subjects

Serum PTH level at 5th Tromsø study (pmol/l)	No. of subjects, by serum PTH level at follow-up				
	0.1–6.4 pmol/l	6.5–6.9 pmol/l	7.0–7.9 pmol/l	8.0–8.9 pmol/l	>8.9 pmol/l
0.1–6.4	104	2			
6.5–6.9	25	1	2	1	1
7.0–7.9	36		2	1	3
8.0–8.9	5	1	2	3	3
>8.9	4	1	1		4

Table 2. Demographic and biochemical variables at follow-up in SHPT and control groups

Variable	Original classification[1]		Follow-up classification[2]	
	SHPT	Controls	SHPT	Controls
Males/females	46/50	56/50	10/12	53/43
Age (years)	60.3 ± 13.9	60.8 ± 13.9	61.1 ± 15.6	61.3 ± 13.4
Smokers/nonsmokers	18/78[†]	36/70	2/20[†]	32/64
BP medication (yes/no)	31/65[‡]	17/89	2/20	15/81
BMI (kg/m^2)	28.1 ± 5.0	27.0 ± 3.9	29.1 ± 7.1	26.9 ± 3.9
Systolic BP (mmHg)	134.1 ± 22.9	128.7 ± 22.6	137.8 ± 22.5	128.2 ± 21.9
Diastolic BP (mmHg)	81.1 ± 11.8[a]	78.0 ± 11.1	83.6 ± 11.4[†]	77.7 ± 11.0
Serum PTH (pmol/l)	6.0 ± 2.2	3.2 ± 1.2	9.1 ± 2.1	3.1 ± 1.1
Serum calcium (mmol/l)	2.29 ± 0.10[‡b]	2.34 ± 0.10	2.21 ± 0.08[‡b]	2.35 ± 0.07
Serum phosphate (mmol/l)	0.99 ± 0.17	1.03 ± 0.14	0.97 ± 0.14	1.03 ± 0.14
Serum creatinine (μmol/l)	87.3 ± 20.0	84.8 ± 14.3	87.1 ± 18.7	85.5 ± 14.5
Serum 25-OH-vitamin D (nmol/l)	60.0 ± 16.7[c]	64.2 ± 18.4	53.5 ± 15.0[‡f]	65.0 ± 18.3
Serum 1,25-$(OH)_2$-vitamin D (pmol/l)	108.8 ± 38.1	110.3 ± 32.1	110.0 ± 42.4	109.8 ± 32.3
Calcium intake (mg/day)	674 ± 359[‡d]	842 ± 393	647 ± 369[†g]	847 ± 392
Vitamin D intake (μg/day)	10.6 ± 9.7	10.8 ± 7.5	10.9 ± 8.9	11.3 ± 7.6
Fractional calcium absorption	0.82 ± 0.28[†]	0.75 ± 0.17	0.75 ± 0.13	0.74 ± 0.17
Urinary Ca excretion (mmol/24 h)	3.59 ± 2.52[‡e]	4.94 ± 2.78	3.31 ± 2.39[†h]	4.90 ± 2.67

[1] Classified on basis of serum PTH levels from the 5th Tromsø study
[2] Those still fulfilling the SHPT and control group criteria at follow-up
[†] $P < 0.05$; [‡] $P < 0.01$ (Student's *t*-test or the chi-squared test)
[a] $P < 0.001$ for women; [b] $P < 0.001$; [c] $P < 0.05$ for nonsmoking men; [d] $P < 0.05$ for nonsmoking men; [e] $P < 0.05$ except for nonsmokers on blood pressure medication; [f] $P < 0.05$; for non-smokers; [g] $P < 0.05$ for men; [h] $P < 0.01$ for those not on blood pressure medication (linear regression)
SHPT, secondary hyperparathyroidism; BP, blood pressure; BMI, body mass index; PTH, parathyroid hormone

attended. Serum PTH and calcium were successfully measured in 7954. Altogether, 1893 subjects (988 men, 905 women; ages 68.0 ± 9.6 and 68.3 ± 10.7 years, serum PTH 3.8 ± 2.2 and 3.8 ± 2.1 pmol/l, and serum calcium 2.35 ± 0.09 and 2.37 ± 0.10 mmol/l, respectively) were excluded on the basis of the questionnaire. Of the 1893 subjects, 112 had SHPT according to our criteria. Among the remaining 6061 subjects (2459 men, 3602 women; age 56.5 ± 14.4 and 57.2 ± 14.0 years, serum PTH 3.3 ± 1.5 and 3.3 ± 1.6 pmol/l, and serum calcium 2.35 ± 0.08 and 2.36 ± 0.09 mmol/l, respectively), 166 subjects were considered to have SHPT. From the hospital records, 37 were found unfit for the follow-up study; accordingly, 129 subjects were invited to participate. Among them, 102 consented to participate, but two were excluded after the medical examination because of severe illness. Among the remaining 100 subjects, 4 were excluded because of a serological diagnosis of celiac disease. Thus, 96 subjects were included in the SHPT group based on serum PTH and calcium values from the 5th Tromsø study. For the control group, 149 subjects were invited, and 107 consented to participate. One subject was excluded because of severe illness at the medical examination. The remaining 106 subjects were included in the study.

At follow-up, 70 of those in the SHPT group now had serum PTH levels <6.5 pmol/l; and among the remaining 26 subjects, 4 had serum calcium >2.39 mmol/l. Accordingly, only 22 of the original SHPT group still met the original inclusion criteria. As expected, the tendency toward normalization of the serum PTH levels was most pronounced among those with marginally elevated serum PTH (Table 1). Among the original 106 control subjects, 96 still met the control subject criteria at follow-up (2 subjects had a serum PTH level >6.4 pmol/l, 7 had a serum calcium level <2.20 mmol/l, and 1 subject had serum calcium >2.60 mmol/l).

The results from the study are given both for the classification based on serum PTH and calcium levels from the 5th Tromsø study and for those still fulfilling the original criteria. They are summarized in Table 2.

SHPT and control group based on original classification from the 5th Tromsø study

The mean age and the male/female ratio were similar in the two groups. There were significantly more smokers in the control group than in the SHPT group (34.0% and 18.8%, respectively; $P < 0.05$). In both groups smokers had lower PTH levels than nonsmokers (5.5 ± 1.4 and 6.1 ± 2.4 pmol/l in the SHPT group, P = NS; and 3.1 ± 1.4 and 3.2 ± 1.1 pmol/l in the control group; P = NS). However, when analyzing the two groups together, the smokers had significantly lower PTH levels: 3.9 ± 1.8 and 4.7 ± 2.4 pmol/l, respectively; $P < 0.05$ (linear regression analysis).

Significantly more subjects in the SHPT group than in the control group used blood pressure medication (diuretics included) (32.3% and 16.0%, respectively; $P < 0.01$). In both groups the serum PTH levels were lower in those on blood pressure medication: for the SHPT group 5.4 ± 1.5 and 6.3 ± 2.4 pmol/l, respectively, and for the controls 3.0 ± 1.0 and 3.3 ± 1.3 pmol/l, respectively. In the SHPT group this difference was statistically significant when evaluated with Student's *t*-test ($P < 0.01$), but using the linear regression model it was significant only in nonsmokers (5.4 ± 1.6 and 6.4 ± 2.6 pmol/l, respectively; $P < 0.01$). In the SHPT group five subjects used a loop diuretic (PTH 5.0 ± 0.9 pmol/l) and three used a thiazide diuretic (PTH 5.1 ± 0.5 pmol/l); and in the control group three subjects used a thiazide diuretic (PTH 2.8 ± 0.6 pmol/l). These PTH levels were lower than in the subjects not using diuretics.

The BMI, systolic blood pressure, serum phosphate, and serum creatinine were nonsignificantly higher in the SHPT group. For diastolic blood pressure there was an interaction between the SHPT/control group and gender. When analyzed in regard to being sex-specific, the diastolic blood pressure was significantly higher in the SHPT females than in their controls (80.9 ± 9.6 and 74.6 ± 11.6 mmHg, respectively; $P < 0.001$), whereas the difference was not significant in the males (82.8 ± 12.4 and 79.6 ± 11.1 mmHg, respectively). As expected, serum calcium was significantly lower in the SHPT group than in the controls ($P < 0.001$).

The calcium intake was significantly lower in the SHPT group than in the controls (Student's *t*-test). However, there were significant interactions between SHPT/control group, gender, and smoking status. Thus, during subgroup analysis, the calcium intake was significantly lower only in nonsmoking males (660 ± 244 and 927 ± 398 mg/day in the SHPT and control groups, respectively; $P < 0.05$). The vitamin D intake was similar in the two groups.

Fractional calcium absorption was not measured in women below the age of 50 years (15 in the SHPT group and 18 in the control group). In addition 2 males in the SHPT group declined to do the test. Thus, 44 males and 35 females in the SHPT group and 56 males and 32 females in the control group underwent the calcium absorption test. Using Student's *t*-test, the fractional calcium absorption was significantly higher in the SHPT group. However, after adjusting for smoking status (in addition to age, these were the only significant predictors of fractional calcium absorption), the difference between the two groups was no longer significant.

The serum 25-hydroxyvitamin D levels were lower in the SHPT group. In the regression model there was an interaction between SHPT/control group, gender, and smoking status. In subgroup analyses, nonsmoking males in the SHPT group had significantly lower 25-hydroxyvitamin D levels than the corresponding controls (65.5 ± 15.8 and 69.9 ± 17.7 nmol/l, respectively; $P < 0.05$). The serum 1,25-dihydroxyvitamin D levels were almost identical in the two groups.

Regarding 24-h urinary calcium excretion, there was in the general linear model an interaction between SHPT/control group, smoking status, and use of blood pressure medication. However, 24-h urinary calcium excretion was significantly lower in the SHPT group than the controls in all subgroups ($P < 0.05$), except for nonsmokers on blood pressure medication.

The 24-h urinary calcium excretion was lower in those on blood pressure medication than in those not on it but significantly so only in the nonsmokers (3.09 ± 2.03 and 4.82 ± 2.82 mmol/day, respectively; $P > 0.001$, linear regression). All types of blood pressure medication, including thiazide and loop diuretics, reduced 24-h urinary calcium excretion.

The cutoff values for the 5th (or when appropriate the 95th) percentile obtained from the control group, and the percentage of those in the SHPT group who had an "abnormal" value, were for the calcium intake 345 mg/day and 17.7%, for the vitamin D intake 3.3 µg/day and 14.6%, for the fractional calcium absorption 0.49 and 3.8%, for the serum 25-hydroxyvitamin D level 37 nmol/l and 8.3%, for the serum creatinine level 114 µmol/l and 7.3%, and for 24-h urinary calcium excretion 10.7 mmol/day and 2.1%. Thus, among the SHPT group 44.8% had one or more "abnormal" values among the above parameters, in comparison to the control group in whom the corresponding figure was 21.7%.

If the smokers and those on blood pressure medication were excluded, there were significantly more females in the SHPT group ($P < 0.05$), but the main results were unchanged with significantly lower calcium intake and 24-h urinary calcium excretion ($P < 0.05$) (Table 3).

SHPT and control subjects who still met the inclusion criteria at follow-up

A statistical analysis similar to that for the original classification was performed. In general, the differences between the two groups were more pronounced than when the original classification was used (Table 2). However, the SHPT group was now considerably smaller, and the differences versus the controls were only statistically significant in the linear regression model for 25-hydroxyvitamin D in nonsmokers (53.1 ± 14.1 and 67.2 ± 18.2 nmol/l, respectively; $P < 0.05$), for calcium intake in males (619 ± 233 and 902 ± 365 mg/day, respectively; $P < 0.05$), and for the 24-h urinary calcium excretion in those not on blood pressure medica-

Table 3. Demographic and biochemical variables at follow-up in the SHPT and control groups for nonsmokers who were not using blood pressure medication

Variable	Original classification[1]		Follow-up classification[2]	
	SHPT	Controls	SHPT	Controls
Males/females	23/27[†]	37/20	10/8	36/18
Age (years)	59.0 ± 15.4	61.4 ± 14.3	63.4 ± 15.5	62.5 ± 13.8
BMI (kg/m^2)	27.9 ± 5.5	26.7 ± 3.4	30.2 ± 7.1[‡b]	26.6 ± 3.4
Systolic BP (mmHg)	130.3 ± 23.1	128.8 ± 18.8	139.4 ± 20.9[a]	129.0 ± 18.7
Diastolic BP (mmHg)	79.3 ± 12.4	79.2 ± 10.4	84.1 ± 12.5	78.9 ± 10.4
Serum PTH (pmol/l)	6.4 ± 2.6	3.2 ± 1.2	9.3 ± 2.1	3.2 ± 1.1
Serum calcium (mmol/l)	2.28 ± 0.10[‡b]	2.34 ± 0.08	2.21 ± 0.09[‡b]	2.35 ± 0.07
Serum phosphate (mmol/l)	0.99 ± 0.17	1.00 ± 0.14	0.96 ± 0.14	1.00 ± 0.14
Serum creatinine (μmol/l)	84.8 ± 18.7	87.4 ± 16.3	87.3 ± 18.8	87.8 ± 16.4
Serum 25-OH-vitamin D (nmol/l)	61.8 ± 17.9	64.9 ± 17.9	53.5 ± 15.6[†]	65.7 ± 17.9
Serum 1,25-$(OH)_2$-vitamin D (pmol/l)	107.6 ± 35.0	116.7 ± 32.8	110.2 ± 37.6	116.3 ± 33.1
Calcium intake (mg/day)	651 ± 320[‡a]	867 ± 407	709 ± 379[c]	864 ± 403
Vitamin D intake (μg/day)	9.6 ± 8.0	11.0 ± 8.0	11.3 ± 9.6	11.4 ± 8.0
Fractional calcium absorption	0.83 ± 0.30	0.78 ± 0.19	0.73 ± 0.11	0.77 ± 0.18
Urinary Ca excretion (mmol/24 h)	4.13 ± 2.71[†a]	5.45 ± 2.81	3.66 ± 2.49[†b]	5.44 ± 2.56

[1] Classified on the basis of serum PTH levels from the 5th Tromsø study
[2] Those still fulfilling the SHPT and control group criteria at follow-up
[†] $P < 0.05$; [‡] $P < 0.01$ (Student's *t*-test or the chi-squared test)
[a] $P < 0.05$; [b] $P < 0.001$; [c] $P < 0.05$ for males (linear regression)

tion (3.4 ± 2.5 and 5.3 ± 2.6 mmol/day, respectively; $P < 0.01$).

Using the same criteria as for the original SHPT group, 18.2% had low calcium intake; 18.2% had low vitamin D intake; none had low fractional calcium absorption; 18.2% had a low serum 25-hydroxyvitamin D level; 4.5% had a high serum creatinine level; and none had a high 24-h urinary calcium excretion. Thus, among the SHPT group 54.5% had one or more "abnormal" values among the above parameters.

In the nonsmokers not on blood pressure medication, BMI and systolic blood pressure were now significantly higher in the SHPT group than in the controls ($P < 0.001$ and $P < 0.05$, respectively) (Table 3).

Discussion

There are several reports on predictors for the serum PTH level. In addition to serum ionized calcium, which is the main regulator of PTH secretion [1], there is general agreement that serum PTH increases with age [2,10], BMI [3,10], creatinine [11,12], and possibly with increasing serum phosphate levels [13]. Furthermore, the serum 25-hydroxyvitamin D level is of importance, and it has been suggested that the reference range for PTH should be viewed in relation to vitamin D status [14]. On the other hand, the present study is, to our knowledge, the first one focusing on causes of SHPT in a general population.

Secondary hyperparathyroidism is the result of the body being in calcium deficit, with increased PTH secretion a compensatory mechanism. The calcium deficit could be caused by reduced calcium intake, reduced intestinal calcium absorption, or increased renal calcium excretion. As for the calcium intake, we found it to be reduced in the SHPT group, which confirms our previous report on subjects with SHPT studied after the 4th Tromsø study [9]. The intake was 20%–25% lower in all subgroups tested, but it reached statistical significance only in nonsmoking males.

The intestinal calcium absorption was measured as fractional absorption of ingested radioactive labeled calcium. The calcium absorption was reduced with age and was also reduced in smokers, as recently reported by Need et al. [15]. However, it was not reduced in the SHPT group. This is also in accordance with another report from Need et al. that in a large group of postmenopausal women no relation was found between the serum PTH level and calcium absorption [16].

Vitamin D is important both for the serum PTH level and intestinal calcium absorption. 1,25-Dihydroxyvitamin D is the only hormone with a direct effect on calcium absorption [17], whereas the 25-hydroxyvitamin D level is the best measure of the body's vitamin D status. We did find the 25-hydroxyvitamin D levels to be lower in the SHPT group; but as for calcium intake, the difference was statistically significant only in nonsmoking males. In our population there is a high intake of fatty fish and frequent use of vitamin D supplementation, which can probably explain the high serum 25-hydroxyvitamin D levels found. In this respect our findings are in accordance with the report from the MORE study where Norwegian postmenopausal women were among those with the highest serum 25-hydroxyvitamin D levels [18]. In populations with a lower 25-hydroxyvitamin D level, vitamin D deficiency is probably a more frequent cause of SHPT than that found by us.

Parathyroid hormone is one of the main regulators of urinary calcium excretion [1], and increased resorption of calcium from the glomerular filtrate is important for conserving body calcium when there is a deficit. Calcium excre-

tion was significantly lower in the SHPT group, except in nonsmokers on blood pressure medication. Accordingly, increased urinary calcium loss is not a frequent cause of increased PTH levels, and the reduced urinary calcium excretion fits well with the observation of reduced calcium intake in the SHPT group. Finally, the serum creatinine levels, which are important for serum PTH [11,12], were almost identical in the two groups.

We tried to estimate the most important causes of SHPT by defining what could be considered an "abnormal" level for the various factors affecting the calcium balance. Lacking a better definition, we chose the upper or lower 5th percentile for the controls as the cutoff level for an "abnormal" value. Using this approach, low calcium intake appeared to be the most important single factor and could "explain" the SHPT in approximately 18%—both when SHPT was classified on the basis of measurements from the 5th Tromsø study and when SHPT was persistent. In the latter group, a low serum 25-hydroxyvitamin D level was also seen in about 18%. However, for the calcium intake and the vitamin D level, as for the other predictors, there was a great overlap between the two groups, and most of those with SHPT had "normal" values for all predictors evaluated in this way.

In addition to established predictors for the PTH level, we also looked specifically at the influence of smoking status and blood pressure medication, as there were several interactions between these variables and the SHPT/control group when used as factors in the regression analyses. Regarding smoking status, the smokers had significantly lower serum PTH levels, which has also been reported from some [10,15] but not all [19,20] previous studies. The number of smokers was significantly higher in the control group, and it is therefore conceivable that smoking did mask SHPT in some of the borderline cases in the control group.

Similarly, those on blood pressure medication had lower PTH levels than those not using blood pressure medication. Although this was significant only in nonsmoking males in the SHPT group, it could possibly also mask some cases of SHPT. It has been reported that antihypertensive drugs, regardless of type, reduce calcium excretion in hypertensive subjects [21], which again could reduce the serum PTH levels. In accordance with this, we found lower urinary calcium excretion in those on blood pressure medication, regardless of the type of drug. We also found the serum PTH levels to be lower in those on diuretics, both loop and thiazide types, in contrast to what Rejnmark et al. [22] reported. In their study, which had an experimental design, both loop and thiazide diuretics caused an increase in serum PTH in postmenopausal women. The number of subjects on diuretics in our study was small, and our observations on diuretics and PTH levels must therefore be viewed with caution.

It has been documented in both in vitro [23] and in vivo [24] studies that an acute elevation of phosphate in the incubation medium or in serum to supraphysiological levels stimulates secretion of PTH. Furthermore, in renal failure the prolonged elevation of serum phosphate appears to increase PTH secretion and gene expression as well as cause parathyroid cell proliferation [13]. However, in our study the serum phosphate levels were only nonsignificantly higher in those with SHPT than in the controls. Accordingly, the serum phosphate level does not appear to be a major determinant of PTH secretion, at least when it is only marginally elevated in subjects with normal kidney function.

As expected, there was a considerable regression toward the mean for the PTH levels in the SHPT group at the follow-up examination, in particular in subjects with marginally increased PTH levels. In many ways those with persistent SHPT would be the most interesting group to study, as differences between these subjects and the controls should be more pronounced. This was also the case in particular for the serum 25-hydroxyvitamin D levels. Similarly, because smoking status and the use of blood pressure medication did affect the results, we also did the analyses with smokers and users of blood pressure medication excluded. Again, the same main findings were disclosed.

The strength of the present study is that our subjects were recruited on the basis of an epidemiological survey and careful adjustment for confounding factors. However, our study has several shortcomings. Although the number of subjects with serum PTH measurement in the 5th Tromsø study was close to 8000, only 96 subjects with SHPT were finally included in the study, in whom SHPT was persistent in only 22. Furthermore, there were several interactions between SHPT/control group, sex, smoking status, and use of blood pressure medication, necessitating the use of subgroup analysis. It follows that these groups became small with accompanying loss of power during statistical testing. In addition, the follow-up examinations were performed 6–12 months after the serum PTH and calcium measurements on which the initial SHPT classification was based; and our classification of SHPT (serum PTH >6.4 pmol/l and serum calcium <2.40 mmol/l) is not in general use. Thus, others have classified SHPT as an increased serum PTH level with serum calcium within the reference range [25]. Our reason for choosing a lower calcium level was to exclude subjects with primary hyperparathyroidism, as it may exist with serum calcium levels in the upper normal range [26]. We also believe that choosing a serum PTH level that was lower than the upper limit in the reference range was reasonable, in view of the report by Souberbielle et al. showing that the upper limit is approximately 10% lower if only considering those with a normal serum 25-hydroxyvitamin D level [14]. Finally, SHPT (at least when persistent) is probably the result of a negative calcium balance that has been ongoing for years. Our measurements at one time point may therefore not give a true picture of a long-lasting situation.

In conclusion, a low calcium intake and a low serum 25-hydroxyvitamin D level for those with persistent SHPT appeared to be the most frequent causes of SHPT in our population. However, no single cause could be found for most subjects, and SHPT, at least when persistent, is probably the result of several factors working together for a long period of time.

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