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ORIGINAL CONTRIBUTION

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The effects of calcium supplementation to patients with primary hyperparathyroidism and a low calcium intake

Summary *Background* In patients with primary hyperparathyroidism (PHPT) a low calcium intake might cause increased bone loss and thus aggravate osteoporosis, and a high intake might increase serum calcium level and the risk of nephrolithiasis. *Aim of the study* Generally, guidelines recommend a normal calcium intake, and accordingly, those with a low intake might benefit from a modest calcium supplementation. This hypothesis was tested in the present study. *Methods* Thirty-one patients with asymptomatic PHPT were recruited from an epidemiological study (The Tromsø study 1994/95). Those with a daily calcium intake below 450 mg were given calcium supplementation (500 mg Ca^{2+}), and those with an intake above 450 mg were followed without supplementation. The study was open and lasted 1 year. Serum levels of calcium, PTH, 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D, urinary calcium excretion, blood pressure, and bone mineral density (BMD) were measured. *Results* Three subjects dropped out without reason, 1 developed abdominal discomfort from the calcium supplementation, and 3 had an increase in serum calcium of more than 0.2 mmol/L and were therefore excluded. The latter three did not differ from the rest of the group at baseline. Of the remaining 24 that completed the study, 17 were given calcium. In this group there was a non-significant increase in serum calcium and urinary calcium excretion, a significant decrease in PTH after 4 weeks (13.2 (6.0) vs 9.4 (3.0) pmol/L, $P < 0.05$), and a significant increase in BMD at the femoral neck at the end of the study (0.849 (0.139) vs 0.870 (0.153) g/cm^2, $P < 0.05$). The blood pressure was not significantly affected. *Conclusions* Most patients with mild PHPT and a low calcium intake tolerate a moderate calcium supplement. This may have beneficial effects on the bones, but the patients must be followed carefully.

Key words calcium supplementation – hyperparathyroidism – parathyroid hormone – bone mineral density

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Introduction

Parathyroidectomy is the appropriate treatment for patients with symptomatic primary hyperparathyroidism (PHPT). However, due to the increasing availability of multianalyzers in clinical chemistry, most patients with PHPT today are diagnosed with mild disease. The treatment of these patients has been much debated and several guidelines and reviews have been published [1–4]. Generally, the guidelines for treatment of PHPT are specific regarding indications for surgery, but they do not give authoritative advice concerning amount of calcium that should be ingested during surveillance. Thus, in the NIH Consensus development conference statement [1] it is only recommended that "the patients should avoid dehydration, immobilization, and a diet with restricted or excess calcium."

EJN 383

Obviously, a diet with excess calcium could lead to increased serum calcium levels, increased urinary calcium excretion and thereby an increased risk of renal stones, which is a frequent complication to PHPT [2, 5]. On the other hand, a low intake of calcium could further increase the tendency towards the osteoporosis frequently found in these patients. One logical solution to this would be to recommend increased intake of calcium to those on a low calcium diet, and not to recommend supplementation to those with an adequate intake.

To our knowledge there are no long-term studies where the effect of calcium supplementation has been evaluated in patients with PHPT. In the fourth Tromsø study in 1994/95 serum calcium was measured in 27,000 individuals, and a substantial group of subjects with asymptomatic PHPT detected [6]. Several of these patients had a very low calcium intake, and the present study with calcium supplementation was therefore undertaken.

Materials and methods

Patients

Patients with asymptomatic PHPT diagnosed following the Tromsø study 1994/95 [6], with serum calcium below 2.85 mmol/L (not adjusted for serum albumin), without serious concomitant disease, with normal kidney function, and age below 80, were recruited to participate in the study.

Study design

At the initial visit all subjects filled out a food frequency questionnaire on dietary habits that included questions on consumption of milk, cheese, yogurt, bread and butter [7]. The intake of calcium was calculated, and if the intake was below 450 mg per day, they were given daily calcium supplementation with one tablet 1260 mg calcium carbonate (500 mg Ca^{2+}) (Weifa-Kalcium, Weifa, Oslo, Norway). If they had an intake at or above 450 mg calcium per day they were not given any calcium supplementation. All subjects were asked to continue their usual diet, and particularly asked not to start any other calcium or vitamin D supplementation. The food frequency questionnaire was repeated after 4, 12 and 52 weeks. The subjects were included during April and May 2000.

Laboratory investigations

Blood samples for serum calcium, phosphate and PTH were drawn at the start of the study and after 4, 12, 30, and 52 weeks in all subjects. In addition, serum calcium and PTH were also measured after one week in those given calcium supplementation. Blood samples for creatinine, 25-hydroxyvitamin D_3 and 1,25-dihydroxyvitamin D were drawn at the start of the study. The subjects were not requested to fast. Twenty-four hour urine samples were collected before and after 4, 12, and 52 weeks and analyzed for calcium.

Serum calcium (reference range 2.20–2.60 mmol/L), urinary calcium (reference range 2–8 mmol/24 h), serum phosphate (reference range 0.75–1.55 mmol/L), serum PTH (reference range 1.1–6.8 pmol/L if age < 50 years, 1.1–7.5 pmol/L if > 50 years), creatinine (reference range 55–100 μmol/L for women, 70–120 μmol/L for men), 25-hydroxyvitamin D3 (reference range 30–110 nmol/L), and 1,25-dihydroxyvitamin D (reference range 50–145 pmol/L) were analyzed as previously described [6]. The 1,25-dihydroxyvitamin D assay gives the sum of 1,25-dihydroxyvitamin D2 and D3.

Blood pressure was measured with an automatic device (Propac S/W version 6.0; Protocol systems, Beaverton, Oregon, USA) before and after 4, 12, and 52 weeks. The subjects were seated for 5 minutes before the first of 3 measurements, one minute apart. The mean of the two last measurements was used in the analysis.

Bone mineral density (BMD) was measured before and at the end of the study using a Lunar DPX-L dual energy X-ray absorptiometer (Lunar Radiation Corporation, Madison, Wisconsin, USA). Separate scans for the lumbar spine in the posterioanterior (L1-L4) projection and the proximal femur (femoral neck, Ward's triangle, and trochanter) were carried out and analyzed with the manufacturer's software version 1.3. Twice a week quality-control scans with a phantom skeleton were performed, and the measurements were stable throughout the study.

New calcium tablets were dispensed and unused tablets counted after 4, 12, and 52 weeks.

Statistics

The results are given as mean (SD) if not stated otherwise. The two groups (those given calcium supplementation and those not) were compared with unpaired Student's *t*-test. Comparison between results before and 4, 12, 30, and 52 weeks after the start of the study was performed with ANOVA. Post hoc testing was done with paired Student's *t*-test with the Bonferroni correction when appropriate. Correlation between serum 1,25-dihydroxyvitamin D and urinary calcium excretion was evaluated with the Pearson correlation coefficient (*r*). All tests were done two-sided, and a P value of less than 0.05 was considered significant. Statistical analysis was carried out using SPSS version 10.0 (SPSS Inc., Chicago, USA).

Ethics

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

Results

Subjects

Thirty-one subjects (7 males) were included. Three females (two assigned to calcium supplementation) only came to the first visit and declined further follow-up. One female assigned to calcium supplementation stopped taking calcium after 10 days because of abdominal discomfort, and was excluded from the study. Three females given calcium supplementation had an increase in serum calcium of more than 0.2 mmol/L. In all three a repeated serum calcium within one week confirmed that the increase was sustained, and according to the protocol, the calcium supplementation was stopped and the patients withdrawn from the study. They did not experience any clinical symptoms of hypercalcemia, and their serum calcium levels returned to baseline after stopping the supplementation. Their individual data are given in Table 1. Of those not receiving calcium supplementation, none had an increase in serum calcium above 0.2 mmol/L.

Baseline data

Of the 24 subjects that completed the study, 17 (5 males) had a calcium intake below 450 mg per day and were thus given calcium supplementation. Their mean (SD) age was 68.9 (8.6) years, serum creatinine 83.2 (12.1) µmol/L, serum 25-hydroxyvitamin D_3 52.6 (18.4) nmol/L, and serum 1,25-dihydroxyvitamin D 143.7 (36.6) pmol/L. The corresponding data in the 7 subjects (2 males) not given calcium supplementation was 65.6 (10.3) years, 79.6 (14.9) µmol/L, 69.4 (20.1) nmol/L, and 145.7 (42.0) pmol/L, respectively. Apart from calcium intake there was no significant difference in baseline data between the two groups (Table 2). There was no significant correlation between serum 1,25-dihydroxyvitamin D and urinary calcium excretion ($r = 0.27$), nor between 1,25-dihydroxyvitamin D and the increase in calcium excretion ($r = -0.34$).

Results during the study

In those given calcium supplementation there was a non-significant increase in serum calcium after 4 and 12 weeks, and a significant decrease in serum PTH after 4 weeks ($P < 0.05$). The serum phosphate levels were not significantly affected. There was a non-significant increase in urinary calcium excretion after 4, 12 and 52 weeks. There was an increase in BMD at all sites mea-

Table 1 Serum calcium, phosphate, PTH, creatinine, 25-hydroxyvitamin D_3, 1,25-dihydroxyvitamin D, 24-h urinary calcium excretion, and dietary calcium intake, before, during, and after termination of calcium supplementation in the 3 subjects with an increase in serum calcium of more than 0.2 mmol/L

	Before	1 week	4 weeks	12 weeks	30 weeks	After
Subject 1 (age73)						
S. calcium (mmol/L)	2.60	2.61	2.66	2.77	2.88	2.70
S. phosphate (mmol/L)	0.81		0.72	0.80	0.91	0.82
S. PTH (pmol/L)	12.7	11.4	9.0	11.9	8.2	15.6
S. creatinine (µmol/L)	92					
S. 25-OH vit D3 (nmol/L)	42					
S. 1,25-OH vit D (pmol/L)	105					
24-h urinary Ca (mmol/day)	4.0		9.5	14.4		
Calcium intake (mg/day)	262.0		172.5	177.0		
Subject 2 (age 75)						
S. calcium (mmol/L)	2.81	3.14				2.89
S. phosphate (mmol/L)	0.64					0.72
S. PTH (pmol/L)	9.8	11.7				9.6
S. creatinine (µmol/L)	85					
S. 25-OH vit D3 (nmol/L)	53					
S. 1,25-OH vit D (pmol/L)	141					
24-h urinary Ca (mmol/day)	2.7					
Calcium intake (mg/day)	332.0					
Subject 3 (age 60)						
S. calcium (mmol/L)	2.76	2.82	2.85	2.90	3.03	2.64
S. phosphate (mmol/L)	0.50		0.81	0.76	0.68	0.73
S. PTH (pmol/L)	12.1	10.0	7.7	10.1	4.7	12.2
S. creatinine (µmol/L)	73					
S. 25-OH vit D3 (nmol/L)	24					
S. 1,25-OH vit D (pmol/L)	191					
24-h urinary Ca (mmol/day)	9.0		12.0	10.8		
Calcium intake (mg/day)	159.0		206.5	411.5		

Table 2 Serum calcium, phosphate and PTH, urinary calcium excretion, dietary calcium intake and bone mineral density, before and during the study, in those given calcium supplementation and in those not

	Before	1 week	4 weeks	12 weeks	30 weeks	52 weeks
Subjects given calcium (n = 17)						
S. calcium (mmol/L)	2.65 (0.13)	2.67 (0.14)	2.68 (0.14)	2.69 (0.14)	2.69 (0.12)	2.60 (0.13)
S. phosphate (mmol/L)	0.83 (0.13)		0.77 (0.12)	0.82 (0.13)	0.84 (0.14)	0.79 (0.13)
S. PTH (pmol/L)	13.2 (6.0)	11.6 (4.3)	9.4 (3.0)*	9.1 (2.9)	11.4 (4.2)	13.0 (4.7)
24-h urinary Ca (mmol/day)	6.5 (2.3)		8.0 (3.6)	8.1 (3.6)		7.9 (4.0)
Calcium intake (mg/day)	244.4 (101.2)		352.0 (182.8)	355.8 (115.8)		378.9 (193.7)
Bone mineral density (g/cm^2)						
Lumbar spine	1.016 (0.187)					1.060 (0.178)
Femoral neck	0.849 (0.139)					0.870 (0.153)*
Ward's triangle	0.708 (0.166)					0.725 (0.172)
Trochanter	0.804 (0.170)					0.825 (0.155)
Subjects not given calcium (n = 7)						
S. calcium (mmol/L)	2.65 (0.12)		2.59 (0.14)	2.60 (0.16)	2.68 (0.14)	2.59 (0.12)
S. phosphate (mmol/L)	0.81 (0.13)		0.79 (0.17)	0.86 (0.13)	0.76 (0.21)	0.79 (0.18)
S. PTH (pmol/L)	17.6 (6.9)		15.6 (6.8)	14.2 (7.6)	15.6 (9.3)	17.4 (9.8)
24-h urinary Ca (mmol/day)	7.6 (5.1)		7.1 (3.9)	6.8 (3.5)		6.6 (3.4)
Calcium intake (mg/day)	912.8 (480.9)		785.7 (602.1)	928.5 (559.8)		675.1 (536.5)
Bone mineral density (g/cm^2)						
Lumbar spine	1.028 (0.164)					1.024 (0.180)
Femoral neck	0.799 (0.133)					0.787 (0.135)
Ward's triangle	0.662 (0.146)					0.656 (0.158)
Trochanter	0.792 (0.145)					0.807 (0.146)

* $P < 0.05$ vs. values before the start of the study

sured, and the increase was significant at the femoral neck ($P < 0.05$). In those not given calcium supplementation, serum calcium, PTH, urinary calcium excretion and BMD remained stable throughout the study (Table 2).

Those initially on a low calcium diet had a non-significant increase in calcium intake of 107–134 mg per day during the study (Table 2).

There was a similar and non-significant decrease in both systolic and diastolic blood pressure in the two groups. For those given calcium the systolic and diastolic blood pressure were 142.6 (15.3) and 86.6 (9.0) before, and 136.4 (13.4) and 81.5 (7.2) mmHg after the end of the study, respectively. The corresponding data for those not given calcium were 146.7 (21.5) and 86.9 (13.5), and 145.5 (21.8) and 82.9 (9.0) mmHg, respectively.

In those given calcium supplementation, the compliance rates after 4, 12 and 52 weeks were 91.9 (19.8), 92.0 (10.7), and 90.1 (17.5) %, respectively.

Discussion

In the present study a moderate calcium supplementation of 500 mg was given to patients with asymptomatic PHPT who where consuming a diet low in calcium. The compliance rate was remarkably high, and an increase in urinary calcium excretion of approximately 25 % was seen. There was an increase in serum calcium level, but the increase was modest, only seen during the first three months, and statistically not significant. This increase in serum calcium was accompanied by a significant decrease in serum PTH. However, at the end of the study, serum calcium and PTH returned to baseline values, in spite of a persistently high compliance rate and a high urinary calcium excretion. This may indicate some sort of adaptation to a new level of calcium intake. Alternatively, it could also be the result of increased cutaneous vitamin D production during the summer months. If so, this would increase the calcium absorption and thereby reduce the serum PTH levels.

The initial increase in serum calcium and decrease in serum PTH are in accordance with earlier reports on short-term effects of oral calcium in patients with PHPT. Thus, Insogna et al. [8] compared the effects of a diet containing 400 mg calcium versus a high/normal diet with 1000 mg calcium. After only three days with the high/normal diet, they found a 3 % increase in serum calcium and a 13 % decrease in serum PTH. Accordingly, the parathyroid function is not autonomous in most patients with PHPT, but subject to suppression by exogenous calcium.

In 17 out of the 21 subjects given calcium, the supplementation was well tolerated. However, one subject stopped taking the calcium tablets because of abdominal discomfort, and three had a sustained increase in serum calcium of more than 0.2 mmol/L. This occurred after only one week in one patient, whereas in the two others this developed gradually and exceeded

0.2 mmol/L first after 30 weeks. In all three the serum calcium returned to baseline values shortly after stopping the supplementation.

At inclusion, these three patients did not differ from the rest of the cohort regarding age, serum calcium, PTH and creatinine. In particular, the levels of 25-hydroxyvitamin D_3 or 1,25-dihydroxyvitamin D were not markedly increased. Furthermore, there was no concurrent illness, history of dehydration, increased dietary calcium, new drugs or vitamin D supplementation that could explain the increase in serum calcium. It is therefore not possible to predict which patients with PHPT will have an unwanted increase in serum calcium after calcium supplementation. Of note was the apparent lack of PTH suppression in the one subject that had an increase in serum calcium from 2.81 to 3.14 mmol/L within one week, indicating an exceptionally autonomous PTH secretion. In the other two, serum PTH was, at least to some extent, suppressed by the increase in serum calcium.

One argument against calcium supplementation in patients with PHPT, apart from increasing the hypercalcemia, is the risk of precipitating the formation of renal stones. This is a frequent complication of PHPT, probably because of the increased urinary calcium excretion [9]. None of our subjects had a history of nephrolithiasis prior to the study, nor did any of them develop symptom-producing stones during the study. However, they did increase their calcium excretion, and one should obviously be careful with calcium supplementation to patients with a history of renal stones. There are previous reports [10, 11] that the urinary excretion of calcium in PHPT is related to the level of 1,25-dihydroxyvitamin D. We could not confirm this in our study, nor was there a relation between the level of 1,25-dihydroxyvitamin D and the increase in urinary calcium after supplementation. However, because of the biological effects of 1,25-dihydroxyvitamin D [12], it is plausible that such a relation could exist, and until larger studies are available, one should be cautious with calcium supplementation if the level of 1,25-dihydroxyvitamin D is particularly high.

Renal stone disease is a strong indication for surgery in PHPT [4]. It is generally believed that surgery has a good effect on renal stone production, but recently a report by Frøkjaer and Mollerup [5] has questioned this relationship. Thus, in their study PHPT patients with renal stone disease did not differ preoperatively from those without renal stones regarding urinary calcium excretion. However, one to three years after surgery those with previous stone disease had higher urinary calcium excretion than those without renal stones. This indicates that factors not related to the hyperparathyroid state could contribute to the disturbance in renal calcium excretion and hence stone formation in PHPT.

Hydrochlorothiazide, which reduces the renal excretion of calcium and enhances calcium balance, is a treatment option for patients with hypercalciuria and renal stones [4]. In PHPT, hydrochlorothiazide is not contraindicated [4], but may, similar to oral calcium supplementation, cause hypercalcemia and careful monitoring is therefore necessary.

Even patients with moderate PHPT have a tendency towards osteopenia [13] which is corrected with parathyroidectomy [14, 15]. Furthermore, there may be an increased risk of fracture in these patients, at least before surgery is performed [16]. An adequate amount of calcium intake is the backbone of osteoporosis prevention [17]. In patients with PHPT a diet low in calcium could further aggravate the risks of osteoporosis, and to such patients calcium supplementation might therefore be of benefit. To assess this, we measured the BMD before and at the end of the study. In those on a low calcium diet given calcium, there was after one year an increase in BMD of 2–6 %, depending on site of measurement. This increase was consistent and was significant at the femoral neck, and in magnitude approximately half that seen after treatment with estrogen or a bisphosphonate [18]. In those not given calcium, no change in BMD was seen.

At inclusion, we considered our patients to be asymptomatic. Their serum calcium levels were below 2.85 mmol/L, none had symptomatic renal stone disease, none had obvious neuropsychiatric problems, and none expressed a feeling of ill-health. For the latter, however, we did not do any detailed examinations, and whether they were truly asymptomatic can therefore be questioned. Thus, in a study by Okamoto et al. [19], in patients with moderate PHPT, careful neuropsychological testing revealed psychological distress, which was ameliorated after surgery, in more than 50 %.

Our patients consumed a diet very low in calcium. The increase in serum calcium of more than 0.20 mmol/L seen in the three patients after normalizing the calcium intake by calcium supplementation may be considered to have disclosed, at least in a biochemical sense, a symptomatic state. Given the generally low BMD in patients with PHPT, and our finding of a positive effect on the BMD by calcium supplementation, it is therefore possible that a sustained increase in serum calcium after normalization of the calcium intake could be considered an indication for surgery.

In the guidelines from the National Institutes of Health [1], management of patients with PHPT, where surgery is not indicated, is to "avoid dehydration, immobilization, and a diet with restricted or excess calcium". Recent reviews are no more specific than this regarding calcium intake. Thus, Zahrani and Levine [2] advise that "until more information is available, patients should moderate their dietary calcium intake and avoid calcium or vitamin D supplements", and Davis et al. [4] include in their conservative treatment of PHPT "maintenance

of normal calcium and vitamin D nutrition". And finally, in a review by Marx [3] it is recommended that patients who do not undergo surgery "should be advised to avoid dehydration and to keep their calcium intake at or below 1000 mg per day". These recommendations and consensus statements are not evidence-based, as there are so far no long-term intervention studies published. Hopefully our study will give at least some evidence on which to base future recommendations. However, before summarizing, several obvious shortcomings in our study must be pointed out. First of all, the study was not placebo controlled. Although the seven subjects not given calcium were similar to the others except for their calcium intake, that group was too small to act as a proper control group. Furthermore, the number of subjects that completed the study was only 17, and additional adverse effects of calcium supplementation may therefore not have been detected by us. Our subjects were also highly selected as they had asymptomatic disease that was detected through a population study. Our results may therefore not apply to those with PHPT usually seen in clinical practice. And finally, the calcium intake was calculated from a food frequency questionnaire, which is not as accurate as an interview by a dietician. However, the reproducibility of this questionnaire has been evaluated, and there is at least a high concordance between answers given to the same questions one year apart [20]. The questionnaire mainly records the dairy intake, which in a Norwegian diet usually represents ≈ 75 % of the total calcium intake. In spite of this, the calculated intake was remarkably low and one may speculate that the subjects themselves had reduced their intake in an effort to lower their serum calcium.

Although there are these limitations, we believe it is prudent to assume that in most patients with asymptomatic PHPT on a diet low in calcium, a moderate calcium supplementation is safe to give, and may probably have beneficial effects on the bones. However, a few patients did show an unacceptable increase in serum calcium. Therefore, these patients have to be followed carefully at least during the first year of calcium supplementation.

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