Health-related quality of life after successful surgery for primary hyperparathyroidism: no additive effect from vitamin D supplementation: results of a double-blind randomized study

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Abstract

Objective: Vitamin D insufficiency is common in primary hyperparathyroidism (pHPT). Patients with pHPT frequently have a reduced health-related quality of life (HRQoL). Our objectives were to evaluate whether HRQoL in pHPT is associated with vitamin D insufficiency and whether vitamin D supplementation after parathyroidectomy (PTX) could improve HRQoL. **Design:** A randomized, double-blind study (ClinicalTrials.gov identifier: NCT00982722).

Methods: The study included 150 pHPT patients randomized, 6 weeks after PTX, to daily treatment with either cholecalciferol 1600 IU and calcium carbonate 1000 mg (D+) or calcium carbonate alone (D−). HRQoL was estimated with SF-36 before and after PTX and after 12 months of study medication.

Results: Three-quarters (77%) of the pHPT patients had vitamin D insufficiency, defined as 25OHD <50 nmol/l. The pHPT patients scored lower than a reference population in all domains of SF-36. A total of 135 patients completed the entire study period. Improvements in nearly all domains were registered at the follow-up 6 weeks after PTX. At the end of the study medication period, the D+ group had a significantly higher median serum (s-) 25OHD concentration (76 (65; 93) (lower; upper interquartile ranges) vs 48 (40; 62) nmol/l, $P < 0.001$) and a lower plasma (p-) parathyroid hormone concentration (40 (34; 52) vs 49 (38; 66) ng/l, $P = 0.01$) than the D− group. The improvements in HRQoL remained unchanged at the follow-up 1 year after PTX. Postoperative vitamin D supplementation had no obvious effect on HRQoL.

Conclusion: PTX resulted in significant improvements in HRQoL. Despite a high prevalence of vitamin D insufficiency, 1 year of postoperative vitamin D supplementation had no obvious beneficial effect on HRQoL.

European Journal of
 Endocrinology
 (2015) 172, 181–187

Introduction

Primary hyperparathyroidism (pHPT) is a common endocrine disorder, characterized by an inappropriately high secretion of parathyroid hormone (PTH) from one or more of the parathyroid glands, causing an elevated plasma concentration of calcium. The incidence increases with age (1). Neurocognitive symptoms, depression, and impairment of health-related quality of life (HRQoL) are

overrepresented in pHPT (2). Successful parathyroidectomy (PTX) has been associated with improvements in HRQoL, but the reported results are not consistent (2, 3, 4, 5, 6, 7, 8). Based on the recent guidelines, data indicating a predictable improvement are still not sufficient to recommend PTX on the basis of these symptoms (2).

Vitamin D insufficiency is more frequent in patients with pHPT than in the general population, but its prevalence differs between pHPT populations (9, 10, 11, 12). Vitamin D is important for calcium homeostasis and a poor vitamin D status may influence the severity of pHPT (12). Vitamin D deficiency has been associated with declining cognitive and physical functions and mood disorders, but the results of interventional studies on the effects of vitamin D supplementation have not been convincing (13).

The international guidelines for the management of asymptomatic pHPT recommend supplementation of vitamin D when the serum concentration of 25OHD is below 50 nmol/l (14). Judicious vitamin D supplementation has been reported to safely improve vitamin D status and decrease PTH in pHPT patients without increasing the calcium concentration in plasma or urine (15). Still questions remain about the effects of vitamin D supplementation in pHPT. The aim of this study was to evaluate the relation between vitamin D status and HRQoL and the effects of postoperative vitamin D supplementation on health recovery.

Materials and methods

Between April 2008 and January 2011, 159 consecutive pHPT patients subjected to PTX were recruited in a double-blinded, randomized clinical trial. The study cohort has been described in detail in two previous publications (16, 17). After successful PTX, 150 patients with pHPT were randomized, 75 patients in each group, to 1-year treatment with either calcium carbonate 500 mg/800 IU cholecalciferol $\times 2$ daily (D+ group) or calcium carbonate 500 mg $\times 2$ daily (D- group) (Fig. 1). Recip AB (Stockholm, Sweden) delivered the specifically prepared study medication. The measurements were repeated 6 weeks before PTX, at randomization 6 weeks after PTX, and after 6 and 12 months of study medication. A safety control of the calcium and creatinine concentrations and the tolerability of the medication were performed after 6 weeks of study medication. Blood samples were drawn after an overnight fasting. Body weight and height were measured and BMI was calculated as weight (kg) divided by the square of height (m). The cohort size was determined by power calculation based on the expected drop in plasma PTH concentration (16, 17). The study population, comprising 135 patients who completed all four surveys (SF-36), was compared with a reference cohort of 459 age- and sex-matched individuals, randomly drawn from the Swedish SF-36 national normative database ($n=8930$) (18). A total of 135 patients completed the

Figure 1

Flowchart of the study.

entire 1-year study period after randomization and these patients were included in the final analysis of HRQoL. Clinical characteristics did not differ between dropouts and those who completed the study (16, 17). The study was approved by the Medical Products Agency and by the local Ethics Committee.

Laboratory methods

Plasma concentrations of total calcium were measured using the Synchron LX 20 System (Beckman Coulter, Inc., Brea, CA, USA). Serum ionized calcium Ca^{2+} was analyzed on ABL 800 (Radiometer, Copenhagen, Denmark). Plasma concentrations of intact PTH were determined using the electrochemiluminescence immunoassay on the Modular E system (Roche Diagnostics GmbH). Serum concentrations of 25OHD were measured by chemiluminescence on Liason XL (DiaSorin, Inc., Stillwater, MN, USA); the interassay coefficient of percentage variation (%CV) is 4.6% at 15.5 nmol/l and 2.7% at 68.3 nmol/l and intraassay %CV is 4.4% at 15.5 nmol/l and 2.6% at 68.3 nmol/l. In order to minimize the interassay variation, the preoperative and postoperative samples of 25OHD were analyzed in the same series on serum previously frozen at -70°C . Values below 50 nmol/l were considered to represent vitamin D insufficiency (19, 20).

Quality-of-life measurements

The SF-36 Healthy Survey, version 2.0 containing 36 questions, has proven reliable and valid in various

groups (18). Individual answers are compiled to create eight scales, of which four (Physical Functioning, Role Physical, Bodily Pain, and General Health (GH)) are measurements of physical health and the remaining four (Vitality, Social Functioning (SF), Role Emotional, and Mental Health) are indicative of mental well-being in the last 4 weeks. The combination of all eight scales constructs two composite scales: the Physical Component Summary (PCS) and the mental component summary. All scales are standardized from 0 to 100, with higher scores signifying better health status.

Statistical analyses

All analyses were performed using the SPSS version 22. Data, since not normally distributed, were analyzed by nonparametric tests. For comparisons between groups, the Mann–Whitney *U* test for unpaired data was used. Kruskal–Wallis one-way ANOVA was used for comparisons with respect to independent categorical variables with more than two levels. For paired analyses, the Wilcoxon's signed rank sum test was used. The scores are presented as median and interquartile range (IQR). χ^2 test was used for the analysis of distribution of categorical variables. Relationships between variables were assessed with Spearman's *P* correlation test. All tests were done two tailed and $P < 0.05$ was considered to be statistically significant.

Results

A total of 135 patients completed the study period. Vitamin D deficiency, defined as s-25OHD < 50 nmol/l, was present in about three-quarters of the patients. The characteristics of the pHPT patients are presented in Table 1. Table 2 presents the SF-36 scores of the reference cohort and of the pHPT patients pre-surgery (baseline), 6 weeks after surgery (the time for randomization to study medication), and after 1 year of treatment. The patients scored significantly lower than the reference population in all eight domains and the two component scales of the SF-36. No correlation was found between SF-36 scores and the concentrations of ionized calcium or p-PTH (data not shown). The baseline HRQoL estimated with SF-36 did not differ between different s-25OHD-quartiles (Table 3).

A single parathyroid adenoma was removed in nearly all cases (132/135); the median adenoma weight was 0.455 g (range 0.075–27.800 g). At follow-up 6 weeks after PTX, the calcium level was normalized in all cases, but the p-PTH concentration was elevated above the normal upper limit of 65 ng/l in 50% of the cases. The s-25OHD was

Table 1 Clinical characteristics at baseline for patients analyzed for outcomes ($n = 135$).

Age, years, median (minimum–maximum)	62 (30–80)
Females/males	109/26
BMI (kg/m ²), median (minimum–maximum)	26.0 (17.1–43.4)
Weight of adenoma (mg) median (minimum–maximum)	455 (75–27 800)
Vitamin D < 50 nmol/l, <i>n</i> (%)	104 (77%)
Diabetes (<i>n</i>)	5
Antihypertensive treatment (<i>n</i>)	59
Osteoporosis (<i>n</i>)	62
Smokers (<i>n</i>)	20
S-Ca ²⁺ (1.15–1.33 mmol/l, median (IQR))	1.43 (1.38; 1.47)
p-PTH (10–65 ng/l, median (IQR))	116 (89; 148)
p-Creatinine ($\varnothing < 90$, $\delta < 100$ μ mol/l, median (IQR))	65 (56; 76)

higher compared with baseline (41 (33; 54) vs 40 (31; 49) nmol/l; $P = 0.005$). Vitamin D insufficiency, defined as s-25OHD below 50 nmol/l, was present in 66% of the patients. The pHPT cohort improved their scores in all except one domain ('Role Physical'; Table 2). At the start of the study medication period, the s-25OHD concentration was similar in the two groups (40 (33; 53) in D+ and 45 (35; 54) nmol/l in D–; $P = 0.247$). The medication was well tolerated and the s-ionized calcium, p-phosphate, p-creatinine, and the urinary calcium concentrations remained unchanged during the study period. In both the D+ and the D– group, no significant changes in the SF-36 scores were observed during the entire period of study medication (Table 4). At the end of the study medication period, the D+ group had significantly higher s-25OHD (76 (65; 93) vs 48 (40; 62) nmol/l; $P < 0.001$) and lower p-PTH (40 (34; 52) vs 49 (38; 66) ng/l; $P = 0.01$). No significant differences in the SF-36 scores between the groups were observed. The pHPT cohort reached the level of the reference population in one domain of SF-36, GH, and in one composite score, PCS (Table 2).

Discussion

The main results of this double-blinded randomized trial were that vitamin D supplementation after successful PTX resulted in higher s-25OHD and lower p-PTH concentrations but had no obvious beneficial effect on HRQoL despite a high prevalence of vitamin D insufficiency in the pHPT cohort.

As shown previously in both observational and randomized studies, pHPT patients express impaired HRQoL. Vitamin D insufficiency is overrepresented in pHPT and may contribute to neuropsychiatric symptoms (21).

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Table 2 SF-36 QoL score in a reference population and in pHPT patients who completed the study period pre-surgery, at randomization (post-surgery) and after 12-month medication in both groups.

SF-36	Reference population		Pre-surgery (n = 135)		Post-surgery (n = 135)		12 months (n = 135)		P ^a	P ^b	P ^c	P ^d
	Median	IQR	Median	IQR	Median	IQR	Median	IQR				
Physical Function (PF)	85	85–90	80	61–95	85	70–95	85	65–95	<0.001	0.003	<0.001	0.428
Role Physical (RP)	100	100–100	75	25–100	100	25–100	100	50–100	<0.001	0.211	<0.001	0.168
Bodily Pain (BP)	72	72–100	62	41–100	74	41–100	72	42–100	<0.001	0.006	0.036	0.211
General Health (GH)	76	75–76	67	47–82	72	60–87	72	57–91	<0.001	<0.001	0.924	0.672
Vitality (VT)	75	75–80	50	30–70	65	45–80	65	45–80	<0.001	<0.001	<0.001	0.596
Social Functioning (SF)	100	100–100	75	50–100	88	63–100	100	75–100	<0.001	<0.001	<0.001	0.225
Role Emotional (RE)	100	100–100	67	0–100	100	33–100	100	67–100	<0.001	<0.001	<0.001	0.173
Mental Health (MH)	88	84–92	72	52–88	84	64–92	82	68–92	<0.001	<0.001	<0.001	0.915
Physical Component Summary	48	48–51	47	38–54	48	40–55	49	40–55	0.001	0.039	0.186	0.708
Mental Component Summary	50	53–55	42	29–53	50	40–56	52	42–57	<0.001	<0.001	<0.001	0.121

IQR, inter quartile range; Wilcoxon's signed rank sum test, paired data.

^aPre-surgery vs reference population.

^bRandomization (post-surgery) vs pre-surgery.

^cOne year of treatment vs reference population.

^dOne year of treatment vs randomization (post-surgery).

In a recent meta-analysis of population-based epidemiological studies that included more than 50 000 study participants, an inverse association has been demonstrated between serum 25OHD and the risk of depression. Based on a meta-analysis, an increase in 25OHD of 25 nmol/l was associated with an 8% decrease in the incidence of depression (22). We used the SF-36 score for estimation of HRQoL. This protocol is well validated and allows comparison between patients and the background population. Our pHPT patient cohort scored significantly worse in all domains than the reference population (18, 23). Major improvements were registered

postoperatively, above ten units in most domains, often recommended as the least significant change (2). However, except for a correlation between baseline s-25OHD and the domain 'Mental Health', we found no correlation between vitamin D status and HRQoL. The minor increase in s-25OHD after PTX confirms earlier findings (10).

The exact mechanism of this increase has not been clarified (13). Theoretically, the postoperative reduction in PTH will result in reduced activation of 25OHD to 1,25(OH)₂D and thereby decreased rate of metabolic clearance (24). In line with other reports, we observed no

Table 3 Baseline clinical characteristics, biochemistry, and HRQoL in different vitamin D quartiles. Mann–Whitney *U* test for unpaired data. Kruskal–Wallis test for unpaired data.

SF-36	I (n = 29 (25%))		II–III (n = 75 (60%))		IV (n = 31 (24%))		P (I–II–III)	P (I–(II+III))
	<31 s-25OH vit D		> 31 s-25OH vit D <50		> 50 s-25OH vit D			
	Median	IQR	Median	IQR	Median	IQR		
Physical Function (PF)	75	50; 90	80	70; 95	80	64; 95	0.284	0.113
Role Physical (RP)	75	25; 100	100	25; 100	100	19; 100	0.531	0.272
Bodily Pain (BP)	62	36; 92	62	41; 100	57	41; 100	0.744	0.471
General Health (GH)	65	45; 77	65	47; 81	72	55; 87	0.516	0.323
Vitality (VT)	50	30; 66	53	30; 70	48	30; 75	0.759	0.465
Social Functioning (SF)	75	50; 100	75	50; 100	81	50; 100	0.615	0.342
Role Emotional (RE)	67	0; 100	67	0; 100	100	33; 100	0.519	0.809
Mental Health (MH)	70	44; 82	74	52; 88	72	59; 89	0.192	0.083
Physical Component Summary	43	34; 54	48	40; 54	47	37; 55	0.584	0.300
Mental Component Summary	41	32; 52	43	29; 54	41	35; 54	0.666	0.486

IQR, inter quartile range.

correlation between SF-36 scores and PTH concentration or the extent of hypercalcemia (4). Improvements in HRQoL after PTX have been reported from many different studies, but studies on long-term effects have yielded inconsistent results (3, 4, 5, 6, 7, 8). A placebo-effect of surgery must always be considered. However, since the improvements in HRQoL remained 1 year after surgery, we consider this less likely. Only exceptionally did the patients reach the levels of the reference population. Possibly, the common coexistence of other disorders, such as hypertension, in the cohort may have contributed to the residual reduction. Judicious replacement of vitamin D in pHPT patients has been reported to be safe, provided the patients are followed closely (15). In our cohort of pHPT patients, vitamin D insufficiency was frequent and equally distributed between the groups at randomization. During 12-month study medication, no changes in SF-36 scores were observed in the D+ and D− groups. The SF-36 scores did not differ between the two groups, either at the beginning or at the end of the study medication period, but the D+ group had higher s-25OHD and lower p-PTH levels. We cannot exclude the possibility that the lower PTH level in the D+ group may have beneficial effects in the long run. The optimal cut-off for vitamin D insufficiency is still controversial. The international guidelines from 2009 recommend measurement of 25OHD in all patients and repletion is recommended when the vitamin D level is below 50 nmol/l (14). Vitamin D insufficiency may be present even with vitamin D levels above 50 nmol/l. Based on a recent report, p-PTH levels continue to decline even when s-25OHD levels increase above 75 nmol/l (25).

The strength of this study is the randomized and double-blinded design. The study has some limitations. The SF-36 may be less sensitive for detecting subtle changes than a disease-specific protocol. However, disease-specific questionnaires such as Pasieka's parathyroid symptoms score correlate well with SF-36 (26). We cannot exclude the possibility that the daily supplementation of 1000 mg calcium carbonate instead of placebo may have interfered with the results. We also have to consider the risk of type 2 errors because the cohort size was determined by power calculation based on the expected drop in plasma PTH, not on the variables estimating HRQoL. Neither can we rule that a higher dose of vitamin D or a longer period with study medication would have affected the outcome. Ten percent of the study cohort was lost to follow-up. We have to be aware of the risk that the incomplete follow-up may bias the results. However, the clinical characteristics did not differ between

dropouts and those who completed the study and the number of drop-outs was similar in the two groups.

In conclusion, this study confirms that successful PTX results in significant improvements in HRQoL. Our findings do not support the assumption that vitamin D insufficiency contributes to impaired HRQoL in pHPT. Postoperative vitamin D supplementation resulted in higher s-25OHD and lower PTH. Despite a high prevalence of vitamin D insufficiency, we observed no additive effect from vitamin D supplementation on the aspects of HRQoL.

Declaration of interest

The authors declare that there is no conflict of interest that could be perceived as prejudicing the impartiality of the research reported.

Funding

Recip AB provided the study medication but were not involved in the design, conduction, implementation, data analysis or manuscript writing.

Author contribution statement

S Norenstedt, Y Pernow, J Zedenius, J Nordenström, M Sääf, and I-L Nilsson were involved in study design; V Åberg, S Norenstedt, Y Pernow, J Zedenius, J Nordenström, M Sääf, I-L Nilsson conducted the study; V Åberg, S Norenstedt, Y Pernow, J Zedenius, J Nordenström, M Sääf, I-L Nilsson involved in data collection; V Åberg and I-L Nilsson. Data interpretation: V Åberg, S Norenstedt, Y Pernow, J Zedenius, J Nordenström, M Sääf, and I-L Nilsson analyzed data. V Åberg, I-L Nilsson, Y Pernow were involved in drafting the manuscript; V Åberg, S Norenstedt, Y Pernow, J Zedenius, J Nordenström, M Sääf, and I-L Nilsson reviewed the manuscript; V Åberg, S Norenstedt, Y Pernow, J Zedenius, J Nordenström, M Sääf, and I-L Nilsson approved the final version of manuscript; I-L Nilsson takes responsibility for the integrity of the data analysis.

Acknowledgements

The authors would like to express our sincere gratitude to the research nurses Agneta Eriksson, and L Ånfalk for taking care of the patients in a professional manner. They also thank all other staff members who contributed to the study.

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Received 18 September 2014

Revised version received 3 November 2014

Accepted 20 November 2014