The Influence of Conventional Treatment on Symptoms and Complaints in Patients With Chronic Postsurgical Hypoparathyroidism

Bettina Stamm, Martina Blaschke, Lara Wilken, Deborah Wilde, Christina Heppner, Andreas Leh, Christoph Herrmann-Lingen, and Heide Siggelkow

1Endokrinologikum Saarbruecken, Saarbruecken, Germany
2Clinic of Gastroenterology, Gastrointestinal Oncology and Endocrinology, University Medical Center Goettingen, Goettingen, Germany
3MVZ Endokrinologikum Goettingen, Goettingen, Germany
4Institute for Medical Statistics, University Medical Center Goettingen, Goettingen, Germany
5Department for Psychosomatic Medicine and Psychotherapy, University Medical Center Goettingen, Goettingen, Germany

ABSTRACT

Quality of life (QoL) is impaired in patients with chronic hypoparathyroidism (HypoPT). With a recently developed specific patient questionnaire, the 28-item Hypoparathyroid Patient Questionnaire (HPQ 28), we were able to demonstrate an effect of laboratory parameters on symptoms and complaints identified by scales and items of the HPQ 28. Here, we evaluated the effect of conventional treatment modalities on QoL using this specific questionnaire. In this cross-sectional study, we included 49 HypoPT (41 female and 8 male) patients. Laboratory values of total serum calcium, magnesium, phosphate, calcium-phosphate product (CPP), and 24-hour urine for calcium and phosphate were analyzed. Patients completed the HPQ 28 questionnaire during the corresponding visit. Mean age was 57.3 ± 10.5 years and duration of disease 12.6 ± 9.8 years. Most patients (86%, n = 42) were treated with the active vitamin D analogs calcitriol, alfacalcidol, or dihydrotachysterol (DHT). The use of calcium and magnesium supplements influenced scales on HPQ 28 in a dose-dependent manner. We detected a dose-dependent increase on the HPQ 28 scales “depression and anxiety” and “pain and cramps,” and the item “numbness and tingling” related to calcitriol. This effect was independent of gender, age, underlying disease, kind of surgery, serum 25-hydroxyvitamin D₃, calcium, or phosphate values. This study presents the first data on specific symptoms of HypoPT patients dependent on different treatment modalities. Our data suggest that in part the reduced QoL in these patients might be caused by conventional treatment. © 2022 The Authors. JBMR Plus published by Wiley Periodicals LLC on behalf of American Society for Bone and Mineral Research.

KEY WORDS: HYPOPARATHYROIDISM; QUALITY OF LIFE; SYMPTOMS AND COMPLAINTS; CONVENTIONAL THERAPY; ACTIVE VITAMIN D TREATMENT

Introduction

Chronic postsurgical hypoparathyroidism (HypoPT) is defined by hypocalcemia and inappropriately low levels of parathyroid hormone (PTH) lasting more than 6 months after the corresponding surgical procedure.[1] The recommended treatment aims to maintain serum calcium levels within the lower normal range or even slightly below. Levels of phosphate and calcium-phosphate product (CPP), magnesium, and 24-hour urine values are supposed to lie within the gender-specific reference ranges, and vitamin D status needs to be adequate.[1] The treatment regimen is designed to free patients of the symptoms and signs of hypocalcemia. The primary therapy recommended is to prescribe activated vitamin D analogs in combination with calcium supplements, with additional measures required for patients in whom the target ranges are unattainable through this treatment. General vitamin D supplementation with 400 to 800 IU/d is part of this recommendation.[1,2] However, not all patients are free of symptoms, nor are their levels within the target ranges under the recommended treatment.

The management required to reach these goals tends to differ from country to country. In the United States, a higher amount of...
calcium and lower doses of activated vitamin D are used to keep phosphate levels down,
\(^{13}\) in comparison to European studies.\(^{14-16}\) Moreover, not all of the activated vitamin D analogs on the global market are available in every country; eg, alfalcac- 
dol is available in Europe\(^ {5,3}\) but not in the United States.\(^ {3}\) As a 
result, there is currently no comparison of the different medica-
tions with respect to the target levels of laboratory parameters according to present guidelines\(^ {1,2}\) and the recommended treat-
ment aims.

Together with recommendations on target levels of labora-
tory parameters, the European guidelines focused for the 
time on the well-being of patients and their quality of life (QoL).\(^ {1}\) By now, a number of studies characterize the impaired 
QoL for patients with HypoPT.\(^ {1,2}\)

Siggelkow and colleagues\(^ {9}\) described interference with the 
activities of daily life and personal relationships in addition to 
cognitive, emotional, and physical symptoms. Meanwhile, the 
influence on work productivity and working ability is also part of 
the studies.\(^ {4,9}\) Comparing HypoPT with the QoL associated 
with other chronic diseases such as diabetes or heart failure\(^ {9}\) 
has underlined the importance of this aspect to the treatment 
of HypoPT, which is now internationally acknowledged.\(^ {10,11}\)

A number of HypoPT-specific instruments to assess symptoms 
relating to QoL have been developed lately.\(^ {12-14}\) We also 
recently developed a disease-specific hypoparathyroid patient 
questionnaire, the 28-item Hypoparathyroid Patient Question-
aire (HPQ 28), to be used in the daily care of HypoPT patients.\(^ {14}\)

This questionnaire enables us to demonstrate an effect of the 
laboratory values on QoL when compared to two control 
grupps.\(^ {15,15}\) Here we analyze the effect of different treatment 
modalities on laboratory values and symptoms using the HPQ 
28 in patients with chronic postoperative HypoPT.

Patients and Methods

Study design

We conducted a cross-sectional study in two different endocri-
nologic centers (Goettingen and Saarbruecken) in Germany. 
Forty-nine HypoPT patients were prospectively enrolled in the 
study as and when they attended the clinic. Patients received 
information on the study during their regular clinical checkup 
visits. After providing informed consent, they completed the 
HPQ 28 during their visit to one of the centers. During their rou-
tine control visit, different serum and urinary parameters were 
analyzed. The study was approved by the Ethics Review Board 
of University Medical Center Goettingen (No. 25/10/15); all the 
subjects provided written informed consent prior to participa-
tion and the data were pseudonymized. All the questionnaires 
were in German.

Patients

We recruited patients determined as suffering from chronic post-
surgical HypoPT, which was defined by the presence of hypocal-
cemia, inappropriately low PTH levels, and patients needing 
treatment at least 6 months after thyroid surgery. 
HypoPT patients were excluded if their HypoPT proved to be 
idiopathic, genetic, or transient (less than 6 months diagnos-
ted with HypoPT), they were under 18 or over 85 years of age, preg-
nant, unable to understand and answer the questionnaires, or 
were suffering from polyglandular autoimmune syndrome.

Laboratory values

Laboratory values were determined immediately after blood 
sampling using standard laboratory methods (total serum cal-
cium, serum albumin, serum magnesium, serum phosphate, 
and 25-OH-vitamin D3). Calcium adapted for albumin and CPP 
were calculated values from the laboratory (amedes MVZ wag-
nerstibbe, Goettingen). Twenty-four-hour urine collections were 
analyzed for calcium, creatinine, and phosphate with standard 
laboratory methods.

Questionnaires

The HPQ 28 is a questionnaire we designed on the basis of pre-
vious testing to measure the symptoms and complaints typical 
in HypoPT patients.\(^ {14}\) The results of initial application in a 
HypoPT study group have been described.\(^ {15}\) The questionnaire 
comprises five different scales and three single items. The scales 
represent identified complaints in HypoPT: pain and cramps 
(PaC); loss of vitality (Vit); gastrointestinal symptoms (GiS); 
depression and anxiety (DaA); and neurovegetative complaints 
(NVS). The single items are numbness and tingling in certain 
parts of the body (numbness and tingling), memory difficulties, 
and heart palpitations.\(^ {14}\)

Statistics

Data were analyzed with IBM-SPSS software version 26 (IBM 
Corp., Armonk, NY, USA). Descriptive data were compared using 
chi-squared or Fisher’s exact test for categorical variables. 
Answers to items on the HPQ 28 were coded as follows: 0 = 
not at all; 1 = slightly; 2 = moderately; and 3 = severely. 
Group differences were evaluated using either one-way analysis 
of variance (ANOVA) for normally distributed continuous values 
or the nonparametric Kruskal-Wallis test (with included Dunn-
Bonferroni test in SPSS) for non-normally distributed data. Data 
are presented as means ± standard deviation (SD) or standard 
error of the mean (SEM) for each of the five scales or single items. 
A pairwise complete case analysis was performed for few missing 
data (4/245 items in PaC scale were missing). For correlation anal-
yses, Spearman’s rank correlation was chosen for non-normally 
distributed values, whereas Pearson correlations were per-
fomed for normally distributed values. For linear regression 
the adjusted r-square (r^2) values were given for the goodness 
of fit, as well as the p values for the significance of linearity and 
the standardized coefficient parameter β. Bonferroni correction 
for the multiple comparison to the eight scales and items in 
the HPQ 28 was applied.

Results

Patient characteristics and laboratory parameters

The main characteristics of the 49 HypoPT patients (n = 35 Goet-
tingen, n = 14 Saarbruecken) participating in this trial have been 
described.\(^ {15}\) Patients were 57.3 ± 10.5 years old and were pre-
dominantly female (84%). The duration of disease in patients 
was 12.6 ± 9.8 years. In 43% of the cases, goiter was the under-
lying disease, followed by carcinoma (29%) and Graves’ disease 
(12%). Most of the patients (84%) underwent a total thyroidec-
tomy. Patient characteristics relating to the different treatment 
modalities are depicted in Table 1.

The laboratory values were well adjusted as recommended in 
the guidelines from 2015.\(^ {11}\) In summary, serum calcium/albumin
values ($n = 46$) were between 1.6 and 2.39 mmol/L (mean 2.09 mmol/L; reference values 2.0–2.6 mmol/L), serum phosphate values ($n = 48$) 0.84–1.75 mmol/L (mean 1.26 mmol/L; reference values 0.8–1.6 mmol/L), CPP ($n = 47$) 1.87–3.63 mmol$^2$/L$^2$ (mean 2.71 mmol$^2$/L$^2$; reference values 1.4–4.4 mmol$^2$/L$^2$), 25OH vitamin D3 ($n = 48$) 13–176 nmol/L (mean 101 nmol/L; reference values 72.5–139 nmol/L), serum magnesium ($n = 39$) 0.60–0.86 mmol/L (mean 0.78 mmol/L; reference values 0.66–1.07 mmol/L), urinary 24-hour calcium excretion ($n = 25$) 0.49–10.99 mmol/d (mean 5.39 mmol/d; reference values 2.5–7.5 mmol/d), and urinary phosphate excretion ($n = 21$) 13.24–35.52 mmol/d (mean 21.76 mmol/d; reference values 19.37–50.55 mmol/d).

**HypoPT medication**

In general, the symptoms HypoPT patients present and report might not only be influenced by the disease itself, but also by the kind of treatment as well as the dose to reach and maintain target ranges according to the guidelines.1 Table 1 presents patients’ characteristics and the different medications used in the study group ($n = 49$).

The majority of HypoPT patients (65%) received some preparation of calcium supplementation, either solely as calcium carbonate, ($n = 24$ patients) or calcium carbonate in combination with native vitamin D (Calcimagon® [500 mg Ca + 800 IU vitamin D], $n = 6$; Calcimed® [500 mg Ca + 1000 IU Vitamin D], $n = 1$; Calcigen® [600 mg Ca + 400 IU vitamin D], $n = 1$).

Magnesium supplements were a component of the medication in 10 patients (20%). At the time point of the study, two patients received teriparatide 1–34. Most patients (86%, $n = 42$) were treated with the active vitamin D analogs calcitriol, alfacalcidol, or dihydrotachysterol (DHT). Half of the patients were treated with alfacalcidol (52%, $n = 22$). One patient was treated with a combination of calcitriol and alfacalcidol. In part, the treatment concept in Saarbrücken aimed at creating and maintaining predominantly high levels of 25-OH-vitamin D3 as the central pillar, adding active vitamin D forms as needed. Thus, patients treated in Saarbrücken ($n = 7$) received a mean dose of 17,960 IU/d of cholecalciferol. Five patients were treated with 20,000–40,000 IU/d. The mean dose was higher than in patients treated with cholecalciferol in Goettingen ($n = 14$, mean dose 2209 IU/d, only one patient was treated with 10,000 IU/d). Values for 25-hydroxyvitamin D3 correlated significantly with the dose of genuine vitamin D$_3$ ($p < 0.001$; $r = 0.512$, data not shown). Seven patients were not treated with active vitamin D analogues, but with either high doses of genuine vitamin D$_3$, or calcium alone, or magnesium alone, or calcium as part of their normal diet or calcium-rich mineral water instead.

Patients supplementing calcium (according to either regimen) mostly took 500 mg/d ($n = 9$) or 1000 mg/d ($n = 10$). The dose of magnesium was 300 mg/d in 40% of patients. Most patients treated with native vitamin D received between 1000 and 2857 IU per day ($n = 14$). Seven patients received thiazides, mostly 25 mg/d ($n = 5$). A detailed table of treatments and doses is provided in Appendix S1, Table A.

**Table 1. Patient Characteristics Relating to the Different Treatment Modalities**

| Parameter                              | No active vitamin D$_3$ ($n = 7$) | Calcitriol ($n = 14$) | Alfacalcidol ($n = 21$) | DHT ($n = 6$) | Calcitriol+Alfacalcidol ($n = 1$) | $p$  |
|----------------------------------------|----------------------------------|-----------------------|-------------------------|--------------|---------------------------------|------|
| Age (years), mean ± SD (range)         | 55 ± 9 (44–69)                   | 56 ± 10 (41–77)       | 59 ± 12 (41–75)         | 56 ± 6 (48–65) | 74                              | 0.70b |
| Gender (male/female)                   | 1/6                              | 3/11                  | 2/19                    | 1/5          | 1/0                             | 0.74c |
| BMI (kg/m$^2$), mean ± SD              | 33.0 ± 4.7                       | 29.4 ± 4.4            | 27.4 ± 9.7              | 30.5 ± 9.1   | 30.1                            | 0.50b |
| Calcium intake (yes/no)                | 2/5                              | 10/4                  | 15/6                    | 4/2          | 0                               | 0.2   |
| Calcium intake$^a$ (mg/d), mean ± SD   | 800 ± 282                        | 1240 ± 1003           | 885 ± 745               | 700 ± 383    | 0.3                             |      |
| Magnesium intake (yes/no)              | 1/6                              | 3/11                  | 4/17                    | 2/4          | 0.8                             |      |
| Magnesium intake$^a$ (mg/d)            | 300                              | 540 ± 393             | 218 ± 96                | 250 ± 71     | 0.7                             |      |
| Native vitamin D (yes/no)              | 4/3                              | 7/7                   | 12/9                    | 2/4          | 0.4                             |      |
| Native vitamin D intake$^a$ (IU/d)     | 5657 ± 9,571                     | 3520 ± 2,941          | 9590 ± 12,547           | 571 ± 606    | 0.50b                           |      |
| Type of surgery                        |                                  |                       |                         |              |                                 | 0.047c |
| Total                                  | 2                                | 8                     | 8                       | 5            | 1.0a                            |      |
| Subtotal                                | 0                                | 2                     | 1                       | 1            |                                 |      |
| Near total                              | 0                                | 1                     | 0                       | 0            |                                 |      |
| Not classified$^a$                      | 5                                | 3                     | 12                      | 0            |                                 |      |
| Underlying disease                     |                                  |                       |                         |              | 0.47c                           |      |
| Carcinoma                              | 1                                | 5                     | 5                       | 2            | 1                               |      |
| Goiter                                 | 3                                | 5                     | 12                      | 1            |                                 |      |
| Graves’ disease                        | 1                                | 2                     | 2                       | 1            |                                 |      |
| Nodules                                | 1                                | 1                     | 1                       | 1            |                                 |      |
| pHPT                                   | 0                                | 1                     | 1                       | 0            |                                 |      |
| Other                                  | 1                                | 1                     | 0                       | 1            |                                 |      |

BMI = body mass index; pHPT = primary hyperparathyroidism; SD = standard deviation.

$^a$Not included in statistical analysis.

$^b$Fisher’s exact test.

$^c$Kruskal-Wallis group analysis.

$^d$All the patients included recorded as taking the respective supplement.
The influence of active vitamin D treatment on laboratory values

To investigate whether the laboratory values for serum calcium, serum phosphate, serum magnesium, CPP, as well as the urinary calcium and urinary phosphate values were dependent on different active vitamin D compounds, we compared HypoPT patients with respect to the active vitamin D form taken (Fig. 1).

The serum values of all patients treated with calcitriol lay within the reference range (Table 2), whereas some patients treated with alfacalcidol (serum calcium, serum phosphate) or treated with DHT (serum magnesium) did not. More patients treated with alfacalcidol had values within the urinary calcium reference range, whereas more patients reached the reference range for urinary phosphate when treated with calcitriol or DHT.

We found no significant differences between the different treatments with respect to serum or urinary parameters (Fig. 1). Pearson correlation analysis between calcitriol or alfacalcidol intake and laboratory parameters revealed no significant correlation to any parameter.

The influence of active vitamin D treatment on scales and items of the HPQ 28

To evaluate whether symptoms according to HPQ 28 were dependent on different active vitamin D compounds although laboratory serum values did not differ (Fig. 1), we compared scales and items in the HypoPT patients with reference to the active vitamin D compound administered (Fig. 2).

We did not detect any statistically significant group differences between the active vitamin D compounds administered in the HypoPT group (Fig. 2). A large variance is evident, however, which is indicative of the possibility of some dose-dependent effects of the different vitamin D metabolites.

The influence of combination therapy on scales and items of the HPQ 28

To analyze the influence of combination therapy in HypoPT patients with calcium, magnesium, and native vitamin D on the symptoms as given in the HPQ 28, we performed a group analysis of variance as well as a Spearman rank correlation (Appendix S2, Table B) of medication doses (magnesium, calcium, and native vitamin D, respectively) to scales and items of the HPQ 28.

With respect to magnesium we grouped the patients into “no intake of magnesium” \((n = 18)\) and “intake of magnesium” \((n = 21)\). Patients treated with magnesium complained significantly more often on the scales GiS and NVS \((p < 0.05, \text{Fig. 3})\). The scale GiS reflects symptoms of abdominal pain and cramps, nausea, or upset stomach, whereas the scale NVS relates to symptoms such as trembling muscles, hot flushes or chills, weakness, dizziness, and diarrhea. No further significant group differences could be detected. The subsequent Spearman rank correlation analysis \((r_s = 0.29; p = 0.049)\) also revealed significant positive correlation between magnesium intake and the scale GiS. None of the other scales or items of the HPQ 28 correlated to the magnesium dose (Appendix S2, Table B).

Regarding calcium, patients were grouped into four groups “no intake” \((n = 18)\), “below 800 mg/d” \((n = 15)\), “800 to 1500 mg/d” \((n = 14)\), and “above 1500 mg/d” \((n = 2)\). Subsequent Spearman rank correlation analysis for calcium intake revealed significant correlation to the scale NVS \((p = 0.044; r_s = 0.29)\) (Appendix S2, Table B). This reflects more complaints represented by NVS, such as trembling muscles, hot flushes or chills,
weakness, dizziness and diarrhea with higher doses of calcium intake (Fig. 4).

Finally, with respect to vitamin D intake, three groups were formed: “no intake of native vitamin D” (n = 24), “approx. 1000–3000 IU vitamin D/d” (n = 19), and 10,000–40,000 IU vitamin D/d (n = 6). Group analysis of native-vitamin D intake revealed no significant influence on any of the scales of the HPQ 28. Subsequent correlation analysis revealed no significant correlation (Appendix S2, Table B).

Correlation of symptoms to the dose of active vitamin D

Table 3 lists the range of doses for the active vitamin D compounds calcitriol (n = 15), alfacalcidol (n = 22), and dihydrotachysterol (n = 6). Peak doses were 0.5 μg/d for calcitriol (43%) and 1 μg/d for alfacalcidol (38%).

Although we found that there were no differences between vitamin D treatment modalities and HPQ 28, there still may be some dose-dependent effect of different active vitamin D compounds. To answer the question as to whether symptoms in HypoPT patients correlate to the dosage of the different active vitamin D compounds administered, we performed a Spearman rank correlation analysis (Table 4). The calcitriol dose correlated positively and significantly with three scales and one item (“pain and cramps”, “depression and anxiety”, “numbness and tingling”, and “heart palpitations”) with a rank correlation coefficient \( r_c \) of ~0.6.

Linear regression analysis revealed a significant influence of calcitriol on the scales PaC (\( r_c^2 = 0.33; p = 0.017 \)), DaA (\( r_c^2 = 0.25; p = 0.038 \)), and the items “numbness and tingling” (\( r_c^2 = 0.51; p = 0.003 \)) and “heart palpitations” (\( r_c^2 = 0.53; p = 0.002 \)).

The calcitriol dose explains 33.0% of the variation of the scale PaC variation, 25% of the scale DaA, 51% of the items “numbness and tingling”, and 53% of the item “heart palpitations”. These are strong effects for every scale or item according to Cohen (0.6–1.1 = effect size).\(^{16}\)

Alfacalcidol and dihydrotachysterol appear to have no detectable effect on any of the symptom scales (Table 4).

Principally, the possibility remains that different doses of calcitriol result in different levels of serum calcium, thus explaining the symptoms. To answer the question as to whether serum calcium levels influence the demonstrated effect of calcitriol on the four parameters, we employed a linear regression analysis model. The results are depicted in Table 5.
The item “heart palpitations” was no longer significant after correction for serum calcium. However, correlation of the calcitriol dose with the scales PaC, DaA, and the item “numbness and tingling” remained significant after correction for serum calcium. This model therefore suggests that certain complaints are dependent on the dose of calcitriol but not on the dose of the other active vitamin D compounds. This effect was also independent of gender, age, underlying disease, kind of surgery, serum 25-hydroxyvitamin D₃, or phosphate values. Higher calcitriol doses had no effect on any of the laboratory values.

Discussion

Lately, we developed the HPQ 28 questionnaire to characterize and quantify symptoms and complaints specifically of...
HypoPT patients. Scales and items of the HPQ 28 reflect different areas of complaints characteristic in patients with HypoPT and correlated to an extent with the laboratory parameters serum calcium, serum phosphate, and CPP. In this study, we investigated whether different treatment modalities influence symptoms and complaints in HypoPT patients.

Different options to treat HypoPT are available throughout the world. International therapy recommendations have been available since 2015, which strongly advocate the use of activated vitamin D analogs in combination with calcium supplements. However, the recommendations do not specify which vitamin D analog is suggested. Table 6 depicts data concerning the pharmacokinetics of vitamin D analogs. In Germany, all different vitamin D compounds have been approved for the treatment of HypoPT patients and are administered regularly.

We detected no difference in serum calcium, serum phosphate, serum magnesium, CPP, calcium in 24-hour urine, or 24-hour phosphate excretion between the different active vitamin D compounds. However, more patients’ parameters were in the reference ranges according to guidelines with calcitriol and DHT than with alfacalcidol.

Principally, the patients were well adjusted to the current guidelines. Eleven patients (73%) treated with calcitriol, three (50%) treated with DHT, 10 (48%) treated with alfacalcidol, and five (71%) not taking any active vitamin D compound were within the reference ranges of all six parameters. One has to take into account that not all data were available for every patient. Regarding the four serum parameters calcium, phosphate, CPP, and magnesium, 100% were in the reference range for calcitriol, 81% for alfacalcidol, and 83% for DHT. Comparing the achievement of the guidelines’ recommendations with the work by Meola and colleagues, we found in those patients (n = 24) with values for serum calcium, serum phosphate, CPP, and urinary calcium, 71% (n = 17) to be within the reference ranges. Our patients are therefore more controlled compared to the Italian study group, which reported that 34.1% met four targets (albumin adjusted serum calcium, phosphate, CPP, and 24-hour urinary calcium).

Regarding symptoms and complaints measured by HPQ 28, there were no differences between the different active vitamin D compounds administered and those patients on other forms of therapy. However, the variance was very high; we therefore analyzed the influence of co-medication with calcium, magnesium, and native vitamin D$_3$ further.

| Table 3. Dosage of Active Vitamin D Treatments in HypoPT Patients |
|---------------------------------|-----|-----|-----|-----|
| Calcitriol (μg/d) | Alfalcacidol (μg/d) | DHT (μg/d) | n |
|-------------------|-------------------|-----------|---|
| 0.13              | 0.5               | 3         | 130 1 |
| 0.25              | 0.75              | 3         | 270 1 |
| 0.50              | 1.00              | 8         | 600 1 |
| 0.75              | 1.25              | 3         | 1000 1 |
| 1                 | 1.5               | 2         | 1500 2 |
| 1.25              | 2.0               | 3         | |
| 3.00              |                   |           | |

DHT = dihydrotachysterol; HypoPT = hypoparathyroidism.

| Table 4. Correlation of Active Vitamin D Medication to Scales and Items of the HPQ 28 |
|---------------------------------|-----|-----|-----|-----|-----|-----|-----|
| Active vitamin D compound | Correlation | PaC | Vit | GiS | DaA | NVS | Heart palpitations |
|---------------------------|-------------|-----|-----|-----|-----|-----|------------------|
| Calcitriol (μg/d) | $r_s^2$ | 0.567 | 0.078 | 0.404 | 0.643 | 0.449 | 0.582 | 0.604 |
| $p^{ab}$ | 0.028 | 0.784 | 0.135 | 0.010 | 0.093 | 0.023 | 0.094 | 0.017 |
| n | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| Alfacalcidol (μg/d) | $r_s$ | 0.277 | 0.056 | 0.097 | 0.039 | 0.028 | 0.029 | 0.029 |
| $p^{ab}$ | 0.453 | 0.056 | 0.097 | 0.039 | 0.028 | 0.029 | 0.029 | 0.029 |
| n | 22 | 22 | 22 | 22 | 22 | 22 | 22 | 22 |
| DHT (μg/d) | $r_s$ | 0.377 | 0.141 | 0.206 | 0.312 | 0.449 | 0.500 | 0.645 |
| $p^{ab}$ | 0.453 | 0.056 | 0.097 | 0.039 | 0.028 | 0.029 | 0.029 | 0.029 |
| n | 6 | 7 | 6 | 7 | 6 | 7 | 6 | 6 |

Significant correlations are marked bold.

DaA = depression and anxiety; DHT = dihydrotachysterol; GiS = gastrointestinal symptoms; HPQ 28 = 28-item Hypoparathyroid Patient Questionnaire; NVS = neurovegetative symptoms; PaC = pain and cramps; Vit = loss of vitality.

$ab$Spearman rank correlation coefficient.

$ap$After Bonferroni correction $p > 0.05$ due to low number of patients and high number of parameters.

| Table 5. Results of Regression Analysis of the Effect of Calcitriol and Calcium Serum Values on the Significant Scales and Items |
|---------------------------------|-----|-----|-----|-----|-----|
| Parameter | Coefficient | PaC | DaA | Numbness and tingling | Heart palpitations |
|-----------|-------------|-----|-----|---------------------|------------------|
| Calcitriol | $\beta$ | 0.564 | 0.569 | 0.633 | 0.479 |
| $p$ | 0.042* | 0.041* | 0.021* | 0.998 |
| Serum calcium | $\beta$ | 0.188 | 0.170 | 0.054 | 0.032 |
| $p$ | 0.46 | 0.503 | 0.823 | 0.908 |

$\beta$ = standardized coefficient parameter $\beta$; DaA = depression and anxiety; $p$ = $p$ value for single parameters; PaC = pain and cramps.

$p < 0.05$ after correction for serum calcium.
The intake of magnesium supplements influenced two scales. In comparison with those not taking magnesium, patients complained more with respect to the scales NVS and GIS. There are items relating to gastrointestinal symptoms/complaints in both scales. For example, the item diarrhea belongs to the NVS scale and the item nausea to GIS. Because we know that the side effects of magnesium intake can include gastrointestinal symptoms, these results are in line with the everyday experience of clinical patient care. Hence, this finding confirms the usefulness of HPQ 28 to characterize patient complaints as specific symptoms.

When correlating calcium intake with HPQ 28 scales and items, we identified more complaints represented by the scale NVS, such as trembling muscles, hot flushes or chills, weakness, dizziness, and diarrhea as doses of calcium intake increased. The items “trembling muscles” and “weakness” correlated to calcium dose particularly, whereas the single item “diarrhea” did not correlate to calcium dose at all. On the one hand the symptoms we identified may be the reason for increasing calcium intake, or the consequence of higher calcium intake on the other hand. We know from individuals taking calcium supplements that calcium medication can cause gastrointestinal (GI) symptoms such as constipation, excessive abdominal cramping, bloating, upper GI events, GI disease, GI symptoms, and severe diarrhea. These symptoms might be experienced by the patient as heart problems. This was suggested by a meta-analysis demonstrating that an increase in the incidence of adverse GI events also increased the number of self-reported myocardial infarctions in calcium-treated patients but not controls. However, the item “heart palpitations” was not influenced by calcium intake in our patients. This may suggest, at least in part, that the symptoms and complaints are the reason for increasing calcium intake.

Although there were no differences between the effect of vitamin D compounds on HPQ 28 parameters, a high variance was evident. We were therefore interested in the effect of different doses of the individual vitamin D compounds. Although no dose effect was detectable in patients treated with alfalcacidol or DHT, in contrast, calcitriol dose effects were significant in three HPQ 28 scales when corrected for the effect of serum calcium. Summarizing these results, patients with higher doses of calcitriol suffer both greater depression and pain. The scale PaC includes the items pain in the (lower) back, joint pain or pain in the limbs, muscle pain, neck or shoulder pain, and muscle cramps. The items “joint pain or pain in the limbs”, “neck or shoulder pain” and most significantly “muscle cramps” were shown to correlate to calcitriol dosage. The scale DaA includes self-blaming emotions, inner tension and restlessness, sorrowful thoughts, melancholia, and difficulty in making decisions. All single items that belong to the DaA scale except the item “difficulty to make decisions” were affected by the calcitriol dose significantly. However, these symptoms are not typical side effects of calcitriol. In the German national pharmaceutical register, known as the “Rote Liste,” the side effects of calcitriol are listed as anorexia, headache, nausea, skin erythema, and bladder infections, none of which appear in any of the significant scales PaC and DaA in HPQ 28. The dose-dependent item “numbness and tingling” would suggest clinically that, in general, those with greater symptom load take more calcitriol. However, the dose of calcitriol is not determined according to symptoms but to attain and maintain the target range of serum calcium; the latter did not influence our results. This would suggest that the identified symptoms/complaints are independent of the actual calcium level determined. However, further analysis to identify other possible interfering parameters did not detect any influence of age, gender, underlying disease, or kind of surgery. Nevertheless, the number of patients is small and there remains the possibility that other, to date unidentified parameters influence our results.

It is of further interest that the other active vitamin D compounds did not demonstrate any dose effects influencing HPQ 28 scales and items. Reviewing the differences of the vitamin D compounds we studied (Table 6), calcitriol with the shortest half-life could possibly result in more and/or greater fluctuations in serum calcium than the others tested; however, no data on this hypothesis exist. However, even fluctuating calcium levels probably do not explain the different pain locations as described by HPQ 28 in this study. These particular pain symptoms or complaints are not common for the majority of HypoPT patients and thus may prove to be a consequence of the therapy.

Hence, our data suggest that calcitriol induces dose-dependent symptoms, in contrast to the other vitamin D compounds we studied.

A limitation of our study is the low number of study participants taking each individual vitamin D compound. A greater number of HypoPT patients would help to strengthen our results and thus conclusions. Patient numbers were too small to correct for all influencing parameters at the same time; the test could only be performed for one factor at a time. Comparison of those individual patients undergoing a change in their medication would be helpful toward future verification of any differential effects of the vitamin D compound actually implemented. Nonetheless, this might not be clinically feasible. Ultimately, this is the first study to our knowledge investigating laboratory values and symptoms dependent on available active vitamin D compounds.

In summary, we compared different treatment modalities in patients with HypoPT, by analyzing and evaluating laboratory values, and QoL according to symptoms and complaints. Although laboratory values in the majority of patients were in the reference ranges, patients reported a huge number of complaints. Using the recently developed HPQ 28 specific questionnaire, we identified effects of medication with calcium, magnesium, and calcitriol. Interestingly, serum values for all the patients treated with calcitriol were 100% in the reference range.

### Table 6. Different Active Vitamin D Compounds to Treat Chronic HypoPT(1)

| Active vitamin D | Finally activated in | Time to onset (days) | Time to offset (days) | Typical dose (μg/d) |
|------------------|---------------------|----------------------|-----------------------|---------------------|
| Calcitriol (1,25(OH)2D3) | Active | 1–2 | 2–3 | 0.25–2.0 |
| Alfacalcidol (1α(OH)D3) | Liver | 1–2 | 5–7 | 0.5–4.0 |
| Dihydrotachysterol (DHT, vitamin D2 derivative) | Liver | 4–7 | 7–21 | 300–1000 |

(1) HypoPT = hypoparathyroidism.
although patients still demonstrated a number of dose-dependent symptoms and complaints according to HPQ 28. This study presents the first data on specific complaints of HypoPT patients dependent on different treatment modalities. Our data would imply that in part the reduced QoL in these patients might be caused by one or a combination of the conventional treatment modalities. For the clinician treating patients with HypoPT, our data would suggest carefully considering patients’ symptoms and complaints not only as caused by the disease itself but by the treatment.

Acknowledgments

We acknowledge support by the German Research Foundation and the Open Access Publication Funds of the Göttingen University. We thank Andrew Entwistle for his assistance with proofreading the manuscript. Open Access funding enabled and organized by Projekt DEAL.

Authors’ roles: DW, CH-L, and HS equally contributed to the conception of the of this project. BS, MB, LW, AL, DW, CH-L and HS contributed to design, analysis, interpretation, and drafting and revision of the manuscript. BS, LW, DW, CH, and HS contributed to the data acquisition. All authors approved the final version of the manuscript.

Conflict of Interest

During the last 3 years, BS has received lecture honoraria from Shire/Takeda, Novartis, Astra Zeneca, and Boehringer Ingelheim, and served as advisory board member of Shire/Takeda. CH-L has received lecture honoraria from Heel, Servier, and Novartis, as well as royalties from Hogrefe Huber publishers. HS has served during the last 3 years as an advisory board member for Shire/Takeda, UCB, and Kyowa Kirin, and received speaker’s fees from Shire/Takeda and Amgen. The other authors stated no conflict of interest.

Peer review

The peer review history for this article is available at https://publons.com/publon/10.1002/jbmr.10586.

References

1. Bollerslev J, Rejnmark L, Marcocci C, et al. European Society of Endocrinology Clinical Guideline: treatment of chronic hypoparathyroidism in adults. *Eur J Endocrinol*. 2015;173(2):G1-G20.
2. Brandi ML, Bilezikian JP, Shoback D, et al. Management of hypoparathyroidism: summary statement and guidelines. *J Clin Endocrinol Metab*. 2016;101(6):2273-2283.
3. Mitchell DM, Regan S, Cooley MR, et al. Long-term follow-up of patients with hypoparathyroidism. *J Clin Endocrinol Metab*. 2012;97(12):4507-4514.
4. Astor MC, Lovas K, Debowksa A, et al. Epidemiology and health related quality of life in hypoparathyroidism in Norway. *J Clin Endocrinol Metab*. 2016;101(8):3045-3053.
5. Sikjaer T, Moser E, Rolighed L, et al. Concurrent hypoparathyroidism is associated with impaired physical function and quality of life in hypothyroidism. *J Bone Miner Res*. 2016;31(7):1440-1448.
6. Meola A, Vignali E, Matrone A, Cetani F, Marcocci C. Efficacy and safety of long-term management of patients with chronic postsurgical hypoparathyroidism. *J Endocrinol Invest*. 2018;41(10):1221-1226.
7. Arlt W, Fremerey C, Callies F, et al. Well-being, mood and calcium homeostasis in patients with hypoparathyroidism receiving standard treatment with calcium and vitamin D. *Eur J Endocrinol*. 2002;146(2):215-225.
8. Undebjerg L, Sikjaer T, Rejnmark L. Health-related quality of life in patients with nonsurgical hypoparathyroidism and pseudohypoparathyroidism. *Clin Endocrinol (Oxf)*. 2018;88(6):838-847.
9. Siggelkow H, Clarke BL, Germak J, et al. Burden of illness in not adequately controlled chronic hypoparathyroidism: findings from a 13-country patient and caregiver survey. *Clin Endocrinol (Oxf)*. 2020;92(2):159-168.
10. Mannstadt M, Bilezikian JP, Thakker RV, et al. Hypoparathyroidism. *Nat Rev Dis Primers*. 2017;3:17055.
11. Vokes T. Quality of life in hypoparathyroidism. *Bone*. 2019;120:542-547.
12. Coles T, Chen K, Nelson L, et al. Psychometric evaluation of the hypoparathyroidism symptom diary. *Patient Relat Outcome Meas*. 2019;10:25-36.
13. Brod M, Waldman LT, Smith A, Karpf D. Assessing the patient experience of hypoparathyroidism symptoms: development of the Hypoparathyroidism Patient Experience Scale-Symptom (HPES-Symptom). *Patient*. 2020;13(2):151-162.
14. Wilde D, Wilken L, Stamm B, et al. The HPQ—development and first administration of a questionnaire for hypoparathyroidism patients. *JBMR Plus*. 2020;4(1):e10245.
15. Wilde D, Wilken L, Stamm B, et al. Quantification of symptom load by a disease-specific questionnaire HPQ 28 and analysis of associated biochemical parameters in patients with postsurgical hypoparathyroidism. *JBMR Plus*. 2020;4(7):e10368.
16. Cohen J. A power primer. *Psychol Bull*. 1992;112(1):155-159.
17. Shoback D. Clinical practice. Hypoparathyroidism. *N Engl J Med*. 2008;359(4):391-403.
18. Domagała-Rodacka R, Cibor D, Szczeklik K, Rodacki T, Mach T, Owczarek D. Gastrointestinal tract as a side-effect target of medications. *Przegl Lek*. 2016;73(9):652-658.
19. Lewis JR, Zhu K, Prince RL. Adverse events from calcium supplementation: relationship to errors in myocardial infarction self-reporting in randomized controlled trials of calcium supplementation. *J Bone Miner Res*. 2012;27(3):719-722.