CLINICAL STUDY

Well-being, mood and calcium homeostasis in patients with hypoparathyroidism receiving standard treatment with calcium and vitamin D

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Abstract

Objective: Standard treatment in hypoparathyroidism consists of calcium and vitamin D (or vitamin D analogs) but does not employ replacement of the actual missing hormone. Only few studies have evaluated the efficacy of calcium/vitamin D treatment in hypoparathyroidism; the impact of chronic hypoparathyroid disease on well-being has not been investigated previously.

Design: Cross-sectional, controlled study in 25 unselected women with postsurgical hypoparathyroidism since 6.4 ± 8.0 years (S.D.) on stable treatment with calcium and vitamin D (or analogs) and in 25 controls with a history of thyroid surgery but intact parathyroid function, who were matched for sex, age and time since surgery.

Methods: Assessment of well-being and mood using validated questionnaires (the revised version Symptom Checklist 90 (SCL-90-R); the Giessen Complaint List (GBB-24); and the von Zerssen Symptom List (B-L Zerssen)), serum and urinary calcium/phosphorus homeostasis, and in the hypoparathyroid patients also screening for secondary disease by kidney ultrasound, ophthalmological split lamp examination, and measurement of bone mineral density.

Results: Serum calcium was in the accepted therapeutic range in the majority of hypoparathyroid patients. However, calcium/phosphorus homeostasis as a whole was clearly non-physiological. Nephrolithiasis was detected in 2 and cataracts in 11 of 25 hypoparathyroid patients. As compared with controls, hypoparathyroid patients had significantly higher global complaint scores in GBB-24 ($P = 0.036$), B-L Zerssen ($P = 0.002$) and SCL-90-R ($P = 0.020$) with predominant increases in the subscale scores for anxiety, phobic anxiety and their physical equivalents.

Conclusions: Current standard treatment in hypoparathyroidism is not only associated with an altered calcium/phosphorus homeostasis but also fails to restore well-being in these patients. Future studies need to address the impact of more physiological treatment options like parathyroid hormone(1–34) or parathyroid transplantation on well-being and mood in these patients.

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Introduction

The reported incidence of permanent hypoparathyroidism following thyroid surgery varies between 0.5 and 4% depending on the extent of operation and the surgical technique as well as on the experience of the surgeon (1–3). In countries with a high prevalence of goiter (4, 5) 500 thyroid surgeries per one million inhabitants are performed every year (1). Thus, in Germany an annual number of 500–1000 new patients with postsurgical hypoparathyroidism (PSHP) is to be expected.

The widely accepted standard treatment for hypoparathyroidism consists of supplementation with calcium

and vitamin D, vitamin D metabolites or vitamin D analogs (6–9), but does not employ replacement of the actual missing hormone, parathyroid hormone (PTH). This is a major difference from the more physiological replacement concepts used in the treatment of other hormonal deficiencies (e.g. adrenal insufficiency or hypothyroidism).

There is no doubt that calcium and vitamin D administration ends life-threatening hypocalcemia and debilitating tetanic symptoms in hypoparathyroid patients. However, calcium/vitamin D does not restore the physiological calcium/phosphorus homeostasis (10). Furthermore, evaluation of the clinical efficacy of calcium/vitamin D treatment in chronic hypoparathyroidism

has been largely neglected and well-being or mood in these patients has not been studied. Thus we performed a cross-sectional study in patients with hypoparathyroidism analyzing calcium homeostasis as well as well-being and mood, comparing the results with those obtained in sex- and age-matched controls with a history of thyroid surgery but intact parathyroid function.

Methods

Patients

We contacted by mail all outpatients with the established diagnosis of hypoparathyroidism currently registered at the Endocrine Ambulatory Unit of the University Hospital Wuerzburg ($n = 36$) and invited them to participate in the study. Twenty-nine of 36 patients were interested in participation (one man and 25 women with PSHP, two women with pseudohypoparathyroidism type Ia, and one woman with idiopathic hypoparathyroidism). In order to recruit a homogenous group, we included only the 25 women with PSHP into the study (mean age 48.4 ± 13.6 years (s.d.) (range 24–66 years); duration of disease, median 3 years, range 0.5–38 years). They suffered from PSHP following subtotal thyroidectomy for goiter ($n = 23$) or parathyroid surgery for hyperparathyroidism ($n = 2$). All patients received long-standing, stable treatment with calcium (0.5–3.0 g/day) and oral vitamin D, vitamin D metabolites or analogs (cholecalciferol 0.625–0.25 mg/day ($n = 2$), α -calcidol 1–2 μ g/day ($n = 3$), calcitriol 0.25–1.25 μ g/day ($n = 13$), or dihydrotachysterol 0.25–0.50 mg/day ($n = 8$). Seven of 25 patients received additional magnesium replacement.

For each hypoparathyroid patient, two potential control subjects with a history of subtotal thyroidectomy for goiter but intact parathyroid function were selected from the register files of the Department of Surgery, University of Wuerzburg. All selected control subjects were matched for sex, age and time since surgery. The first of the two potential controls agreeing to participate in the study was included. Thus, it was possible to compare the 25 patients with PSHP with a control group of 25 women with normal parathyroid function (mean age 49.5 ± 13.2 years, range 24–67 years).

Fifteen female volunteers as well as 15 of the female PSHP patients were postmenopausal; two and three respectively received estrogen/progestin replacement. Twenty of the 25 PSHP patients and 22 of the 25 controls took thyroxine replacement (75–150 μ g/day). In all subjects thyrotropin measurements reflected euthyroid function. At the time of testing, none of the participants suffered from any other chronic or acute disease. Further exclusion criteria were history of past psychiatric disease and past or current use of psychotropic drugs.

Prior to initiation of the study, the Ethics Committee of the University of Wuerzburg approved the study protocol, and all patients gave written informed consent.

Evaluation

All participants reported to the ambulatory unit during the morning having taken their usual medication (calcium, vitamin D or analogs, and thyroxine). After history taking and clinical examination, psychometric evaluation was carried out starting with a detailed and standardized instruction in how to complete the three different questionnaires. Afterwards, blood was drawn from all participants for determination of parameters of calcium homeostasis and renal function. In the hypoparathyroid patients this was followed by kidney ultrasound, measurement of bone mineral density (BMD) and ophthalmological split lamp examination. Patients and controls were instructed how to collect a 24 h urine and asked to bring it with them on one of the future appointments. Six weeks after the initial psychometric evaluation, an identical set of questionnaires was mailed to all participants, who were asked to send it back after completion.

Measurements

Psychometric evaluation of patients and controls was performed using three validated questionnaires, the revised version Symptom Checklist 90 (SCL-90-R), the von Zerssen Symptom List (B-L Zerssen), and the short form of the Giessen Complaint List (GBB-24). With the help of these questionnaires mood and well-being were assessed, the latter mainly as the subjective health status. All questionnaires are self-report or self-assessment questionnaires, which do not require the active participation of an interviewer or investigator but are presented as a self-explanatory written multiple-choice test.

The SCL-90-R (11) is a multidimensional self-report symptom inventory consisting of 90 items measuring a global severity index (GSI) and nine psychological dimensions (or subscales): somatization, obsessive-compulsive traits, interpersonal sensitivity, depression, anxiety, hostility, phobic anxiety, paranoid ideation, and psychotic tendencies. The responders are asked to rate items on five-step scales from 'I completely disagree' (or 'not at all') to 'I completely agree' (or 'extremely') taking into account their feelings during the preceding 7 days including the day of the testing. For calculations, the items on the scales are transformed into values from 0 (not at all) to 4 (extremely) and subscale scores are calculated by adding up the respective ratings and dividing by the number of items. The GSI is calculated from the sum of all ratings divided by the number of rated items. The average scores from the SCL-90-R can be additionally converted to standard T-scores (ranging from a minimum of 30 to

a maximum of 80) by referring to the appropriate female population-based norm tables provided by the test manual based on a reference sample of 18- to 60-year-old healthy women ($n = 501$) (12). A T-score of 50 represents the mean T-score of the respective normal population and the T-score range from 40 to 60 represents the normal range (as defined by the mean $\pm$ s.d.). T-scores >55 represent an already significant impairment and a T-score >60 represents a pathological result.

The B-L Zerssen (13) is a general well-being scale consisting of two similar questionnaires (B-L and B-L') with 24 items each. The items are rated on a four-step scale from 0 to 3 and scores are subsequently calculated by summing the item ratings. The global score is calculated from the mean of both scores and then further converted to a T-score and a percentile value by referring to the norm tables for females deriving from a population-based reference sample of 20- to 64-year-old women ($n = 988$) (13).

The short form of the GBB-24 (14) consists of 24 items defining four subscales (exhaustion tendency, gastric symptoms, pain in the limbs, and heart complaints) each including six items with ratings from 0 to 4. Additionally, a global score of discomfort (GSD) is calculated by adding up the four subscale scores. The GSD and the four subscale scores can be further converted to quartile values by referring to age-dependent norm tables for females provided by the test manual (15) based on a reference sample of healthy 18- to 60-year-old women ($n = 732$) stratified by age decade.

The higher the score or subscale score in any of the three psychometrical instruments, the greater the impairment of well-being as assessed by the respective questionnaire.

In patients and controls, biochemical measurements included calcium and phosphorus in serum and in 24 h urine, as well as serum renal function parameters (creatinine, urea, albumin and total protein). These measurements were carried out using enzymatic colorimetric standard methods.

The hypoparathyroid patients underwent additional tests including ophthalmological split lamp examination, imaging of the kidneys by abdominal ultrasound and measurement of BMD.

BMD measurements were carried out at the lumbar spine (L1–L4) and at the hip (neck and trochanter) by dual-energy X-ray absorptiometry (DXA) using a Lunar-DPX-Scanner (Lunar Corporation, Madison, WI, USA). Additionally, volumetric total and trabecular density were measured at the non-dominant distal radius by peripheral quantitative computed tomography (pQCT) using an XCT900 scanner (Stratec Medizintechnik, Pforzheim, Germany). Daily quality control was assured in both scanners, using the European Spine Phantom and the European Forearm Phantom. The results of lumbar spine and hip BMD were

compared with population-based European reference ranges (16, 17). Results at the distal radius were compared with a population-based German reference sample (18).

Statistical analysis

Data are presented as means $\pm$ s.d. Comparison of data was performed by *t*-test for unpaired samples, and if parameters were not normally distributed, by the non-parametric Mann–Whitney test. In addition, linear regression analyses were performed. Significance was defined as $P < 0.05$.

Although the psychometric test instruments have shown good re-test reliability (12, 13, 15), we employed two separate psychometric evaluation sessions; once during the clinic visit and once at home 6 weeks later. From the results of the two responses the average was taken and used for further statistical analysis.

The individual BMD results from both DXA and pQCT measurements were transformed into z-scores using European and German reference databases (16–18). The data of the two patients with a history of previous hyperparathyroidism were excluded from statistical analysis. Four patients did not participate in BMD measurements, hence we were able to analyze BMD data from 19 hypoparathyroid patients.

Results

Calcium and phosphorus homeostasis

Serum calcium values in 18 of 25 hypoparathyroid patient sera were within the accepted therapeutic range (i.e. the lower normal range, 2.00–2.35 mmol/l), in the others serum calcium was either within the higher normal range (2.36–2.70 mmol/l, $n = 4$) or slightly below the normal range ($n = 3$). Serum phosphorus was within the normal range (0.8–1.5 mmol/l) in 20 of 25 hypoparathyroid patients. However, in comparison with controls, patients with hypoparathyroidism had a significantly lower mean serum calcium (patients vs controls 2.15 ± 0.21 vs 2.27 ± 0.09 mmol/l, $P = 0.016$) and a significantly higher mean serum phosphorus concentration (1.32 ± 0.22 vs 1.03 ± 0.13 mmol/l, $P < 0.0001$). In the hypoparathyroid patients, there was a negative correlation between serum calcium and serum phosphorus ($r = -0.42$, $P = 0.035$) (Fig. 1A) while there was a positive one in the controls ($r = 0.46$, $P = 0.019$) (Fig. 1B). In 5 of 22 patients (and in 1 of 23 controls) urinary 24 h excretion of calcium exceeded the upper limit of the normal range (3–8 mmol/day). The two groups did not differ concerning 24 h urinary calcium excretion (patients vs controls 5.51 ± 4.17 vs 4.08 ± 2.03 mmol/24 h, $P = 0.15$) or 24 h phosphorus excretion (26.1 ± 8.8 vs 24.9 ± 8.7 mmol/24 h,

Figure 1 Serum calcium vs serum phosphorus in (A) patients with hypoparathyroidism ($n = 25$) receiving long-standing therapy with oral calcium and vitamin D preparations ($r = -0.42$, $P = 0.035$) and in (B) controls ($n = 25$) with intact parathyroid function ($r = 0.46$, $P = 0.019$).

Figure 2 Serum calcium vs 24 h urinary excretion of calcium in patients with hypoparathyroidism ($n = 22$) receiving long-standing therapy with oral calcium and vitamin D preparations ($r = 0.48$, $P = 0.024$) and in controls ($n = 23$) with intact parathyroid function ($r = 0.49$, $P = 0.016$).

$P = 0.64$). Urinary calcium excretion and serum calcium correlated positively in both groups (patients, $r = 0.48$, $P = 0.024$; controls, $r = 0.49$, $P = 0.016$), with an upward shift of the regression line in the hypoparathyroid patients (Fig. 2) that illustrates the non-physiological calcium/phosphorus homeostasis in these patients.

Well-being and mood

In comparison with controls, hypoparathyroid patients had significantly higher SCL-90-R subscale scores for somatization, depression, anxiety, and phobic anxiety, with differences so pronounced that they even accounted for a significantly higher GSI (Table 1). Test scores taken during the clinic visit did not differ from those taken at home. In the hypoparathyroid patients conversion to standard T-scores revealed pathologically elevated mean T-scores for anxiety, phobic anxiety, somatization and the GSI, while mean T-scores in the controls generally varied around the mean of the normal range (Table 1). Looking at individual T-scores for the GSI revealed that 12 of 25 patients but only 6 of 25 controls had a T-score higher than 60, equivalent to severe impairment of well-being and mood and an additional 5 patients and 3 controls presented with a T-score higher than 55, representing an already significant impairment of mood.

The results of the GBB-24 further confirmed this pattern. As compared with controls, patients had significantly higher scores for exhaustion tendency, pain in the limbs, heart complaints and the GSD (Table 2). The differences between patients and controls were so pronounced that they even accounted for significantly different quartile values for heart complaints (i.e. palpitations) and the GSD (Table 2).

Consistent with these findings, the global score of the B-L Zerssen was significantly higher in the hypoparathyroid patients (patients vs controls 29.6 ± 14.0 vs 18.7 ± 9.5 , $P = 0.002$). According to T-scores (patients vs controls 62.3 ± 10.6 vs 53.8 ± 7.7 , $P = 0.002$) and percentiles (79.7 ± 22.5 vs 62.0 ± 24.2 , $P = 0.009$), controls ranged near the normal mean while in the patients mean scores exceeded the upper normal limit.

There was no correlation between duration of hypoparathyroidism and global complaint scores (GSI (SCL-90-R): $r = 0.12$, $P = 0.57$; global score Zerssen: $r = -0.16$, $P = 0.46$; GSD (GBB-24): $r = -0.08$, $P = 0.72$) or one of the SCL-90-R subscale scores (somatization: $r = -0.02$, $P = 0.95$; anxiety: $r = -0.24$, $P = 0.25$; depression: $r = -0.30$, $P = 0.14$; phobic anxiety: $r = -0.11$, $P = 0.60$).

Similarly, serum calcium in the patients was correlated neither with one of the global complaint scores (GSI (SCL-90-R): $r = 0.11$, $P = 0.60$; B-L Zerssen: $r = 0.08$, $P = 0.70$; GSD (GBB-24): $r = 0.001$, $P = 1.0$) nor with one of the SCL-90-R subscale scores (somatization: $r = 0.02$, $P = 0.92$; anxiety: $r = -0.08$, $P = 0.70$;

Table 1 SCL-90-R subscale scores and standard T-scores (means $\pm$ s.d.) in female patients with hypoparathyroidism ($n = 25$) and in sex- and age-matched controls ($n = 25$) with a history of thyroid surgery but intact parathyroid function. Normal range for females according to (12).

SCL-90-R subscales	Score	Patients	Controls	P-value	Female normal range (means $\pm$ s.d.)
Somatization	Score value	1.02 $\pm$ 0.69	0.65 $\pm$ 0.40	0.023	0.41 $\pm$ 0.31
	T-value	64.4 $\pm$ 12.2	57.4 $\pm$ 10.2	0.032	50 $\pm$ 10
Obsessive-compulsive traits	Score value	0.81 $\pm$ 0.55	0.57 $\pm$ 0.11	0.138	0.51 $\pm$ 0.39
	T-value	56.6 $\pm$ 11.5	50.1 $\pm$ 14.2	0.082	50 $\pm$ 10
Interpersonal sensitivity	Score value	0.60 $\pm$ 0.47	0.43 $\pm$ 0.56	0.244	0.47 $\pm$ 0.41
	T-value	53.5 $\pm$ 10.6	48.3 $\pm$ 12.5	0.116	50 $\pm$ 10
Depression	Score value	0.70 $\pm$ 0.46	0.42 $\pm$ 0.46	0.037	0.49 $\pm$ 0.42
	T-value	54.7 $\pm$ 10.0	47.2 $\pm$ 11.3	0.016	50 $\pm$ 10
Anxiety	Score value	0.76 $\pm$ 0.12	0.33 $\pm$ 0.35	0.003	0.35 $\pm$ 0.35
	T-value	59.8 $\pm$ 11.1	49.2 $\pm$ 10.4	0.001	50 $\pm$ 10
Hostility	Score value	0.44 $\pm$ 0.35	0.18 $\pm$ 0.23	0.004	0.38 $\pm$ 0.36
	T-value	52.2 $\pm$ 9.5	44.0 $\pm$ 8.3	0.002	50 $\pm$ 10
Phobic anxiety	Score value	0.49 $\pm$ 0.59	0.21 $\pm$ 0.43	0.0626	0.17 $\pm$ 0.26
	T-value	57.9 $\pm$ 12.1	49.9 $\pm$ 10.5	0.017	50 $\pm$ 10
Paranoid ideation	Score value	0.54 $\pm$ 0.40	0.41 $\pm$ 0.57	0.357	0.38 $\pm$ 0.38
	T-value	54.2 $\pm$ 9.6	49.4 $\pm$ 11.5	0.122	50 $\pm$ 10
Psychotic tendencies	Score value	0.28 $\pm$ 0.28	0.11 $\pm$ 0.20	0.023	0.21 $\pm$ 0.26
	T-value	53.2 $\pm$ 9.2	45.4 $\pm$ 8.2	0.003	50 $\pm$ 10
Global severity index (GSI)	Score value	0.67 $\pm$ 0.38	0.44 $\pm$ 0.36	0.034	0.39 $\pm$ 0.26
	T-value	59.1 $\pm$ 11.2	51.2 $\pm$ 11.9	0.020	50 $\pm$ 10

depression: $r = -0.22$, $P = 0.30$; phobic anxiety: $r = -0.19$, $P = 0.38$). The exclusion of patients with insufficiently controlled hypoparathyroidism (serum calcium less than 2.00 or higher than 2.40 mmol/l) did not affect the outcome, e.g. the scale value for the GSI (SCL-90-R) was 0.44 ± 0.36 in the controls and 0.67 ± 0.38 in all patients with 0.70 ± 0.38 in the well-controlled patients ($n = 17$) and 0.57 ± 0.37 for poorly controlled patients ($n = 18$). Thus, poorly controlled patients presented with even less impaired well-being.

Secondary disease

In all patients and controls, serum parameters of renal function were within the normal range. Abdominal ultrasound detected previously asymptomatic unilateral kidney stones in 2 of 25 hypoparathyroid patients; there was no case of nephrocalcinosis.

Ophthalmological split lamp examination revealed incipient ($n = 8$) and manifest ($n = 3$) cataract in 20 patients examined (localization: unilateral 2 of 11, bilateral 9 of 11; type: nuclear ($n = 2$), cortical ($n = 8$) and subcapsular ($n = 1$). Patients with cataract tended to have a longer duration of hypoparathyroidism than those without (7.5 ± 11.0 vs 4.8 ± 4.0 years, $P = 0.49$). Patients with cataract also tended to be older (53.6 ± 15.3 vs 43.2 ± 11.5 years, $P = 0.11$), although cataracts were also diagnosed in two 24- and 25-year-old women with a duration of disease of 5 and 11 years respectively.

BMD

BMD in the hypoparathyroid patients was significantly higher than in normal persons of similar age, both at the lumbar spine (BMD (L1–L4) 1.28 ± 0.18 g/cm²,

Table 2 GBB-24 scores and quartile values (means $\pm$ s.d.) in female patients with postsurgical hypoparathyroidism ($n = 25$) and in sex- and age-matched controls ($n = 25$).

Scales	Score	Patients	Controls	P-value
Exhaustion tendency	Score	8.9 $\pm$ 5.6	5.6 $\pm$ 4.9	0.027
	Quartile value	3.1 $\pm$ 1.1	2.3 $\pm$ 1.3	0.069
Gastric symptoms	Score	4.2 $\pm$ 3.6	2.6 $\pm$ 2.7	0.084
	Quartile value	3.2 $\pm$ 1.1	2.5 $\pm$ 1.3	0.066
Pain in the limbs	Score	10.1 $\pm$ 6.3	6.9 $\pm$ 4.4	0.039
	Quartile value	3.1 $\pm$ 1.0	2.6 $\pm$ 1.2	0.097
Heart complaints	Score	6.8 $\pm$ 5.2	3.8 $\pm$ 3.1	0.021
	Quartile value	3.2 $\pm$ 0.8	2.7 $\pm$ 1.0	0.048
Global score of discomfort (GSD)	Score	30.0 $\pm$ 17.5	18.9 $\pm$ 11.6	0.011
	Quartile value	3.1 $\pm$ 1.0	2.5 $\pm$ 1.1	0.036

z-score 1.11 ± 1.14 , $P = 0.0005$) and at the hip (BMD femoral neck 0.96 ± 0.16 g/cm², z-score 0.69 ± 1.13 , $P = 0.015$; BMD trochanter 0.85 ± 0.10 g/cm², z-score 0.88 ± 0.65 , $P < 0.0001$). Z-scores of radius BMD did not differ significantly from the age-matched expected mean values of the reference database (total radius -0.21 ± 0.88 , $P = 0.32$; trabecular radius -0.27 ± 1.06 , $P = 0.28$).

Discussion

Our study gives compelling evidence that patients with chronic hypoparathyroidism receiving standard treatment with calcium and vitamin D suffer from a significant impairment of well-being and mood. The global scores of different psychometric questionnaires exceeded by one standard deviation the means of the respective normal ranges and the scores found in the matched controls. Furthermore, subscale analysis revealed a characteristic pattern of mood alterations with predominantly high scores for anxiety, phobic anxiety and their physical equivalents (e.g. heart complaints/palpitations). The need for chronic intake of replacement therapy as such cannot explain the mood impairment observed in the hypoparathyroid patients, as more complex replacement regimens in other endocrinopathies are not associated with a similar impairment of well-being (19).

Patients and controls did not differ concerning sex, age, time since thyroid surgery, menopausal status or frequency of estrogen/progestin and thyroxine replacement therapy. We cannot exclude that variations in magnesium levels or intake were a confounding variable for our findings, as only 7 of 25 patients regularly took magnesium replacement. As both patients and controls had previously undergone neck surgery, we can exclude influences of the surgical procedure itself on well-being. However, the postoperative experience of tetanic episodes may have triggered changes in well-being. Although we cannot fully exclude this possibility, it seems unlikely as in this case a gradual improvement in well-being with time after surgery should be expected, which was not observed. It is unlikely that our findings are influenced by a selection bias, as we included all patients responding to our initial mail contact, i.e. 80% of the total unselected outpatient pool. However, patients seen in a secondary/tertiary center like ours might be more 'difficult' than hypoparathyroid patients routinely treated by a general practitioner. However, such a bias is unlikely to explain the observed extent of impairment and the characteristic pattern of alterations in mood.

In patients with long-standing hypoparathyroidism (i.e. duration of disease longer than 8–10 years) basal ganglia or even diffuse brain calcification may occur (20–23). While this condition is generally asymptomatic, in some cases an association with cognitive

dysfunction (23) and even with organic mood disorder (24, 25) has been reported. We did not perform computerized tomography scans of the brain in our patients. However, it is not likely that the observed mood impairment can be explained by cerebral calcifications, as only 5 of the 25 patients had a duration of disease longer than 8 years. Moreover, regression analysis did not reveal any correlation between duration of disease and well-being or mood scores. Thus, the observed mood alterations are more likely due to functional rather than structural changes. However, serum calcium did not significantly correlate with mood scale scores in the hypoparathyroid patients.

It is conceivable that the impairment of well-being results directly from PTH deficiency not involving changes in calcium homeostasis. PTH specifically binds to the recently discovered PTH2 receptor, which is expressed in several brain regions (26). However, recently a brain-specific ligand to the PTH2 receptor, a hypothalamic neuropeptide, has been described (27). Also the expression of 25-hydroxyvitamin D-1 alpha-hydroxylase, a target enzyme of PTH action in the kidney, has been recently demonstrated in brain tissue (28). However, its physiological role in the central nervous system remains to be determined.

The majority of the hypoparathyroid patients presented with serum calcium levels in the accepted therapeutic target range; thus they could be considered as adequately treated. However, as compared with the controls, mean serum calcium was significantly lower while mean serum phosphorus was significantly higher in the patients with hypoparathyroidism. There was a positive correlation between serum and urinary calcium in both our patients and controls; however, in comparison with controls the regression line of the patient group showed an upward shift. This reflects the reduced tubular calcium reabsorption in hypoparathyroidism (29) leading to hypercalciuria even in the presence of normal serum calcium levels (10). The simultaneously decreased tubular phosphorus secretion is reflected by the negative correlation between serum calcium and serum phosphorus seen in the patients, but not in the controls. Thus, our results confirm that calcium and vitamin D treatment is unable to restore a physiological calcium/phosphorus homeostasis putting hypoparathyroid patients at a higher risk of extra-osseous calcification. The patients from our study group diagnosed with nephrolithiasis or cataracts further illustrate this.

In accord with previous studies in smaller numbers of patients (30–32) we found normal to increased BMD at all sites of measurement in the hypoparathyroid patients. Similar to the results of Duan *et al.* (33) in a longitudinal study with ten patients, BMD in our patients was higher at the lumbar spine than at the distal radius. Langdahl *et al.* (34) found a reduction in bone resorption rate and activation frequency and a prolonged quiescent period in bone biopsy specimens

from 12 hypoparathyroid patients, thereby giving further evidence to the notion that vitamin D alone is not able to normalize bone turnover.

In conclusion, we have shown that patients with PSHP receiving calcium and vitamin D standard treatment exhibit not only the known dysregulation of calcium/phosphorus homeostasis but do also suffer from a clinically relevant major impairment of mood with a pattern usually seen in anxiety disorders. Thus more physiological treatment options for hypoparathyroidism including their impact on well-being need to be evaluated. After initial attempts to restore normal PTH secretion in hypoparathyroidism by parathyroid allotransplantation (35, 36), during recent years important progress has been made in this field now opening up the perspective of parathyroid allotransplantation without the requirement of immunosuppression (37–39). Moreover, it has been shown recently that s.c. injected PTH(1–34) restores the physiological calcium homeostasis in patients with hypoparathyroidism (40). As PTH may soon become available as a new treatment option for osteoporosis, the time for its evaluation in the treatment of chronic hypoparathyroidism may have come.

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