The Effect of PTH(1–84) on Quality of Life in Hypoparathyroidism

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Context: Complaints from hypoparathyroid patients often reflect a reduction in quality of life (QOL), yet few data exist characterizing these complaints or the potential effects of PTH therapy to ameliorate them.

Objective: We tested the hypothesis that PTH(1–84) therapy improves QOL in hypoparathyroidism.

Design: Fifty-four hypoparathyroid subjects received open-label recombinant human PTH(1–84). Before and during PTH(1–84), subjects completed the RAND 36-Item Health Survey, a measure of health-related QOL covering 8 domains of physical and mental health.

Results: At baseline, subjects scored significantly lower than the normative reference range in all 8 domains (T-scores -1.35 to -0.78; $P < 0.001$ for all). With PTH(1–84), the total score improved as early as month 1 and remained higher through 1 year (400 ± 200 to 478 ± 230; $P = 0.001$). The overall mental component summary score improved (204 ± 110 to 247 ± 130; $P = 0.001$), as did 3 mental health domains (vitality, social functioning, and mental health), all within 1 month (T-scores improving from -1.3 to -0.7, -1.0 to -0.6, and -0.9 to -0.3, respectively; $P < 0.05$ for all). The overall physical component summary score also increased by 1 month and remained higher at 1 year (196 ± 110 to 231 ± 130; $P = 0.003$) as did 2 physical health domains (physical functioning and general health: T-scores improving from -0.8 to -0.4, -1.2 to -0.8, respectively; $P < 0.01$ for both).

Conclusions: These data suggest that hypoparathyroidism is associated with compromised QOL. Along with improved biochemical control, these results indicate that PTH(1–84) treatment of hypoparathyroidism improves physical and mental functioning. **(*J Clin Endocrinol Metab* 98: 2356–2361, 2013)**

Hypoparathyroidism is a disorder characterized by hypocalcemia and absent or deficient PTH. It is the only classic endocrine deficiency disorder for which the missing hormone, PTH, is not yet an approved therapy. Standard treatment consists of oral calcium and vitamin D supplementation. This approach presents a therapeutic challenge because large amounts of calcium and vitamin D are often required and attendant concerns about long-term complications are often expressed (1–4). PTH treatment presents an attractive alternative (5–10).

Many patients with hypoparathyroidism complain of reduced quality of life (QOL) in ways that are difficult to quantify but that are nevertheless of concern. Biochemical control with standard therapy is rarely accompanied by improved functioning or sense of well-being (11). Complaints of cognitive dysfunction are common, with the term brain fog typically described by patients (1). Few attempts have been made to quantify the QOL complaints of hypoparathyroidism (11) or the potential effects of PTH therapy to ameliorate them (12).

Subjects and Methods

Study design

We conducted an open-label uncontrolled study of recombinant human PTH(1–84) (NPS Pharmaceuticals, Bedminster,

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Abbreviations: BP, bodily pain; GH, perception of general health; MCS, mental component summary; QOL, quality of life; RE, role limitations due to emotional health problems; RF, role limitations caused by physical health problems; SF, social functioning; VT, vitality.

New Jersey) at a dose of 100 μg sc every other day. This dose was selected because we previously showed that this regimen restores markedly reduced bone turnover markers to levels within the normal range and reduces requirements for calcium and vitamin D supplementation (8).

Subjects

The diagnosis of hypoparathyroidism in men and women was established by the simultaneous presence of serum calcium and PTH concentrations below the lower limits of normal on at least 2 occasions separated by at least 30 days. Hypoparathyroidism was present for at least 2 years to define a chronic hypoparathyroid state. All subjects had to be on stable regimens of supplemental calcium and vitamin D intake for at least 6 months before enrollment. Subjects were excluded if they 1) had been treated with a bisphosphonate within 5 years or for more than 6 months duration at any time, 2) were women within 5 years of menopause, or 3) were using any of the following medications: estrogens, progestins, raloxifene, calcitonin, systemic corticosteroids, fluoride, lithium, statins, loop diuretics, or methotrexate. The following potentially confounding disorders were also exclusionary criteria: Paget's disease of bone, diabetes mellitus, chronic liver or renal disease, acromegaly, Cushing's syndrome, rheumatoid arthritis, or multiple myeloma.

Patients were recruited from the Metabolic Bone Diseases Unit of Columbia University Medical Center and from the Hypoparathyroidism Association. The study was approved by the Institutional Review Board of Columbia University Medical Center. All subjects gave written informed consent. Some of these subjects have been included in cohorts previously published by our group (8, 10).

Biochemical evaluation

Blood was collected at baseline 3 times before treatment and at months 1, 2, 3, 4, 5, 6, 9, and 12 months. The average of the pretreatment serum calcium values was used for the baseline calcium value. Blood sampling was performed 48 hours after the last PTH injection. Biochemistries were measured by automated techniques.

QOL evaluation

The RAND 36-Item Health Survey (version 1.0) was developed as part of the Medical Outcomes Study (13, 14). It is one of the most widely used measures of health-related QOL and has been applied in various populations (13–18). It consists of 36 items covering 8 domains of physical and mental health: physical functioning (PF), role limitations caused by physical health problems (RF), bodily pain (BP), perception of general health (GH), vitality (VT), social functioning (SF), role limitations due to emotional health problems (RE), and mental health (MH). Scores on all subscales ranged from 0 to 100; higher scores indicate more favorable physical functioning and psychological well-being. The 8 domains may be further grouped into 2 summary measures: the physical component summary (PCS) comprised of PF, RF, BP, and GH and the mental component summary (MCS) comprised of VT, SF, RE, and MH (13, 14).

Statistical analysis

A linear mixed model for repeated measures approach was applied with a single fixed effect of time and baseline level of the outcome entered as a continuous covariate. The autoregressive covariance structure (AR[1]) was determined before inferential testing to provide the best covariance model fit across all of the outcomes to be tested. This analysis assesses the reliability of the within-subject change from baseline (SAS Proc MIXED, version 9.2; SAS Institute, Cary, North Carolina). Our primary analysis investigated the changes in RAND 36-Item Health Survey scores from baseline to 1 year of therapy with PTH(1–84). T-scores were calculated from the normal ranges for healthy U.S. men and women using the RAND 36-Item Health Survey (13, 14). As secondary analyses, we investigated changes at other time points, including through 2 years of PTH(1–84) therapy; whether there were differences in scores between subjects that discontinued therapy versus those that remained in the study at 1 year; whether

Table 1. Baseline Characteristics of the Hypoparathyroid Population (n = 54)

	n	Mean ± SD	Range (Median)
Age, y		46 ± 14	18–71 (45)
Sex			
Female	40		
Premenopausal	25		
Postmenopausal	15		
Male	14		
Etiology			
Postoperative	27		
Autoimmune	26		
DiGeorge	1		
Duration of hypoparathyroidism, y		13 ± 12	2–46 (8)
Fractures in adulthood	14[a]		
Kidney stones	8		
Basal ganglia calcifications	3		
Calcium supplement dose, g/d		2.34 ± 2.0	0–9.0 (2.0)
Calcitriol supplement dose, μg/d		0.70 ± 0.5	0–3.0 (0.5)
Daily parent vitamin D dose, IU/d		2625 ± 12 000	0–75 000 (0)
Thiazide dose, mg (n = 18)		27 ± 20	6.25–100 (25)

[a] Among the patients that fractured, there were 7 digit, 3 rib, 3 hand, 2 foot, 1 tibia, 1 pelvis, 1 collarbone, 2 wrist, and 1 facial bone fracture; 4 subjects were missing baseline fracture data.

Table 2. Baseline Biochemistries[a]

	Mean	Range (Median)	Normal Range
Serum calcium, mg/dL[b]	8.6 ± 2	6.3–10.1 (8.7)	8.6–10.2
PTH, pg/mL	2 ± 10	<3–21 (<3)	10–64
Creatinine, mg/dL	0.86 ± 0.3	0.60–1.80 (0.90)	0.50–1.30
Phosphate, mg/dL	3.8 ± 1	3.0–6.7 (4.4)	2.5–4.5
Total alkaline phosphatase activity, U/L	57 ± 10	41–106 (61)	33–96
Urinary calcium excretion, mg/d	189 ± 120	37–564 (216)	50–250[c]
25-Hydroxyvitamin D, ng/mL	47 ± 80	12–571 (32)	30–100
1,25-Dihydroxyvitamin D, pg/mL	34 ± 20	14–145 (36)	15–60

[a] Values are mean ± SD.

[b] Serum calcium concentration was typically normal as a result of calcium and vitamin D supplementation.

[c] For men, 50–300 mg/d.

there were differences in scores due to etiology of hypoparathyroidism; and whether the change in calcium or 1,25-dihydroxyvitamin D supplement dose correlated with changes in SF-36 scores. We compared subjects that discontinued therapy before 1 year to subjects that continued through 1 year and subjects that continued through 2 years to the entire cohort using *t* tests for continuous variables and χ^2 for discrete variables. All reported analyses are intention-to-treat, save for the comparison between subjects that discontinued therapy versus those that remained in the study at 1 year. Data in the body of the text are reported as model-estimated means and SDs, and differences between baseline and subsequent times were tested by simultaneous confidence intervals. *P* values $< .05$ were used to establish significance.

Results

Baseline characteristics and adherence to treatment

Table 1 shows the baseline characteristics of the 54 hypoparathyroid subjects. The mean age was 46 ± 14 (range 18–71) years, and 74% were female, consistent with the demographics of the disease. The two major etiologies of hypoparathyroidism were surgical and autoimmune. The mean duration of hypoparathyroidism was 13 ± 12 (range 2–46) years.

Fifty-four subjects are included in this analysis. Two subjects who recently entered the study provided only baseline data. Ten subjects discontinued the intervention between months 1 and 6 (mean 3.5 ± 2 months) due to loss to follow-up (n = 4), adverse events (nausea or gastrointestinal illness; n = 2), unrelated health issues (n = 2), logistics of travel (n = 1), or nephrolithiasis (n = 1).

Biochemical evaluation

Baseline biochemistries are shown in Table 2. Serum calcium concentration was typically normal as a result of supplementation with calcium and vitamin D. Mean serum calcium was maintained in the intended low-normal range throughout the study (8.6 ± 2 mg/dL at baseline to 8.3 ± 2 mg/dL at 1 year). Calcium supplementation requirements decreased by 52% during the course of the study, from 2.54 ± 2.1 g/d at baseline to 1.21 ± 2.5 g/d at 1 year ($P < .0001$). 1,25-Dihydroxyvitamin D supplementation requirements decreased by 51%, from 0.74 ± 0.9 μg/d at baseline to 0.36 ± 1.0 μg/d at 1 year ($P < .0001$). Urine calcium excretion declined, from 253 ± 240 g/d at baseline to 191 ± 310 g/d at 1 year ($P = .018$). Serum phosphorus level also declined, from 4.4 ± 1 mg/dL at baseline to 4.1 ± 1 mg/dL at 1 year ($P = .003$).

QOL evaluation

The results of the RAND 36-Item Health Survey data at baseline and after treatment with PTH(1–84) at 1, 2, 6,

Table 3. RAND 36-Item Health Survey Total, Component, and Individual Domain Scores at Baseline and Through 1 Year of PTH(1–84) Therapy[a]

Time	Total	MCS	VT	SF	RE	MH	PCS	PF	RF	BP	GH
Baseline	400 ± 200	204 ± 110	33 ± 30	60 ± 40	53 ± 60	58 ± 20	196 ± 110	66 ± 30	46 ± 50	43 ± 30	47 ± 30
1 month	471 ± 260[d]	251 ± 150[d]	47 ± 40[d]	68 ± 50[b]	68 ± 80	68 ± 30[d]	220 ± 150[b]	68 ± 40	51 ± 80	45 ± 40	55 ± 40[c]
2 months	494 ± 270[d]	263 ± 150[d]	50 ± 40[d]	76 ± 50[d]	67 ± 90	72 ± 30[d]	233 ± 150[c]	75 ± 40[c]	56 ± 90	47 ± 40	57 ± 40[c]
6 months	499 ± 230[d]	258 ± 130[d]	47 ± 30[d]	72 ± 40[c]	70 ± 70[c]	70 ± 30[d]	240 ± 130[d]	75 ± 30[c]	63 ± 70[c]	47 ± 30	55 ± 30[c]
12 months	478 ± 230[c]	247 ± 130[c]	46 ± 30[d]	70 ± 40[b]	62 ± 70	70 ± 30[d]	231 ± 130[c]	75 ± 30[c]	54 ± 70	47 ± 30	56 ± 30[c]

[a] Values are mean ±SD.

[b] $P < .05$ compared with baseline.

[c] $P < .01$ compared with baseline.

[d] $P < .001$ compared with baseline.

Table 4. RAND 36-Item Health Survey Domain T-Scores at Baseline and at 1 Year of PTH(1–84) Therapy[a]

Time	VT	SF	RE	MH	PF	RF	BP	GH
Baseline	−1.32 ± 1.4[b]	−1.03 ± 1.6[b]	−0.87 ± 1.9[b]	−0.92 ± 1.4[b]	−0.78 ± 1.3[b]	−1.04 ± 1.9[b]	−1.35 ± 1.2[b]	−1.23 ± 1.4[b]
12 months	−0.70 ± 1.6[e]	−0.60 ± 1.8[c]	−0.59 ± 2.2	−0.27 ± 1.6[e]	−0.41 ± 1.5[d]	−0.80 ± 2.1	−1.17 ± 1.3	−0.81 ± 1.6[d]

[a] Values are mean ± SD.

[b] $P < .05$ compared with normal population.

[c] $P < .05$ compared with baseline.

[d] $P < .01$ compared with baseline.

[e] $P < .001$ compared with baseline.

and 12 months are shown in Tables 3 and 4. At baseline, hypoparathyroid subjects scored lower than the normative reference range in all 8 domains, with T-scores ranging from −1.35 to −0.78 ($P < .05$ for all). After treatment with PTH(1–84), the total score increased significantly at 1 month (400 ± 200 to 471 ± 260; $P < .001$) and remained above the pretreatment value through 12 months (478 ± 230; $P = .001$). The MCS score increased significantly at 1 month (204 ± 110 to 251 ± 150; $P < .001$) and remained above baseline through 12 months (247 ± 130; $P = .001$). Three of the individual mental health domain scores also increased significantly early in treatment and remained above baseline at 12 months: VT (33 ± 30 to 47 ± 40 at 1 month, $P < .0001$; and 46 ± 30 at 1 year, $P < .001$), SF (60 ± 40 to 68 ± 50 at 1 month, $P = .024$; and 70 ± 40 at 1 year, $P = .014$), MH (58 ± 20 to 68 ± 30 at 1 month, $P < .001$; and 70 ± 30 at 1 year, $P < .001$) (Figure 1). T-scores in these domains improved from −1.32 ± 1.4 to −0.70 ± 1.6, −1.03 ± 1.6 to −0.60 ± 1.8, and −0.92 ± 1.4 to −0.27 ± 1.6, respectively ($P < .05$ for all). The PCS score increased at 1 month (196 ± 110 to 220 ± 150; $P = .03$) and remained higher at 12 months (231 ± 130; $P = .003$). Two physical health domain scores also increased significantly early in treatment and remained above baseline at 12 months: PF (66 ± 30 to 75 ± 40 at 2 months, $P = .005$; and 75 ± 30 at year, $P = .006$) and GH (47 ± 30 to 55 ± 40 at 1 month, $P = .003$; and 56 ± 30 at 1 year; $P = .008$). T-scores in these domains improved from −0.78 ± 1.3 to −0.41 ± 1.5 and −1.23 ± 1.4 to −0.81 ± 1.6, respectively ($P < .01$ for both).

Secondary analyses

There were no significant between-group differences when we compared the 27 subjects with postsurgical hypoparathyroidism to the 26 subjects with an autoimmune etiology. There were no significant correlations between adjustments in calcium supplement use and any domain. There were moderate correlations between adjustments in 1,25-dihydroxyvitamin D supplement use and RF score ($r = −0.34$; $P = .034$), BP score ($r = −0.43$; $P = .007$), and MH score ($r = −0.41$; $P = .01$).

There were no differences between subjects that completed at least 1 year of therapy and subjects that discontinued before 1 year with respect to age, gender, etiology, duration of hypoparathyroidism, baseline calcium or 1,25-dihydroxyvitamin D supplementation, or baseline serum or urine calcium. As compared with those who continued therapy, the 10 subjects who discontinued PTH before 1 year had significantly lower MH (41 ± 130 vs 70 ± 30; $P = .001$) and SF (42 ± 190 vs 70 ± 50; $P = .026$) scores at 1 month.

We were also able to evaluate 34 subjects through 2 years. There were no differences between subjects that

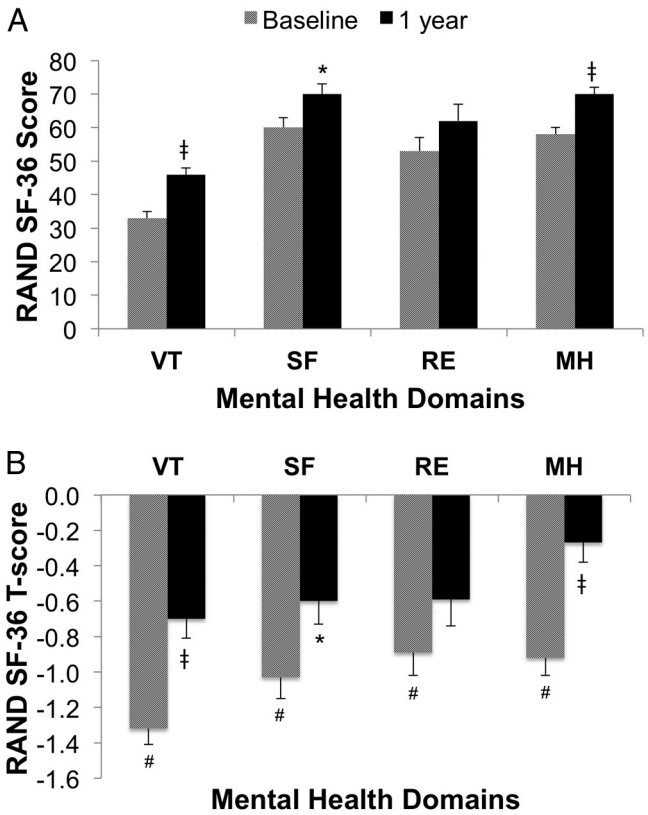

Figure 1. Changes in the mental health domains with PTH(1–84) therapy. A, Change in RAND 36-Item Health Survey domain scores from baseline to 1 year. B, Change in RAND 36-Item Health Survey domain T-scores from baseline to 1 year. Values are mean ± SE. #, $P < .05$ compared with normal population; *, $P < .05$ compared with baseline; ‡, $P < .001$ compared with baseline.

completed 2 years compared with the entire cohort with respect to age, gender, etiology, duration of hypoparathyroidism, baseline calcium or 1,25-dihydroxyvitamin D supplementation, or baseline serum or urine calcium. Significant improvements persisted in all the findings described above for 12 months (P values for 24 months compared with baseline): total score (490 ± 270, $P < .001$), MCS (247 ± 159, $P = .001$), VT (46 ± 39, $P < .0001$), SF (69 ± 50, $P = .03$), MH (68 ± 40, $P = .001$), PCS (244 ± 150, $P < .0001$), PF (76 ± 40, $P = .003$), and GH (56 ± 40, $P = .004$).

Discussion

Hypoparathyroidism is the only classic endocrine deficiency disorder for which the missing hormone, PTH, is not yet an approved therapy. PTH(1–34) and PTH(1–84) have both been shown to decrease calcium and vitamin D supplementation requirements (5–10). PTH(1–34) and PTH(1–84) have also been shown to improve abnormal skeletal properties in some subjects with hypoparathyroidism (19, 20). This is one of the first studies to investigate the effects of PTH therapy to improve QOL in hypoparathyroidism (12).

Our results demonstrate that at baseline, hypoparathyroidism is associated with QOL deficits, even in the presence of adequate calcium and vitamin D therapy to maintain eucalcemia for most subjects. Therapy with PTH(1–84) significantly improved QOL indices, particularly those related to mental health. Three of 4 mental health indices (vitality, social functioning, and mental health) increased significantly with PTH, as early as 1 month, and showed continued improvement during the course of treatment. Two of 4 physical health indices (physical functioning and general health) also increased significantly by 1 to 2 months of therapy and remained elevated at 12 months. The MCS and PCS scores as well as the total score also increased early in the therapy course and remained elevated at study conclusion. Reduction in supplement use was not well correlated with these improvements.

The baseline data are consistent with a study of 25 women with postsurgical hypoparathyroidism (age 48.4 ± 13 years, mean duration 6.4 ± 8 years) on stable treatment with calcium and vitamin D supplementation versus 25 age- and sex-matched controls (11). Despite most subjects demonstrating eucalcemia, hypoparathyroid patients had significantly higher global complaint scores in various validated QOL questionnaires (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 predominant increases in the subscale scores for anxiety, phobic anxiety, and their physical equivalents.

The PTH1 receptor is activated by both PTH and PTHrP and is primarily found in bone and kidney, whereas the PTH2 receptor, activated by PTH and tuberoinfundibular peptide of 39 residues (TIP39), is particularly abundant in the brain (21, 22). The locations of the PTH2 receptor in the brain of primates suggest involvement in the regulation of fear and anxiety (22). PTH has been demonstrated in cerebrospinal fluid samples (23, 24) and may cross the blood-brain barrier (25). The logical inference that PTH may have central nervous system effects may account for our observations that hypoparathyroidism is associated with neurocognitive complaints and that replacement therapy with PTH(1–84) may ameliorate these deficits. It is also consistent with observations that the mental and physical functioning does not appear to be improved despite normalization of the serum calcium for most subjects.

The strengths of this study include the unusually large cohort of subjects with hypoparathyroidism and the fact that PTH(1–84), the natural secretory product of the parathyroid glands (as distinguished from PTH[1–34]), was employed. A well-validated survey instrument was used. Although a majority of subjects remained in the study, subjects who discontinued PTH did not appear to benefit to the same extent with regard to QOL measures as those that continued the intervention, and this may have introduced attrition bias despite our use of an intention-to-treat analysis. We cannot exclude the possibility that our clinical trial subjects may not be representative of the hypoparathyroid population or that comorbid medical conditions may have resulted in lower baseline values. Another limitation to the investigation is its open-label design and lack of a control group of hypoparathyroid subjects not treated with PTH(1–84). The persistence of our findings through 24 months is reassuring, although it does not remove the possibility of confounding. Because the study design called for serum measurements after the first 24 hours of PTH administration, earlier changes in serum calcium, if they occurred, would have been missed. In a study investigating the pharmacodynamics of PTH(1–84) 100 μg daily in hypoparathyroid patients (26), 41% of subjects developed mild asymptomatic hypercalcemia. However, the dose of PTH was higher than that used in our study and the baseline serum calcium was substantially higher than in our subjects. Based upon the small increments in serum calcium after administration of PTH(1–84) in healthy postmenopausal women (27) and subjects with hypoparathyroidism

(26), we do not believe that our subjects would have experienced significant hypercalcemia in the time period preceding our measurement. Higher mean serum calcium values would not necessarily explain the improvement in QOL scores that we noted. Sikjaer et al (12) reported no improvement in QOL in their hypoparathyroid subjects randomized to PTH(1–84) 100 μg daily versus placebo, noting that large fluctuations in serum calcium may have negated any potential advantage.

Beyond improved biochemical control in hypoparathyroidism, these results indicate that PTH(1–84) treatment may lead to important improvements in QOL in most treated patients with hypoparathyroidism. Future studies that are blinded and controlled will help to confirm these observations. The effect of a more physiological mode of PTH delivery on QOL in these patients would also be of interest.

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