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# Quality of life in hypoparathyroidism

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ABSTRACT

Hypoparathyroidism is a rare endocrine disorder where deficiency (or lack of effect) of parathyroid hormone results in disordered mineral metabolism leading to hypocalcemia and hyperphosphatemia. Many patients with this disorder have physical, emotional and cognitive complaints suggestive of impaired quality of life (QOL). Several recent studies have demonstrated that hypoparathyroid patients treated with calcium and vitamin D (conventional therapy) have reduced QOL compared to either suitable controls or general population. QOL has also been studied during treatment with PTH1–84, which has been FDA approved in the USA as an adjunct to calcium and vitamin D in patients not adequately controlled on conventional therapy. In open label studies, PTH therapy has resulted in dramatic improvements in SF-36 scores. In placebo-controlled, double-blinded studies the effect of PTH on QOL has been less striking. In one such study there was no improvement, possibly due to high incidence of hypercalcemia in the PTH-treated group. In contrast, in the pivotal trial leading to PTH1–84 approval, were hypercalcemia was less common, SF36 scores improved in the PTH-treated but not in the placebo group although between-group differences were not statistically significant. In the same study, patients who started with lower baseline QOL scores had greater improvements, suggesting that patients with poor wellbeing may be particularly suitable for this new therapy.

In the future, it will be necessary to develop disease specific instruments to better define the nature of QOL impairments in this disease. In addition, further studies should focus on the possible relationship between biochemical variables and QOL parameters during treatment with different regimens.

## 1. Introduction

Hypoparathyroidism is a rare disease where parathyroid hormone is absent or inappropriately low resulting in low levels of serum calcium and magnesium, high serum phosphate, and urine calcium that is too high for the level of serum calcium. In 70–80% of adult cases this condition arises from accidental removal of parathyroid glands during thyroid surgery (usually for thyroid cancer, but also for benign thyroid diseases like goiter or Graves's disease), surgery for hyperparathyroidism, or for head and neck cancer. In the remaining ¼ of patients the disease is either isolated or a part of genetic syndrome. Hypocalcemia is the main mechanism by which hypoparathyroidism affects the well-being. Patients with hypoparathyroidism on conventional therapy with calcium and vitamin D often have complaints that suggest impaired quality of life (QOL) [1,2]. These complaints broadly fall into physical, emotional and mental domains. Physical complaints include fatigue, muscle twitching and spasms, pain, paresthesia, weakness and in severe cases seizures, cardiac abnormalities and coma. Emotional complaints are variable and include anxiety, depression and personality disorders. Cognitive difficulties are often described as “brain fog” and seem to refer to an impairment of mental processing, inability to concentrate and/or multitask. There is a wide variability in the way hypoparathyroidism affects different people. Some patients with this disease are able to lead a relatively normal life, including successful professional careers and high levels of physical activity (running marathons), while others find themselves severely incapacitated. Although, some studies find that patients with nonsurgical hypoparathyroidism seem to be less symptomatic compared to those with postsurgical hypoparathyroidism [3] this difference in the severity of QOL impairment between the two forms has not been confirmed by all studies [4–6].

## 2. Studies of QOL in patients treated with calcium and vitamin D

Systematic studies of QOL in hypoparathyroidism have been relatively recent. The challenges in investigating QOL in this disease are related to the above mentioned variability of symptoms both within and between patients. In addition, there are no validated disease-specific instruments and instead more general surveys are used which may not reliably reflect the nature of the QOL impairments in hypoparathyroidism. A more disease-specific instrument would likely emphasize symptoms such as muscle spasms, cramping and twitching, tingling and numbness, fatigue and decreased exercise tolerance, and confused

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thinking ("brain fog"). Nevertheless, several publications are now available (including a recent systematic review [7]) reporting QOL deficits in patients with hypoparathyroidism on "conventional therapy" with calcium and active vitamin D as well as the QOL response to treatment with PTH. In these studies, the QOL results from hypoparathyroid patients are compared either to suitable controls (case-controlled studies) or to population based norms.

### 2.1. Case-control studies

The first study that evaluated QOL in hypoparathyroidism is from Germany [8]. Arlt et al. compared 25 women who had postsurgical hypoparathyroidism to 25 women who also had thyroid surgery and were hypothyroid on replacement but had preserved parathyroid function. Despite the fact that hypoparathyroid women had levels of calcium that would be considered adequately controlled for this disease, they had more severe symptoms than the controls on all 3 validated instruments including higher global complaint score on Giesen Complaint List, Symptom Check List 90 and Von Zerseen Symptom list. The predominant increase was in the subscales for anxiety, phobic anxiety and their physical equivalents. More recently a study with a similar design was conducted in Brazil [9]. In this study 37 patients who had hypoparathyroidism (31 were postsurgical and also had hypothyroidism) were compared to the 20 controls who only had hypothyroidism. Hypoparathyroid patients had higher global severity index than the controls with no correlation between the severity of symptoms and serum calcium levels.

A study from India compared neuropsychological function of 62 patients with non-surgical hypoparathyroidism and 70 controls using a battery of cognitive tests [10]. A significantly higher percentage of patients than controls (32 vs. 6) had neuropsychological dysfunction.

The remaining studies (described below) mostly used SF36 (36-Item Short-Form Health Survey), a commonly used and validated non-disease-specific instrument for overall assessment of health and wellbeing [11]. It is important to understand how the scores are generated as this may be of importance when interpreting the studies of QOL in hypoparathyroidism. SF-36 survey consists of 36 questions the answers to which are grouped into eight domains of physical and mental health: physical functioning (PF), role physical (RP), bodily pain (BP), general health (GH), vitality (VT), social functioning (SF), role emotional (RE), and mental health (MH). These eight domains are then summarized into a physical component summary (PCS) score and a mental health summary (MCS) score. The scores are recalculated on a scale from 0 to 100. In some studies, the results are given as raw scores and in others as a norm-based score derived from comparison to normal population where the mean is 50 and standard deviation is 10. In most studies of QOL in hypoparathyroidism the norm based scores are calculated relative to the US population. It is important to note that the range of responses to each survey question is limited (between 2 and 6) i.e. patients do not have a range between 0 and 100 to choose from. It is not clear whether this may in some way diminish the sensitivity of this instrument to subtle alterations in wellbeing of patients with hypoparathyroidism.

Using SF36 a well-designed study from Denmark compared 22 patients who had both postsurgical hypoparathyroidism and hypothyroidism, 22 controls who had only hypothyroidism but had preserved parathyroid function and 22 matched controls with no deficiency of either hormone [12]. As seen on Fig. 1, patients with hypothyroidism had lower scores for several domains (RP, BP, VT, and MH). However, those with both hypothyroidism and hypoparathyroidism had lower SF36 scores than the healthy controls for 7 out of 8 domains (all except RE) and were lower than the hypothyroid patients for 2 domains (PF and RP) as well as for PCS. This study also evaluated muscle strength and performance and found that while hypothyroid patients did not differ from controls, hypoparathyroid patients performed worse than both the controls and the hypothyroid patients for many of the muscle groups tested as well as in the Timed Up and Go Test and in Repeated Chair Stands Test. This study also addresses an important unresolved question: is impaired QOL in postsurgical hypoparathyroidism due solely to abnormal calcium homeostasis? Or is it mediated by the effects of hypothyroidism and/or supra-physiologic doses of thyroid hormone that are often employed in the care of patients who had surgery for thyroid cancer? Based on the findings from this study it appears that while hypothyroidism may play some role, hypoparathyroidism per se has a much greater negative effect on wellbeing.

The final case-controlled study had an unusual design [13]. In this study from the Harvard system the cases were 340 patients with surgical hypoparathyroidism who completed the SF36. The controls completed a modified SF36 and included two groups of individuals: 200 healthy controls were given the standard preoperative description of hypoparathyroidism and then asked to imagine how they would feel if they had it. The other control group comprised of 102 experienced endocrine surgeons. All SF36 scores were lower in the patients than in either control group. The authors conclude that the impact of postoperative hypoparathyroidism is very much underestimated by subjects who receive surgical consultation and also by the surgeons who perform the surgery. This failure of medical profession to fully appreciate the extent of suffering of patients with hypoparathyroidism is likely one of the factors that contributes to the fear and anxiety that these patients often experience.

### 2.2. Studies comparing patients with hypoparathyroidism to general population or registry controls

Underbjerg et al. compared 688 patients with surgical hypoparathyroidism from the Danish national registry to age matched controls (3 controls for each patient) [14]. The patients had higher scores for depression and other neuropsychiatric diseases as well as for infections but fewer arm fractures and gastrointestinal malignancies. Using the same registry the same authors found 180 patients with non-surgical hypoparathyroidism [6]. Compared to controls, the patients had 2.45 times higher risk of neuropsychiatric complications.

In a more recent study, Underbjerg et al. tested QOL using SF36 and WHO-5 Well Being index in 57 patients with non-surgical hypoparathyroidism and 30 patients with pseudohypoparathyroidism (most but not all from the registry above) [4]. Compared to the population-based norms, non-surgical patients had lower SF36 scores for all 8 domains while the pseudohypoparathyroid patients were lower in 5 domains. Women were more affected than men. The authors also compared these patients to post-surgical hypoparathyroid patients that were previously enrolled in their clinical trial [15], and found that nonsurgical cases had lower SF36 scores than previously reported post-surgical patients. This observation is in contrast to other studies [3] and general belief that post-surgical patients tend to have more severe symptoms that the non-surgical ones. It is not clear, however, whether the post-surgical cases enrolled in the clinical trial actually had somewhat better care and biochemical control than the non-surgical cases recruited from the registry.

The final two registry based studies are different in design as they invited patients to participate and thus may have some degree of bias with patients with worse symptoms being more likely to respond to the invitation (although this assumption may not be correct and has not been tested). In a Norwegian study there were 522 patients with hypoparathyroidism identified in electronic hospital registry and all 511 living patients were invited to participate in the survey that used SF36 and Hospital Anxiety and Depression scale [3]. Among the 283 respondents the scores for both instruments were worse than the population norms with poorer scores in surgical than nonsurgical or pseudohypoparathyroid cases and in female compared to male participants. Similarly, a web-based study from the US, Paradox, found that the majority of the 374 respondents reported fatigue, emotional and cognitive problems [16].

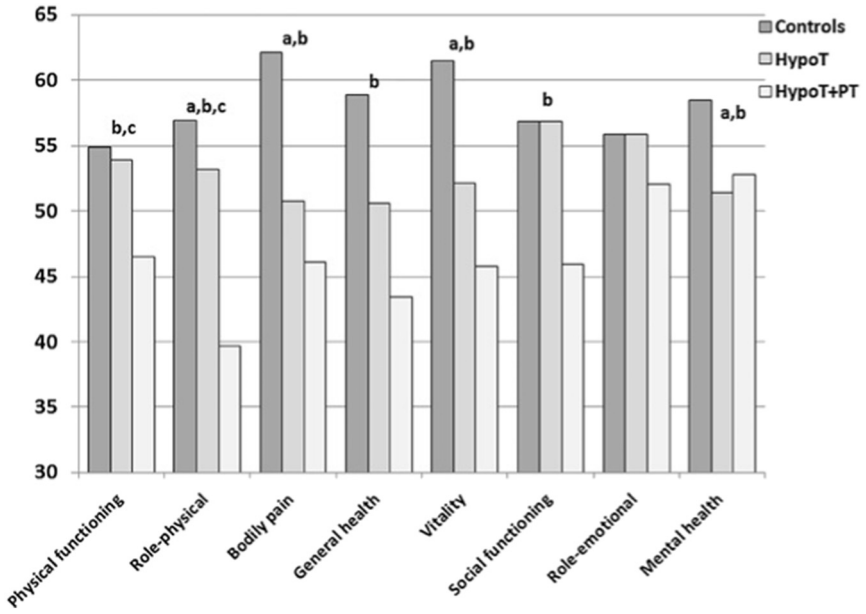


**Fig. 1.** Findings on the eight subscales of quality of life as measured by the SF-36v2 in patients on treatment for postsurgical hypothyroidism (HypoT), postsurgical hypothyroidism and hypoparathyroidism (HypoT + PT), and healthy controls. Post hoc tests: $P < 0.05$ for (a) controls versus HypoT, (b) controls versus HypoT + PT, (c) HypoT versus HypoT + PT. Reproduced with permission from Sikjaer et al. [12].

### *2.3. Baseline QOL data from clinical trials of PTH and its analogues*

When examining the baseline SF36 scores from the currently published clinical trials [5,17–19], several conclusions emerge. First, there is variability between different studies in severity of the QOL impairments. Second, in practically all of the studies the SF36 scores in the patients are lower than in general population. Thirdly, there is at least some concordance between studies in terms of what aspects of well-being are affected.

## 3. QOL response to PTH therapy

The first studies of PTH use in hypoparathyroid patients were conducted by Karen Winer's group using PTH 1–34 [20–24]. The results of these studies are presented in the companion article.

Several more recent studies have formally evaluated QOL response to PTH therapy, some with and others without placebo control.

### *3.1. Open label studies without placebo control*

Two groups have examined QOL response to PTH in investigator initiated open label studies. The first is from Columbia University in New York City. Cusano et al. reported SF36 scores obtained in 54 patients at 0, 1, 2, 6, and 12 months after starting PTH 1–84 given at 100 μg every other day [17]. This dose was chosen because it was previously found to normalize bone turnover. The supplement dose of calcium and calcitriol were adjusted to maintain normoclacemia and indeed had decreased by 52% and by 51%, respectively, during the study. At study enrollment, serum calcium was at a level consistent with acceptable control for this disease and was maintained at that level throughout the study. SF36 scores, which were low prior the administration of PTH, improved significantly at 1 month and remained above the baseline for the duration of the study. The same group also reported SF36 scores after a total of 5 years of therapy [25]. In this extension study a total of 69 patients were enrolled but only 25 patients had data for the whole 5 years. While some patients did not yet reach the 5-year time point, there were 27 patients who actually stopped participation in the study. Interestingly, these patients had lower SF36 scores for at least some domains but did not differ in age, duration of hypoparathyroidism, etiology, supplement doses, serum or urine calcium. Re-analyzing the data after eliminating patients who discontinued the study did not materially change the conclusions although it does raise a question of possible individual differences in the effect of PTH therapy on wellbeing. As mentioned above, all patients started the study by taking PTH 1–84 at 100 μg every other day. However, when other doses became available, the dose of PTH1–84 and of the supplements was adjusted according to the individual patients' needs. Serum calcium was at acceptable level of control for the duration of the study. SF36 scores were assessed at 2 and 6 months and every 6 months thereafter. The improvement in QOL that was evident at 2 months persisted for the duration of the study (Fig. 2).

The second open label study is from Italy [18]. Participants were 42 patients with surgical hypoparathyroidism who received 20 μg of PTH1–34 twice a day for 6 months. In contrast to all other studies described in this review, patients had poor metabolic control at enrollment - mean calcium level was low at 7.6 ± 0.9 mg/dL. In response to PTH1–34, calcium level increased to 9.1 ± 0.9 mg/dL and their SF36 scores improved significantly across all domains. Because the increase in QOL scores occurred concurrently with the improvement in serum calcium it is not clear whether the QOL improvements were just a reflection of better calcemic control or the effect of PTH1–34 therapy. The same study was extended to 2 years during which calcium level was maintained at a target range [26]. The improvement in the SF36 scores that were reported at 6 months persisted for the duration of the study although at least for some scores the levels were lower at 2 years than at

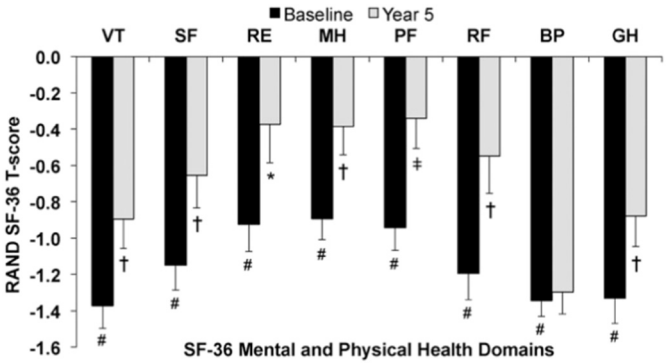


**Fig. 2.** RAND 36-item health survey domain T-scores at baseline and 5 years of PTH(1–84) therapy. Values are mean ± SE. #, $P < 0.001$ compared to normal population. *, $P < 0.05$ compared to baseline. †, $P < 0.01$ compared to baseline. ‡, $P < 0.001$ compared to baseline. Reproduced with permission from Cusano et al. [25].

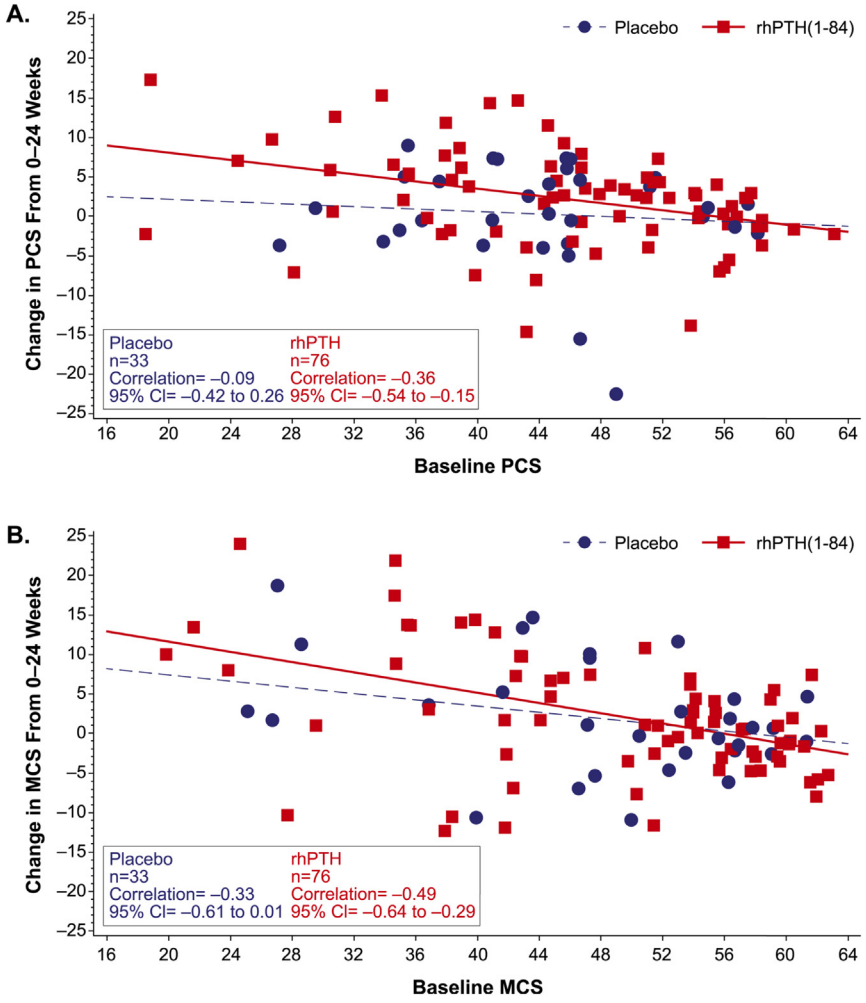


**Fig. 3.** Change from baseline in SF-36 PCS and MCS scores. The change in (A) PCS score and (B) MCS score from baseline to week 24 is plotted as a function of baseline score in patients who received rhPTH(1–84) or placebo (red squares and blue circles, respectively). The regression line for rhPTH(1–84)-treated patients (solid red line) had a slope that did not encompass zero, whereas the slope of the line for placebo-treated patients (broken blue line) did. For all domains, normal population has the mean of 50 and a standard deviation of 10. CI, confidence interval. Reproduced with permission from Vokes et al. [19]. (For interpretation of the references to colour in this figure legend, the reader is referred to the web version of this article.)

6 months.

### 3.2. Placebo controlled studies

The first study was an investigator initiated trial conducted in Denmark where 32 patients were treated with a daily injection of 100 µg per day of PTH1–84 and 30 patients received a matching placebo for 6 months [5]. The supplement dose was not adjusted unless the patients developed hypercalcemia. Consequently, hypercalcemia was considerably more common in patients assigned to PTH such that 96% of hypercalcemic episodes were in the PTH and only 4% in the placebo arm [15]. QOL was assessed using SF36 and WHO-5 Well-Being index. QOL did not improve in PTH-treated patients. Actually, after 6 months of therapy placebo group had numerical higher SF36 scores in 4 subscales (RP, BP, VT, and RE) and in the MCS but not PCS. In contrast, PTH group had an increase in only one subscale (BP) and the percent change in any of the subscales or summary scores did not differ significantly between the groups. This study also included objective evaluation of muscle strength and postural stability. Contrary to the investigators expectations there was a slight decrease in strength for at least some muscle groups in response to PTH therapy compared to placebo with no difference in the postural stability. It is possible, however, that these negative results are due to occurrence of hypercalcemia and/or fluctuations in serum calcium in PTH treated patients. It should be noted that all biochemical measurements were done in a fasting state, prior to the injection of PTH1–84. Since peak serum calcium after the injection of PTH tends to be higher by an average of 1 mg/dL [27], the reported incidence of hypercalcemia is likely an underestimate as it reflects the trough levels.

The second placebo-controlled study of PTH1–84 effect on QOL was derived from the multinational, multicenter trial, REPLACE, that lead to the FDA approval of the PTH1–84 in the US. The details of the trial and biochemical effects were reported by Mannstadt et al. [28] while QOL effects were more recently described by Vokes et al. [19]. The design of this study is important for the interpretation of the results and will be described in some detail. After enrollment in REPLACE, before receiving the study drug, patients underwent an “optimization period” lasting 2 to 16 weeks during which the supplement doses were adjusted to bring serum calcium into the target (close to normal) range. As a result of the optimization, serum calcium increased by an average of 0.5 mg/dL and was perhaps a little higher overall than the level maintained in clinical practice. This was done to prevent dangerous hypocalcemia in patients randomized to placebo which might occur when supplement doses were decreased per protocol after starting the study drug. After the optimization, 83 patients were randomized to receive once daily injection of PTH 1–84 starting at 50 µg per day (a relatively low dose) and 39 to receive a matching placebo. At that point the dose of active vitamin D was reduced (unless the patient was still hypocalcemic) to prevent hypercalcemia in patients randomized to the active drug. The dose of PTH 1–84 could be increased to 75 and then the maximum of 100 µg once per day while reducing the doses of calcium and active vitamin D. The goal was to reduce or eliminate the supplements while maintaining serum calcium at the lower end of the normal range and keeping urine calcium at a reasonable level. How this was accomplished was largely left at the discretion of the investigator. However, up titration of PTH was only allowed in the first 12 weeks

(titration phase) while during the remaining 12 weeks (maintenance phase) the PTH doses could be reduced and the supplement doses changed according to the investigator's discretion. As a result, serum calcium was maintained at relatively normal levels in both arms and at the end of the study did not differ significantly between the groups. QOL was evaluated using SF36 at randomization (not prior to optimization) and at 4, 12 and 24 weeks.

When examining the changes in the SF36 scores between randomization and end of study, the pattern of response was different between the two arms of the study. In the placebo-treated patients there was no improvement in any of the domains of the SF36. In contrast, in the PTH-treated patients, there was an improvement in 3 individual domains (BP, GH, and VT) and in the PCS summary score, even in a multivariate model adjusted for region, sex, visit, treatment-by-visit interaction, age, baseline QOL score and baseline-by-visit interaction. (Analysis without adjustment showed significant improvements in several other domains.) The between group differences in the percent change from baseline to 24 weeks were not statistically significant [19]. This study also examined possible predictors of QOL response and found that baseline QOL was strongly negatively correlated with the response to PTH therapy such that patients who started with lower scores had a greater improvement in response to treatment (Fig. 3). The other, less strong but statistically significant predictor of response was the percent reduction in the supplement dose (positive association, data not shown). This suggests that patients who have poor QOL on conventional therapy and/or those who require large doses of supplements may be particularly suitable for treatment with PTH1–84.

### 3.3. Comparison between studies

The logical question is why we observe such divergent results from different studies of QOL during treatment with PTH. Since open label studies seem to document the greatest improvement one could argue that this is likely largely due to a placebo effect. This is, however, unlikely as a sole explanation since in REPLACE we did not see an improvement in SF36 scores in the placebo-treated group [19]. It is tempting to speculate that improved calcemic control was responsible but that is also not a likely explanation. While calcium level improved from very low to acceptable in the Italian study [18] this was not the case in the New York study where serum calcium was close to the target before and during PTH therapy [17,25]. Thus, the reason for the differences between open label and placebo-controlled studies is not clear at this point. Similarly, it is not entirely clear why the two placebo-controlled studies have dissimilar results [5,19] such that the Danish investigator-initiated study showed no QOL benefit at all [5] while the international REPLACE study showed improvements in the PTH but not in the placebo-treated group (although the differences between the two arms were not statistically significant) [19]. The most likely explanation is that the Danish study had a fairly high incidence of hypercalcemia, which may have mitigated the positive effects of PTH [5]. In contrast, in REPLACE the supplement doses were decreased prospectively after the addition of the study drug, a maneuver that was aimed at preventing hypercalcemia in patients randomized to PTH1–84 [28].

### 3.4. Possible mechanism underlying QOL improvements in response to PTH therapy

There is no universal agreement between researchers regarding this issue. The key question is whether the improvement is due to better calcemic control or to some other, perhaps CNS, effects of PTH [2]. Serum calcium is likely still very important since we saw no QOL improvements in the Danish study were hypercalcemia was fairly common [5]. Several authors have looked at the possible correlation between serum calcium and QOL and failed to find such relationship [3,4,19]. It should be noted, however, that even in clinical trials serum calcium was generally measured relatively infrequently (once every 1–2 weeks or even less often) and always in the fasting state, before the administration of PTH. Thus it is still possible that improved wellbeing is a result of more stable serum calcium throughout the day during therapy with PTH compared to conventional treatment with calcium and vitamin D supplements. Consistent with that, Winer reported that patients who received PTH 1–34 by a pump, and presumably had more stable serum calcium, preferred this therapy to twice daily injections (formal assessment of QOL was not reported) [24]. Futures studies are needed, preferably using more sensitive disease-specific instruments that would relate serum calcium throughout the day to wellbeing, mood and cognition.

## 4. Conclusions and future directions

There is now a substantial body of evidence indicating that hypoparathyroidism, at least when treated with conventional therapy with calcium and vitamin D, is associated with impaired quality of life. The exact nature of the impairments, however, are less clear likely due to differences between individuals, assessing QOL using different instruments which may not be sensitive enough, and methodological differences between the studies. The improvements in QOL in response to PTH therapy are equally if not more controversial [29] for the same reasons – individual differences between patients, different study designs, and lack of reliable, disease specific instruments. The next step in investigating QOL in hypoparathyroidism is likely the development of disease specific instruments, and designing studies that will better define the nature of QOL impairment in the physical, emotional and cognitive domains on conventional and PTH-based therapies. In addition, it will be important to determine whether different dosing regimens of PTH have an impact on QOL and if so, whether the effects are mediated by a more consistent control of serum calcium throughout 24 h. Ideally, the currently approved once daily injection of PTH 1–84 should be compared to twice daily injection and to pump therapy both in terms of biochemical control and in the specific effects on physical, emotional and cognitive symptoms. Finally, defining differences between patients in QOL and its response to PTH therapy should allow us to in the future have a more individualized approach to this rare but at times debilitating disease.

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## Conflict of interest

Dr. Vokes serves as a consultant, investigator and speaker for Shire.

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