Quality of life in hypoparathyroidism

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In hypoparathyroidism, cardinal symptoms relate to hypocalcemia causing increased neuromuscular excitability with paresthesia's, which in severe cases may develop into epileptiform seizures. Conventional treatment of hypoparathyroidism includes activated vitamin D analogues and calcium supplements that in most instances result in a normalized serum calcium and thereby reduces the burden of hypocalcemic symptoms. A number of recent studies, however, have documented that hypoparathyroidism is a complex disease which cannot be considered adequately treated just by archiving normocalcemia. Patients are at increased risk of a number of complications including renal insufficiency, psychiatric diseases, and infections. Furthermore, patients often have neurocognitive complains. Symptoms such as impaired ability to focus, concentration problems, and memory loss are collectively called “brain fog”. In this issue of *Endocrine*, Büttner et al. [1], highlights an additionally important complication to hypoparathyroidism in terms of a reduced quality of life (QoL). By performing a systematic literature review, Büttner et al. [1] identified five studies using validated questionnaires to assess QoL in patients with hypoparathyroidism. Three of the studies used the SF-36/ RAND36-Item Health Survey, all showing a lower QoL in patients with hypoparathyroidism compared with norm-based controls. Similarly, a reduced QoL was found in two studies comparing patients with matched healthy controls. Interestingly, QoL seems to be more reduced in patients with postsurgical hypo

parathyroidism compared with non-surgical hypoparathyroidism. As many patients with non-surgical hypoparathyroidism have been born with the disease, it seems likely that patients who have acquired the diseases may feel more affected, as they know how they felt prior to being diseases. As reported by Büttner et al. [1], most patients with post-surgical hypoparathyroidism are also suffering from post-surgical hypothyroidism. It may therefore be questioned whether the impaired QoL is due to the co-existence of hypothyroidism. Although only limited data are available, patients with both hypoparathyroidism and hypothyroidism seem to have a larger impairment in QoL-scores than patients only suffering from hypothyroidism, suggesting that hypoparathyroidism independently of hypothyroidism contributes to an impaired QoL [2].

Interestingly, studies evaluating QoL have reported that both the mental and physical domains are affected, even though calcium levels in studied patients have been fairly well regulated. An impairment of physical function as determined by QoL measures is in good agreement with many patients complaining of muscular symptoms, as well as studies have shown a reduced muscle strength/function compared with healthy controls [2]. As correctly noted by Büttner et al. [1], conventional therapy with active vitamin D and calcium supplements does restore the physiological calcium/phosphorus homeostasis. In people with intact parathyroid function, serum calcium levels are tightly controlled. Although normocalcemia most often is archived by conventional therapy, patients are still unable to fine-tune their calcium homeostasis, and fluctuations in serum calcium may occur. This may sometimes be attributable to e.g., physiological stress such as exercise. However, fluctuations often occur unexpectedly and without any obvious reasons. Due to the importance of calcium on neuromuscular

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excitability, it seems obvious to speculate that such fluctuations may impair muscle function. Impairment of the mental QoL component is less easily explained. However, it is well recognized that calcium also is of importance to the function of the central nervous system. This is also supported by findings in patients with severe primary hyperparathyroidism who may develop psychiatric symptoms. Furthermore, as mentioned by Büttner et al. [1], PTH receptors are expressed by cells in various tissues, including the central nervous system. It is possible that too high PTH levels (as in primary hyperparathyroidism) as well as too low levels in hypoparathyroidism may be of importance.

Interestingly, patients treated with PTH-injections have reported an improved well-being, suggesting that PTH by itself may influence QoL [3, 4]. However, a significant beneficial effect of PTH-replacement therapy has so far not been documented in double-blinded randomized trials. The two largest double-blinded trials performed so far compared effects of 6 months of replacement therapy with PTH(1–84) with placebo [5, 6]. In one of the trials, several participants, however, develop hypercalcemia in response to PTH(1–84) therapy, which may have blunted potential beneficial effects [5]. Furthermore, both trials used once-a-day injections of PTH(1–84). Similar to conventional therapy, once-a-day injections with PTH does not result in a normalization of calcium homeostasis. In the circulation, PTH has a short plasma half-life, and following a subcutaneous injection, PTH is only present in the circulation for less than 12 h. Furthermore, in terms of pharmacodynamics effects, once-a-day injections cause a rise in serum calcium levels in the hours after an injection (sometimes causing hypercalcemia), which is followed by a decline in calcium levels until the next dose is injected [7]. Such fluctuations are probably not of benefit to well-being, as patients often report that they feel unconfutable if such swings occur. In a study by Winer et al. [8], once-a-day injection with PTH(1–34) were compared with twice-a-day injection, showing less fluctuations in calcium levels if PTH was injected twice-a-day. Furthermore, although the study did not include a formal examination on QoL, patients reported that they preferred twice-a-day injections, despite being troubled by injecting themselves two times a day. Further studies are needed to determine whether this preference for twice-a-day injections is due to less fluctuation in calcium levels or PTH being present in the circulation for a longer time if injected twice-a-day. Finally, as noted by Büttner et al. [1], QoL in hypoparathyroidism has so far only been evaluated using questionnaires developed to assess general health issues. There is a need for a disease specific questionnaire, which to

a greater extent can measure indices of specific importance to hypoparathyroidism.

The systematic review by Büttner et al. [1] emphasizes that patients with hypoparathyroidism are suffering from a complex disease, which implicate more than “just” a normalization of serum calcium levels. Hopefully, further studies will improve our knowledge on which measures to use to avoid adverse outcomes and how to improve the QoL. Until then, it is of importance to acknowledge the QoL related symptoms reported by many patients. Although this is no cure, it may help patients to cope better with their disease.

Compliance with ethical standards

Conflict of interest Lars Rejnmark has received consulting and/or speakers fee from NPS Pharmaceuticals, Shire, Alexion, Ultragenyx, and Eli Lilly.

References

1. M. Büttner, T.J. Musholt, S. Singer, Quality of life in patients with hypoparathyroidism receiving standard treatment: a systematic review. *Endocrine* **58**(1), 14–20 (2017)
2. T. Sikjaer, E. Moser, L. Rolighed, L. Underbjerg, L.S. Bislev, L. Mosekilde, L. Rejnmark, Concurrent hypoparathyroidism is associated with impaired physical function and quality of life in hypothyroidism. *J. Bone. Min. Res.* **31**(7), 1440–1448 (2016)
3. K.K. Winer, C.W. Ko, J.C. Reynolds, K. Dowdy, M. Keil, D. Peterson, L.H. Gerber, C. McGarvey, G.B. Cutler Jr., Long-term treatment of hypoparathyroidism: a randomized controlled study comparing parathyroid hormone-(1-34) versus calcitriol and calcium. *J. Clin. Endocrinol. Metab.* **88**(9), 4214–4220 (2003)
4. N.E. Cusano, M.R. Rubin, D.J. McMahon, D. Irani, L. Anderson, E. Levy, J.P. Bilezikian, PTH(1–84) is associated with improved quality of life in hypoparathyroidism through 5 years of therapy. *J. Clin. Endocrinol. Metab.* **99**(10), 3694–3699 (2014)
5. T. Sikjaer, L. Rolighed, A. Hess, A. Fuglsang-Frederiksen, L. Mosekilde, L. Rejnmark, Effects of PTH(1–84) therapy on muscle function and quality of life in hypoparathyroidism: results from a randomized controlled trial. *Osteoporos. Int.* **25**(6), 1717–1726 (2014)
6. M. Mannstadt, B.L. Clarke, T. Vokes, M.L. Brandi, L. Ranganath, W.D. Fraser et al., Efficacy and safety of recombinant human parathyroid hormone (1–84) in hypoparathyroidism (REPLACE): a double-blind, placebo-controlled, randomised, phase 3 study. *The Lancet Diabetes Endocrinol.* **1**(4), 275–283 (2013)
7. T. Sikjaer, A.K. Amstrup, L. Rolighed, S.G. Kjaer, L. Mosekilde, L. Rejnmark, PTH (1–84) Replacement therapy in hypoparathyroidism: a randomized controlled trial on pharmacokinetic and dynamic effects following 6 months of treatment. *J. Bone Miner. Res.* **28**(10), 2232–2243 (2013)
8. K.K. Winer, J.A. Yanovski, B. Sarani, G.B. Cutler Jr., A randomized, cross-over trial of once-daily versus twice-daily parathyroid hormone 1–34 in treatment of hypoparathyroidism. *J. Clin. Endocrinol. Metab.* **83**(10), 3480–3486 (1998)