Teriparatide Administration By The Omnipod Pump: A Self-Managed Therapeutic Option for Refractory Hypoparathyroidism

Karine Aouchiche
Aix-Marseille Universite

Rachel Reynaud
Aix-Marseille Universite

Vincent Amodru
Aix-Marseille Universite

Thierry Brue
Aix-Marseille Universite

Thomas Cuny (✉️ thomas.cuny@ap-hm.fr)
Aix-Marseille Universite  https://orcid.org/0000-0002-8440-0030

Research Article

Keywords: hypoparathyroidism, hypocalcemia, teriparatide, Omnipod, pump

Posted Date: October 26th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-1002651/v1

License: 😊  This work is licensed under a Creative Commons Attribution 4.0 International License.  Read Full License
Abstract

Context

: Hypoparathyroidism (hypoPTH) in adults is mainly due to total thyroidectomy. Conventional therapies (calcium, active vitamin D) can fail to normalize calcemia, expose the patient to hypercalciuria and impact quality-of-life. Human parathormone (hPTH) replacement therapy is a suitable option in these cases, although few clinical reports have been published so far.

Methods

case report lives two cases of refractory postsurgical hypoPTH for which subcutaneous infusion of recombinant parathormone (teriparatide) through the Omnipod® pump was started after failure of all other therapeutic options. Besides, we performed a review of literature of hypoPTH cases treated by continuous infusion of teriparatide.

Results

two women aged 46 and 61yo failed to normalize calcemia either with conventional treatments (calcium 8g/d + calcitriol 9µg/d and calcium 5g/d + calcitriol 12µg/d) or with thrice-daily subcutaneous injections of teriparatide. As a last resort, teriparatide infusion via Omnipod® device normalized their calcemia and allowed calcium/vitamin D withdrawal, with average teriparatide dose of 23 and 32 µg/day, respectively. Notably, a dedicated protocol currently allow each patient to be autonomous with its pump without adverse dyscalcemia until now. In the literature, 15 adult cases (13 women, mean age 44.5 ± 5.2 yo) are reported. HypoPTH was consecutive to surgery in all of them. Mean dose of teriparatide administered was 25 ± 6 µg/d with improvement of calcemia level and quality-of-life in all patients.

Conclusion

Continuous administration of teriparatide through Omnipod® is a safe and efficient therapeutic option in refractory hypoPTH, which can, furthermore, be safely self-managed by the patient.

Introduction

Hypoparathyroidism (hypoPTH) defines a metabolic state in which human parathormone (hPTH) is no longer or insufficiently produced by parathyroid glands, a condition which leads to calcium concentration below the normal range with undetectable or inappropriately low levels of hPTH [1]. In adults, 75% of cases of hypoPTH occurred after neck surgery, of which, ≈25% will be transient and, eventually, 2 to 5% will result in chronic hypoPTH [2, 3]. The latter is defined as persistence of hypoPTH 6 months after surgery [4, 5], and exposed the patient to painful neuromuscular symptoms [6, 7], as a result of enhanced
excitability, a 5-fold greater risk to develop kidney stones [8], impairment of bone remodeling characterized by low bone turnover [9, 10], and, eventually, a reduced quality-of-life [11–13]. First-line conventional therapies of hypoPTH comprise oral calcium and active vitamin D analogues [14], however, in some patients, even high doses will not succeed to normalize calcemia, either because of an obvious reason (digestive malabsorption, poor compliance), or, in others, for an undetermined cause. This condition is known as refractory hypoPTH [15] and justify to use PTH replacement therapy, usually as a once-, twice- or thrice-daily subcutaneous injection of rhPTH[14]. Two forms of the native human hormone currently exist. First one, is the recombinant human PTH(1-84) [rhPTH(1-84)] which is FDA-approved for the treatment of hypoparathyroidism (www.fda.gov), and has, today, a “conditional approval” in Europe (www.ema.european.eu). The second form is its active fragment, rhPTH(1-34), known as Forsteo® or Forteo®, and approved for the treatment of osteoporosis. Its off-label use was tested in refractory cases of hypoPTH, and led to a better control of the calcemia, as compared to conventional therapies alone, with a reduction of supplemental calcium and vitamin D intake[16, 17]. Moreover, a lower risk to develop hypercalciuria and a significant improvement in the quality of life were also noted [12, 17]. Unfortunately, a subset of patients still not respond enough to rhPTH (1-34) injections, even at the cost of high doses (4 to 6 injections / day), a problematic whose real incidence remains currently unknown. In these cases, continuous infusion of teriparatide was administered as an alternative option with conclusive results [18], however it is not clear if patients could manage by themselves the flow of the pump, following an educational program.

We, here, describe two cases of patient with severe and refractory hypoPTH who spectacularly benefited from off-label treatment by continuous infusion of rhPTH(1-34) (teriparatide) using the Omnipod device. We established a dedicated protocol to both patients allowed them to be fully autonomous for managing their teriparatide pump. Eventually, we reviewed and discussed the published cases of continuous infusion of rhPTH(1-34) in cases of hypoPTH.

**Material And Methods**

The institutional review board of Aix Marseille University, Marseille, France approved the therapeutic assay, and both patients included in this study gave her consent for non-conventional treatment as well as for the clinical report. For establishing the pump device, we used the teriparatide pre-filled pen (teriparatide; European Union trade name, Forsteo; U.S. tradename, Forteo; 20µg/80µl,1ml = 250µg of teriparatide; Lilly France) and the Omnipod® pump (Insulet Corp., Boston, MA) in which two milliters represent a total of 200 international units (IU). Omnipod is usually employed for insulin administration [19]. We diluted 1.2 ml of teriparatide to 0.8 ml of sterile water for injection, as previously described [20] to reach a total volume of 2 ml in the reservoir of the pump. As such, 200 IU in the pump equal to 300 µg of teriparatide. The reservoir and the infusion sets were changed every 3 days by a qualified nurse in a first time, then by the patients.

We initiated a flow of 0.5 IU/hour, which corresponding to 18 µg/24h of rhPTH (1-34), an initial dose close to the one reported to be effective in other case reports [21–23]. During hospitalization stay, we daily
adapted the flow depending on the calcemia of the patient. After hospital discharge, the flow was adapted on the protocol we established, to reach corrected calcemia level between 2.15 and 2.40 mmol/L (Figure 1).

Practically, the patient was hospitalized the day before we initiated the pump infusion, for a complete laboratory workup and an electrocardiogram. On day 2, we started the pump (6.00am), and calcitriol (1µg) was given to the patient in the morning (6.00 am) and the afternoon (6.00 pm), after what, all the oral medications were discontinued. The patient was hospitalized for a theoretical stay of seven days, which could have been longer if necessary.

Vital clinical parameters were daily recorded. The biochemical analysis at admission included albuminemia, total/corrected calcemia, phosphatemia, magnesemia, 25OH vitamin D, serum creatinine and urinary calcium excretion (UCR, appreciated by the ratio mmol calcium/mmol creatinine. Albuminemia, total/corrected calcemia, phosphatemia and UCR were daily assessed during hospitalization. After hospital discharge, total/corrected calcemia and phosphatemia were weekly assessed. Every month, 25OH vitamin D level and UCR were measured. In case of hypo-/hypercalcemia and/or modification of the pump flow, total/corrected calcemia was systematically analyzed after 24 hours.

Assays

Calcemia was measured by automated techniques, with a normal range of 2.2 - 2.55 mmol/L and adjusted for albumin by the following formula: Corrected calcemia = 0.025 x (40 - albuminemia). Phosphatemia, magnesemia and creatinine were also measured by automated techniques. Urinary calcium was measured by colorimetric method.

Clinical Cases

Patient 1 is a woman born in 1975 and referred to our center in 2016 for the treatment of a chronic hypoPTH. She underwent a total thyroidectomy in 2015 for a benign multinodular goiter. HypoPTH occurred in the immediate postoperative period. We first met her in 2017, after she was referred by her surgeon to our department (the patient was aged 42). She had no medical history of kidney stones or evidence of it on specific imaging (kidney ultrasonography and CT scan). Bone mineral density (BMD) assessed by X-ray absorptiometry (DXA) remained stable between 2018 and 2021 with a T-score (bone lumbar and hip) in the normal range (-0.2 and 0.1 SD, respectively). Circulating PTH was undetectable, always below 4 pg/mL (N: 10 - 65 pg/ml) and calcemia always remained below 2 mmol/L, while she was treated with high doses of calcitriol (Rocaltrol®, 3µg x 3/d) and oral calcium carbonate (2g x 4/d) (Table 1). Investigations ruled out poor therapeutic compliance and/or digestive malabsorption. Urinary calcium was high, comprised between 4.8 and 7.2 mg/kg/24h (Upper limit of normal: 4 mg/kg/24h), with an UCR of 1.3 (N < 0.5). 25-hydroxyvitamin D level was at the lower limit of normal (61 nmol/L, N: 75-250).
Magnesemia was in the normal range. At the clinical level, she complained of severe and disabled weakness, muscle cramps and joint pains, which not allowed her to practice her job. She was hospitalized at least once every three months for intravenous infusions of calcium gluconate for symptomatic hypocalcemia. Because PTH 1-84 is not available in our country, we started off-label twice-daily subcutaneous administration of rhPTH 1–34 at a dose of 20 µg/12h, according to previously published data [24, 25]. Her calcemia normalized and a significant improvement of her symptoms occurred for one month, after what, she experienced, again, symptomatic hypocalcemia despite 4 injections/d. Finally, we offered her to be treated with continuous teriparatide infusion using the Omnipod device system. At that time, she was aged 46 yo. Her calcemia normalized in the first 8 hours following the beginning of the infusion (Figure 3A) and a remarkable improvement of her clinical symptoms occurred in the first 48 hours. It is noteworthy that the patient stopped her antidepressive treatment with success. Her calcemia remained above 2 mmol/L until now (6 months up to now), except from week 14 to 20, where several episodes of hypocalcemia reoccurred. The later was related to a lipodystrophy in the site of injection of the pump catheter and has been resolved by changing the site of injection. Her UCR decreased from 1.18 To 0.37 after 6 months. Vitamin D supplementation was initiated (vitamin D3 100,000 IU every 3 months) and she succeeded to discontinue calcitriol and calcium supplementations.

Ultimately, the patient followed an educational program before hospital discharge that currently allows her to manage by herself the flow of the pump and filling its reservoir. On the last follow up, the flow of the pump was 0.65 UI/h corresponding to 23.4 µg of teriparatide per day. We plan to continue the treatment as long as her calcemia is normalized and her symptoms remains controlled. She will be followed every 6 months at the clinical levels and dedicating imaging procedures (radiography, MRI) will be performed if bone pain manifest.

Patient 2 is a 61 yo woman who was operated of total thyroidectomy in 2003 for Grave's disease. She immediately developed hypocalcemia in the postoperative period with low levels of PTH. During 15 years she was treated with high dose of calcitriol (Rocaltrol®, up to 4x1µg thrice daily) and calcium carbonate (500mg) for a total of 5 g/d (Table 1). She was referred to our department for the first time in 2017. Because of the existence of Grave's disease, we ruled out celiac or Biermer's disease that could be the source of digestive malabsorption. Despite high doses of calcium and calcitriol, she experienced chronic asthenia, paresthesia of extremities, which not allowed her to exert any physical activities. In parallel, her calcemia remained below 1.8 mmol/L, the reason why she was regularly admitted in our unit for i.v. calcium gluconate treatment. Her magnesemia was normal and vitamin D level was low, at 45 nmol/l. Subcutaneous injection of teriparatide (20µg each, 3-times daily) were started in 2018, however were inefficient and calcemia level remained below 2 mmol/L. She was operated of a bilateral posterior subcapsular cataracts, a likely complication of her chronic hypoPTH, but no history of kidney lithiasis was recorded, or demonstrated by kidney imaging. Her BMD assessed by X-ray absorptiometry (DXA) showed osteopenia at the L1-L4 lumbar spine (Tscore -1.3 SD) and femoral neck (Tscore -1.7SD) levels.

In 2021, the patient gave her informed consent to be treated with continuous teriparatide infusion by the Omnipod device system. We started at 0.5UI/h and, eventually, reached a current flow of 0.9 UI/h. Once
the pump was started, corrected calcemia reached after 16 hours, and for the first time, 2 mmol/L, then normalized from day 3. The patient noticed a very significant improvement in her clinical symptoms, more specifically, her joint and muscle pains fully disappeared. We did not observe any substantial change in her UCR. During the follow up, she needed continuous paramedical home care the first month to adapt the flow of the pump and to fill the reservoir. Because she had been operated of bilateral cataract, we paid attention that she could manage to fill the reservoir by herself. After 3 months, she is autonomous and the flow of the pump is 0.9UI/h (equivalent to 32.4 µg/d of teriparatide). Last but not least, she stopped her calcium and calcitriol supplementation, but we prescribed her vitamin D3 (100,000 IU every 3 months) because of her vitamin D deficiency. The treatment will be continued as long as it results in normalization of her calcemia and improvement of her quality-of-life. However, like for the other patient, a careful follow-up is planned twice-yearly at the bone level (physical exam and radiology in case of pain or palpated mass).

Discussion

Over the past years, refractory hypoparathyroidism (hypoPTH) progressively emerged as a challenging medical problem clinicians have to deal with, mainly because the incidence of total thyroidectomy is constantly increasing, as a direct consequence of an increasing incidence of thyroid cancers [26]. In order to replace the lacking hormone, PTH, several therapeutic options are currently discussed: parathyroid allotransplantation [27], oral transconPTH, a slow-release prodrug of PTH [28], or subcutaneous injection of PTH. The latter was experimented for the first time in 1929, when bovine extract of PTH was injected to a patient [29]. In 1996, Winer et al. demonstrated in a pilot study, that once-daily [16], and, thereafter, twice-daily [30], subcutaneous injections of hPTH(1-34), succeeded to maintain normocalcemia in hypoPTH patients, similar to what was observed in patients treated with high dose of calcitriol and calcium carbonate, however without exposing the patient to the risk of hypercalciuria [25]. Similar results were observed in children suffering of hypoPTH [31, 32] or adults with postoperative hypoPTH [12, 33]. Subsequently, a recombinant form of the native human hormone, namely rhPTH(1-84), was tested in patients with hypoPTH, in a double blind, placebo-controlled, clinical trial named the REPLACE study [34]. A total of 134 patients were randomized in a 2:1 ratio of drug: placebo over a 24-weeks period, with the possibility to titrate up rhPTH(1-84) from 50µg to 100µg per day as a single dose. The primary endpoint (% of patients with ≥ 50% reduction from baseline in their daily dose of oral calcium and active vitamin D while maintaining a calcemia concentration greater than or the same as baseline concentrations and less than or equal to the upper limit of normal) was achieved in 53% of patients in the group rhPTH(1-84) vs. 2% in the group placebo (p < 0.001)[35]. In parallel, phosphate homeostasis and vitamin D metabolism significantly improved in the rhPTH(1-84) group [36]. In a follow-up study, up to 8 years, prolonged treatment with rhPTH (1-84) allowed to further reduce calcium supplementation by 57% and vitamin D by 76%, respectively, even though, any patient could stop this supplementation. Likewise, calcemia was maintained in the low normal range with a 38% reduction of mean urinary calcium [37]. Overall, subcutaneous rhPTH injections were associated with a remarkable improvement of patient’s quality-of-life and almost inexistent collateral effects. Our clinical cases similarly illustrate that treatment with
rhPTH has a positive impact on the patient’s quality-of-life, as the result of 1) decrease/withdrawal of daily calcium/calcitriol supplementation (not that well tolerated at the digestive level by patients) 2) resolution of disabling symptoms like asthenia, muscle cramps as well as notable improvement of mental health field, as it was shown elsewhere by using the SF-36 scale [17], and 3) less/no more admission for emergency hospitalizations. In addition, our clinical cases underline the fact that, sometimes, twice-daily (or even more) subcutaneous injections of teriparatide cannot be sufficient to sustainably restore normocalcemia. Reasons of this escape remain elusive. Development of anti-PTH autoantibodies, as described in patients with idiopathic elevated serum PTH levels [38], has never been reported so far, as a cause of teriparatide inefficacy. Another explanation may lie in the specific pharmacokinetic of rhPTH (1-34), marked by a rapid absorption (maximum concentration achieved within 30 min) of the peptide, its rapid elimination (half-life of 1 h), and therefore a total duration of exposure of approximately 4 h [39]. As such, twice-daily rhPTH(1-34) administration does not properly cover the physiological pattern of PTH secretion, characterized by a basal circadian rhythm of secretion, superimposed by frequent low-amplitude pulses [40, 41]. For the first time in 2012, Winer et al compared, in a randomized cross-over clinical trial including 8 patients with postsurgical hypoPTH, continuous administration of rhPTH(1-34) with periodic pulses versus twice-daily subcutaneous administration of the peptide [42]. They showed less fluctuations of calcemia with the pump and, more importantly, a 65% reduction in the PTH dose to maintain eucalcemia (13 ± 4 (0.17 ± 0.03) vs. 37 ± 14 µg/d (0.47 ± 0.13 µg/kg · d), P < 0.001) [18]. While encouraging, these data resulted from a formalized clinical study, with pre-determined end points and time-specific clinical visits. On the contrary, very few studies reported the efficacy of continuous infusion of teriparatide in a real-life setting. In 3 children affected by autoimmune or idiopathic hypoPTH, two of which being refractory to conventional therapy, Linglart et al. succeeded to achieve normocalcemia, by administrating teriparatide via the Paradigm insulin pomp, over a period of 36 months [20]. In the adult population, 7 case reports of hypoPTH (5 females, mean age 43 ± 8.5 yrs) treated with continuous infusion of teriparatide were published so far (Table 2). Another group of 8 adults (7 women, 1 man) were included in the clinical trial conducted by Winer et al [18]. All the 15 patients described in the literature had postsurgical hypoPTH either for benign goiter, Graves disease or thyroid carcinoma. The dose of teriparatide that was administered to the patients ranged between 15 and 35 µg/day, roughly similar to our patients who had respective posologies of 23 and 32µg/day. Normocalcemia was achieved in all the case reports published with either discontinuation (n = 3), like in our cases, or decrease in the posology (n = 4) of both calcium and calcitriol supplementation. Results regarding the decrease of calciuria are less obvious, patient 1 having significant decrease of her urinary calcium excretion but not the other.

Refractory hypoPTH represents the typical example of chronic, long-term disabling disease, for which self-managed therapies offer a seducing alternative to patients. To the best of our knowledge, we report here the first cases of teriparatide infusion managed by patients themselves, thanks to a dedicated protocol for the adaptation of the pump flow. Until now (6 months for patient 1, 3 months for patient 2), no serious dyscalcemia have been observed and/or have justified an emergency hospitalization. Moreover, our protocol was established according to the guidelines for the management of chronic
hypoPTH which recommend to maintain calcemia in the low normal range (no more than 0.125 mmol/L below normal)[5, 14]. As such, the calcemia cut-off above which the flow pump has to be decreased was 2.4 mmol/L. For the same reason, in case of moderate hypocalcemia (i.e., calcemia between 2 and 2.15 mmol/L), we proposed to recontrol calcemia after 24 hours before modifying the basal flow. Finally, more severe dyscalcemia (i.e., calcemia < 1.8 mmol/L or > 2.65 mmol/L) needed to be medically advised in our protocol. Besides calcemia, bone mineral density (by DEXA) and renal ultrasound will be annually performed in the follow up. Our current report also underlies critical remarks that need to be stressed. First is that teriparatide infusion was used in our patients as a last resort since this molecule is off-label in this rare disease. FDA-approved daily injections of rhPTH(1-84) could represent a suitable option, nonetheless, its availability is country-dependent and, sometimes, problematic, like in our cases. As mentioned earlier, daily injection can also be insufficient to maintain calcemia in the normal range in a subset of patients, a situation in which, continuous administration through a pump currently represents the lonely real solution. Previously, it has been emphasized that teriparatide could lead to the development of osteosarcomas in rats [43]. However, this risk has not demonstrated in patients treated with teriparatide (for osteoporosis) according to the data of a recent large epidemiological study from North America [44]. Still, we keep in mind, that the daily posology of teriparatide in our patients, are slightly higher (30µg versus 20µg) than the one used in osteoporosis and therefore, prompt us to plan a careful follow-up of our patients, especially, at the bone level. In particular, we will be vigilant in ensuring that our patients ill not experienced, on the opposite, a relative hyperparathyroidism due to rhPTH, as it was recently described by others [45].

In summary, hypoPTH represents one of the last classical endocrine deficiency diseases for which the missing hormone eventually became available. The best way to administrate it to the patient is still under investigation, and, hopefully, recent development of long-release oral form of PTH will open a new era in the treatment of this chronic debilitating disease [28]. In the meanwhile, we, here, confirmed that continuous infusion of rhPTH(1-34) using the Omnipod device, together with an adapted protocol for the modulation of the pump flow, is an efficient, sustainable and safe way to both, restore normocalcemia and improve quality-of-life in patients suffering from refractory hypoparathyroidism.

Declarations

Author Contributions: Conceptualization, K.A. and T.C.; validation, R.R. and T.B.; writing—original draft preparation, K.A. and T.C.; writing—review and editing, R.R., V.A. and T.B.; supervision, R.R. and T.B. All authors have read and agreed to the published version of the manuscript.”

Funding: This research received no external funding

Institutional Review Board Statement: The study was conducted according to the guidelines of the Declaration of Helsinki, and approved by the Institutional Review Board of Aix-Marseille Université (01/01/2021)

Informed Consent Statement: Informed consent was obtained from all subjects involved in the study.
Conflicts of Interest: The authors declare no conflict of interest.

References

1. R.I. Gafni, M.T. Collins, N. Engl. J. Med. 380, 1738 (2019)
2. B.L. Clarke, E.M. Brown, M.T. Collins, H. Jüppner, P. Lakatos, M.A. Levine, M.M. Mannstadt, J.P. Bilezikian, A.F. Romanischen, R.V. Thakker, J. Clin. Endocrinol. Metab. 101, 2284 (2016)
3. J. Powers, K. Joy, A. Ruscio, H. Lagast, J. Bone Miner. Res. 28, 2570 (2013)
4. J.P. Bilezikian, J. Clin. Endocrinol. Metab. 105, (2020)
5. L.A. Orloff, S.M. Wiseman, V.J. Bernet, T.J. Fahey, A.R. Shaha, M.L. Shindo, S.K. Snyder, B.C. Stack, J.B. Sunwoo, M.B. Wang, Thyroid 28, 830 (2018)
6. P. Han, B.J. Trinidad, J. Shi, ASN Neuro 7, (2015)
7. C. Cipriani, J.P. Bilezikian, J. Endocr. Soc. 5, bvab003 (2021)
8. L. Underbjerg, T. Sikjaer, L. Mosekilde, L. Rejnmark, J. Bone Miner. Res. 28, 2277 (2013)
9. M.R. Rubin, Endocrinol. Metab. Clin. North Am. 47, 825 (2018)
10. B.C. Silva, M.R. Rubin, N.E. Cusano, J.P. Bilezikian, Osteoporos. Int. 28, 463 (2017)
11. W. Arlt, C. Fremerey, F. Callies, M. Reincke, P. Schneider, W. Timmermann, B. Allolio, Eur. J. Endocrinol. 146, 215 (2002)
12. A. Santonati, A. Palermo, E. Maddaloni, D. Bosco, A. Spada, F. Grimaldi, B. Raggiunti, R. Volpe, S. Manfrini, F. Vescini, A.M.E. Hypoparathyroidism, Group, J. Clin. Endocrinol. Metab. 100, 3590 (2015)
13. T. Sikjaer, E. Moser, L. Rolighed, L. Underbjerg, L.S. Bislev, L. Mosekilde, L. Rejnmark, J. Bone Miner. Res. 31, 1440 (2016)
14. M.L. Brandi, J.P. Bilezikian, D. Shoback, R. Bouillon, B.L. Clarke, R.V. Thakker, A.A. Khan, J.T. Potts, J. Clin. Endocrinol. Metab. 101, 2273 (2016)
15. L. Masi, in (2015), pp. 279–286
16. K.K. Winer, J.A. Yanovski, G.B. Cutler, JAMA 276, 631 (1996)
17. A. Palermo, A. Santonati, G. Tabacco, D. Bosco, A. Spada, C. Pedone, B. Raggiunti, T. Doris, D. Maggi, F. Grimaldi, S. Manfrini, F. Vescini, J. Clin. Endocrinol. Metab. 103, 271 (2018)
18. K.K. Winer, B. Zhang, J.A. Shrader, D. Peterson, M. Smith, P.S. Albert, G.B. Cutler, J. Clin. Endocrinol. Metab. 97, 391 (2012)
19. H.C. Zisser, Diabetes Ther. 1, 10 (2010)
20. A. Linglart, A. Rothenbuhler, I. Gueorgieva, P. Lucchini, C. Silve, P. Bougnères, J. Clin. Endocrinol. Metab. 96, 3308 (2011)
21. M. Puig-Domingo, G. Díaz, J. Nicolau, C. Fernández, S. Rueda, I. Halperin, Eur. J. Endocrinol. 159, 653 (2008)
22. K. Frey, S. Burger-Stritt, S. Horn, B. Willinger, M. Fassnacht, B. Allolio, S. Hahner, Exp. Clin. Endocrinol. Diabetes 122, (2015)
23. M. Saraiva, A.C. Chaves, G. Assunção, J. Saraiva, R. Carvalho, Am. J. Case Rep. 22, e931739 (2021)
24. A. Santonati, A. Palermo, E. Maddaloni, D. Bosco, A. Spada, F. Grimaldi, B. Raggiunti, R. Volpe, S. Manfrini, F. Vescini, A.M.E. Hypoparathyroidism, Group, J. Clin. Endocrinol. Metab. 100, 3590 (2015)
25. K.K. Winer, C.W. Ko, J.C. Reynolds, K. Dowdy, M. Keil, D. Peterson, L.H. Gerber, C. McGarvey, G.B. Cutler, J. Clin. Endocrinol. Metab. 88, 4214 (2003)
26. G. Pellegriti, F. Frasca, C. Regalbuto, S. Squatrito, R. Vigneri, J. Cancer Epidemiol. 2013, 965212 (2013)
27. R. Mihai, R.V. Thakker, Eur. J. Endocrinol. 184, R165 (2021)
28. A.A. Khan, L. Rejnmark, M. Rubin, P. Schwarz, T. Vokes, B. Clarke, I. Ahmed, L. Hofbauer, C. Marroccoli, U. Pagotto, A. Palermo, E. Eriksen, M. Brod, D. Markova, A. Smith, S. Pihl, S. Mourya, D.B. Karpf, A.D. Shu, J. Clin. Endocrinol. Metab. (2021)
29. F. Albright, R. Ellsworth, J. Clin. Invest. 7, 183 (1929)
30. K.K. Winer, J.A. Yanovski, B. Sarani, G.B. Cutler, J. Clin. Endocrinol. Metab. 83, 3480 (1998)
31. K.K. Winer, N. Sinaii, D. Peterson, B. Sainz, G.B. Cutler, J. Clin. Endocrinol. Metab. 93, 3389 (2008)
32. K.K. Winer, N. Sinaii, J. Reynolds, D. Peterson, K. Dowdy, G.B. Cutler, J. Clin. Endocrinol. Metab. 95, 2680 (2010)
33. M. Shah, I. Bancos, G.B. Thompson, M.L. Richards, J.L. Kasperbauer, B.L. Clarke, M.T. Drake, M.N. Stan, JAMA Otolaryngol. Head Neck Surg. 141, 822 (2015)
34. M. Mannstadt, B.L. Clarke, T. Vokes, M.L. Brandi, L. Ranganath, W.D. Fraser, P. Lakatos, L. Bajnok, R. Garceau, L. Mosekilde, H. Lagast, D. Shoback, J.P. Bilezikian, Lancet. Diabetes Endocrinol. 1, 275 (2013)
35. M. Mannstadt, B.L. Clarke, T. Vokes, M.L. Brandi, L. Ranganath, W.D. Fraser, P. Lakatos, L. Bajnok, R. Garceau, L. Mosekilde, H. Lagast, D. Shoback, J.P. Bilezikian, Lancet. Diabetes Endocrinol. 1, 275 (2013)
36. B.L. Clarke, T.J. Vokes, J.P. Bilezikian, D.M. Shoback, H. Lagast, M. Mannstadt, Endocrine 55, 273 (2017)
37. S. Störmann, J. Schopohl, Expert Opin. Pharmacother. 19, 1187 (2018)
38. B. Cavaco, V. Leite, M.M. Loureiro, M.F. Ferreira, M.C. Pereira, M.A. Santos, L.G. Sobrinho, J. Endocrinol. Invest. 22, 829 (1999)
39. J. Satterwhite, M. Heathman, P.D. Miller, F. Marín, E.V. Glass, H. Dobnig, Calcif. Tissue Int. 87, 485 (2010)
40. M.H. Samuels, J. Veldhuis, C. Cawley, R.J. Urban, M. Luther, R. Bauer, G. Mundy, J. Clin. Endocrinol. Metab. 77, 399 (1993)
41. H.M. Harms, U. Kaptaina, W.R. Külpman, G. Brabant, R.D. Hesch, J. Clin. Endocrinol. Metab. 69, 843 (1989)
42. K.K. Winer, B. Zhang, J.A. Shrader, D. Peterson, M. Smith, P.S. Albert, G.B. Cutler, J. Clin. Endocrinol. Metab. 97, 391 (2012)
43. J.L. Vahle, G.G. Long, G. Sandusky, M. Westmore, Y.L. Ma, M. Sato, Toxicol. Pathol. 32, 426 (2004)
44. E.B. Andrews, A.W. Gilsenan, K. Midkiff, B. Sherrill, Y. Wu, B.H. Mann, D. Masica, J. Bone Miner. Res. 27, 2429 (2012)
45. C. Goujard, S. Salenave, K. Briot, P. Chanson, G. Grimon, P. Kamenický, Lancet 395, 1304 (2020)
46. K.K. Winer, K.A. Fulton, P.S. Albert, G.B. Cutler, J. Pediatr. 165, 556 (2014)
47. G. Díaz-Soto, M. Mora-Porta, J. Nicolau, V. Perea, I. Halperin, M. Puig-Domingo, Horm. Metab. Res. 44, 708 (2012)
48. J. Ilany, I. Vered, O. Cohen, Gynecol. Endocrinol. 29, 807 (2013)
49. Z. Pekkolay, F. Kılınç, H. Soylu, B. Balsak, M. Güven, Ş Altun Tuzcu, A.V. Kara, A.K. Tuzcu, Turkish J. Phys. Med. Rehabil. 65, 198 (2019)
50. A. Haider, O. Symczyk, Y. Couso, T. Cater, S. Bryan, Case Rep. Endocrinol. 2021, 5593653 (2021)

Tables
Table 1
Clinical and biochemical characteristics of two patients with refractory hypoparathyroidism.

|                                      | Patient 1             | Patient 2             | Normal values |
|--------------------------------------|-----------------------|-----------------------|---------------|
| Sex                                  | F                     | F                     | /             |
| Age (yo)                             | 46                    | 61                    | /             |
| Weight (kg)                          | 69                    | 103                   | /             |
| BMI (kg/m²)                          | 24.4                  | 41                    | 19-24         |
| HypoPTH (year of diagnosis)          | 2016                  | 2003                  | /             |
| Cause of HypoPTH                     | Postsurgical (Benign goiter) | Postsurgical (Graves disease) | /             |
| Symptoms                             | General weakness      | General weakness      | /             |
|                                      | Muscle and joint pain | Muscle cramps and joint pain |               |
|                                      | Depression             |                       |               |
| Complications of hypoPTH             | None                  | Bilateral posterior subscapular cataract | /             |
| Parathormone (pmol/L)                | < 0.64                | 2.8                   | 1.6 - 6.9     |
| Albuminemia (g/L)                    | 42.1                  | 35 - 52               |               |
| Calcemia (adjusted to albuminemia)   | 1.48                  | 1.6                   | 2.15 - 2.50   |
| Phosphoremia                         | 1.96                  | 1.22                  | 0.81 - 1.45   |
| 25OH vitamine D (nmol/L)             | 91                    | 45                    | 75 - 250      |
| Magnesemia                           | 0.70                  | 0.83                  | 0.66 - 1.07   |
| Urinary calcium excretion (mmol calcium / mmol creatinine) | 1.3                  | 0.26                  | < 0.5         |
| CrCl (ml/min/1.73m²)                 | 102                   | 95                    | > 90          |
| Calcium Supplementation              | Calcium carbonate (500mg) | Calcium carbonate (500mg): 5g/d | /             |
|                                      | 8g/d                  | iv 10% calcium gluconate every 10 days |               |
|                          | Patient 1                                      | Patient 2                                      | Normal values |
|--------------------------|-----------------------------------------------|-----------------------------------------------|---------------|
| **Calcitriol Supplementation** | 1µgx3, thrice daily                           | 1µgx4, thrice daily                           | /             |
| **Emergency hospitalizations** | 4                                              | 10                                             | /             |
| for hypocalcemia over last 12 months |                                                |                                                |               |

Due to technical limitations, table 2 is only available as a download in the Supplemental Files section.

**Figures**

![Control of corrected calcemia (Ca++)](image)

**Figure 1**

Algorithmic representation of the protocol delivered to patients after hospital discharge for managing the flow of the Omnipod device. Ca++ referred to corrected calcemia adjusted to albuminemia.
Figure 2

Graphical representation of the corrected calcemia (solid line, circle) in the two patients (A for patient 1, B for patient 2) and the corresponding flow of the Omnipod pump (dashed line, triangle). Time is represented in hours, days and weeks and correspond to 6 and 3 months for patient 1 and patient 2, respectively. Grey area, limited by dashed lines, represents upper and lower bounds of normal calcemia in serum.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.

- Table2.jpg