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► **To cite this version:**

Karine Aouchiche, Rachel Reynaud, Vincent Amodru, Thierry Brue, Thomas Cuny. Teriparatide administration by the Omnipod pump: preliminary experience from two cases with refractory hypoparathyroidism. *Endocrine*, 2022, 76 (1), pp.179-188. 10.1007/s12020-021-02978-6 . hal-03780218

HAL Id: hal-03780218

<https://amu.hal.science/hal-03780218v1>

Submitted on 14 Feb 2023

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Teriparatide administration by the Omnipod pump: preliminary experience from 2 cases with refractory hypoparathyroidism

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Key words: hypoparathyroidism, hypocalcemia, teriparatide, Omnipod, pump

Abstract (248 words)

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 (PTH) replacement therapy is a suitable option in these cases, although few clinical reports have been published so far.

Methods: we describe two cases of patients with refractory postsurgical hypoPTH, in whom subcutaneous infusion of recombinant PTH (teriparatide) through the Omnipod® pump was initiated 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 9mcg/d and calcium 5g/d + calcitriol 12mcg/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 mcg/d, respectively. The flow of teriparatide was adapted according to a protocol based on measured calcemia, under medical supervision. 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 mcg/d with improvement of calcemia level and quality-of-life in all patients.

Conclusion: Continuous administration of teriparatide through Omnipod® appears as an efficient therapeutic option in refractory hypoPTH, whose administration to the patient can be assisted by medically-supervised protocol.

Introduction

Hypoparathyroidism (hypoPTH) defines a metabolic state in which human parathormone (PTH) 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 PTH [1]. In adults, 75% of cases of hypoPTH occurred after neck surgery, of which, \approx 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 once-, twice- or thrice-daily subcutaneous injections [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 hypoPTH (www.fda.gov), while having a “conditional approval” in Europe (www.ema.europa.eu). The second form is its active fragment, PTH(1-34), known as Forsteo® or Forteo®, and approved for the treatment of osteoporosis. Its off-label use was assessed in refractory cases of hypoPTH, and resulted in a better control of calcemia, as compared to conventional therapies alone, with a reduction of supplemental calcium and vitamin D intake, a lower risk to develop hypercalciuria, and a significant improvement of quality of life [12,16,17]. However, recent data emphasized that response to PTH 1-34 also depends on the etiology of hypoPTH [18]. As such, twice-daily PTH 1–34 therapy maintains both mean serum and urinary calcium levels in the normal range, in

patients with postsurgical hypoPTH, whereas similar results were unmet in others causes of hypoPTH (autoimmune, CaR, idiopathic) [18]. Consequently, a subset of patients will not respond enough to PTH (1-34) injections, even at the cost of high doses (4 to 6 injections per day), a problematic whose real incidence remains currently unknown. Two previous reference randomized crossover trials assessed continuous infusion of synthetic human PTH (1-34) as compared to twice daily injections of PTH, and showed better outcomes in terms of calcemia fluctuations, decrease of calciuria or reduction of PTH dose to maintain eucalcemia [19,20]. We, here, report two cases of patient with severe and refractory hypoPTH who benefited from off-label treatment by continuous infusion of PTH(1-34) (teriparatide) using the Omnipod device. After hospital discharge, we proposed the patient to continue administration by the pump with its flow which was adapted, under medical supervision, based on the measure of serum calcium. Eventually, we reviewed and discussed the published cases of continuous infusion of PTH(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. Because we had never experienced teriparatide administration through a pump, our aim was to carefully initiate, namely at a low dose (0.75 mcg/h, 18 mcg/d) of teriparatide. This initial dose was set up on the basis of published other case reports [21–23].

For establishing the pump device, we used the teriparatide pre-filled pen (teriparatide; European Union trade name, Forsteo; U.S. tradename, Forteo; 20mcg/80mcg,1ml = 250 mcg of teriparatide; Lilly France) and the Omnipod® pump (Insulet Corp., Boston, MA) in which two milliliters represent a total of 200 international units (IU). Omnipod is usually employed for

insulin administration [24]. The nurse diluted 1.2 ml of teriparatide to 0.8 ml of sterile water for injection, as previously described [25] to reach a total volume of 2 ml in the pump reservoir. As such, 200 IU in the pump equal to 300 mcg 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 under medical supervision. The patient was hospitalized for a total of 7 days. The day before we started the pump, we performed an electrocardiogram and a complete laboratory workup which included albuminemia, total / corrected (if albumin was abnormal) calcemia, phosphatemia, magnesemia, 25OH vitamin D, serum creatinine and urinary calcium excretion. On day 1, we started the pump at 6am, and calcitriol (1mcg) was given to the patient in the morning (6am) and the afternoon (6pm). Calcemia was measured every 4 hours on day 1, then, daily (6 am) from day 3 to day 7. Our goal was to achieve calcemia between 2.15 and 2.4 mmol/l. To do so, the first day, the flow was adapted on the measure of calcemia (every 4 hours) by increasing or decreasing of 0.1 IU/h (0.15 mcg/h). From day 2, the flow was adapted based on the protocol we established (Figure 1). Likewise, 24hrs-calciuria was measured every 48 hours during hospitalization (Day 2, 4 and 6), and we determined the urinary calcium/creatinine ratio (UCCR, mmol/mmol), known to be strongly correlated with 24-hours calciuria [26] . Normal value of UCCR is below 0.5 in adults. Vital clinical parameters were recorded daily.

Hospital discharge eventually occurred on day 7. From that point onward, calcemia and phosphatemia were measured weekly and 25OH vitamin D level and 24h-calciuria were measured monthly. The flow of the pump was adapted under medical supervision by following the protocol. Accordingly, in case of moderate hypocalcemia (i.e., $1.8 \leq \text{Ca}^{++} < 2.15$ mmol/l), we proposed to recontrol calcemia after 24 hours before modifying the basal flow. For the same reason, if calcemia exceeded 2.40 mmol/l, the flow had to be immediately modified. Every time the pump flow was changed, a control of the calcemia was performed after 24h until it reached the range of 2.15 - 2.4. Once reached, calcemia was controlled after 7 days. Finally, in case of

severe dyscalcemia (i.e., calcemia < 1.8 mmol/l or > 2.65 mmol/l), a medical appointment was mandatory.

Assays

Calcemia was measured by automated techniques, with a normal range of 2.15 - 2.55 mmol/l and did not need to be adjusted for albumin as albuminemia was normal in both patients. 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 2017 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. Her medical history was marked by hysterectomy, however she had no history of either kidney or brain calcifications, either at the clinical or imaging levels (kidney ultrasonography and CT scan). Her thyroid function was normal with levothyroxine 137 mcg/day. Her height and weight were 168 cm and 69kg, respectively, and her body surface area (BSA) 1.794 m². Bone mineral density (BMD) was 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). At the biological level, circulating PTH was undetectable (N: 1.6 - 6.9 pmol/l) since surgery. She took high doses of calcitriol (Rocaltrol[®], 6-9mcg, divided into three equal doses) and oral calcium carbonate (2g x 4/d), the maximum doses she tolerated (Table 1), for a period of at least 3 years between 2018 and 2021. Over this period, her mean calcemia was 1.83 ± 0.15 mmol/l and her 24h-calcium excretion was high with a mean of 12.5 ± 2 mmol/24h/1.73m² (N: 2.5 - 7.5) and her mean UCCR was 0.77 ± 0.14 . Her vitamin D level was low at 61 nmol/l (N: 75-250), and magnesemia

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. Until 2020, 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 finally decided to propose her off-label administration of PTH (1–34) at a dose of 20 mcg twice-daily, according to previously published data [12,27]. She had the treatment during 2 months in total. Her calcemia was assessed weekly and a significant improvement of her symptoms occurred during the first 4 weeks. Her mean calcium level during this first month was 2 ± 0.12 mmol/l. We had one value of calciuria of 4.14 mmol/24h/1.73m² (UCCR = 0.04). Unfortunately, she experienced again symptomatic hypocalcemia despite 4 injections/d, the reason why the treatment was stopped after 4 weeks. During this period, her mean calcemia decreased to 1.88 ± 0.08 mmol/l, her calciuria was 8.18 mmol/24h/1.73m² and her UCCR increased to 0.35. Finally, in March 2021, we proposed her continuous teriparatide infusion using the Omnipod pump. 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. Her mean calcemia was 2.21 ± 0.17 mmol/l on day 1 (6 am to 6 am) and 2.26 ± 0.15 mmol/l from day 2 to day 7. During the first week of hospitalization, mean calciuria was 4.93 ± 2.5 mmol/24h/1.73m² and mean UCCR was 0.4 ± 0.1 , respectively. After hospital discharge, mean calcemia was 2.19 ± 0.13 mmol/l from week 2 to week 24. Her calcemia remained above 2 mmol/l until now, except from week 14 to 20, where several episodes of hypocalcemia reoccurred. The later was related to a subcutaneous induration which occurred in the site of injection, and spontaneously disappeared by changing the site of injection. Over this period, her mean calciuria was 3.56 ± 3 mmol/ 24h/1.73m² and mean UCCR was 0.26 ± 0.21 . 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 the flow of the pump and filling its reservoir under medical supervision. On the last follow up, the flow of the pump was 0.65 UI/h corresponding to a dose of teriparatide of 0.975 mcg/h (0.34 mcg/kg/d). We plan to continue the treatment as long as her calcemia is normal and her symptoms remain controlled. She comes every month in the outpatient clinic department and will be followed every 6 months in our daily hospital with dedicating imaging procedures (radiography, MRI) if bone pain manifest.

Patient 2 is a 61 yo woman who was operated of total thyroidectomy in 2003 for Grave's disease and immediately developed hypocalcemia in the postoperative period with low, but not undetectable, levels of PTH. She was referred to our department for the first time in 2017. Her medical history was marked by hypertension (for which she was daily treated by beta blockers and thiazide diuretics), carpal tunnel syndrome, dyslipidemia, and bilateral posterior subcapsular cataracts, a likely complication of her chronic hypoPTH. Conversely, there was no history or evidence for nephrocalcinosis or brain calcifications (Fahr syndrome). For 15 years, she was treated with high dose of calcitriol (Rocaltrol[®], 9 - 12 mcg/d, divided into three equal doses) and calcium carbonate (500mg) for a total of 5 g/d (Table 1). She was euthyroid with levothyroxine 175 mcg/d and in 2017, her height and weight were 165 cm and 100 kg, respectively, with a BSA of 2.14 m². Because of the existence of Grave's disease in the past, we ruled out celiac and Biermer's disease and any other source of digestive malabsorption. Despite high doses of calcium and calcitriol, she complained of chronic asthenia, paresthesia in her hands, and had to stop physical activities. With this therapeutic regimen, her mean calcemia was 1.78 ± 0.12 mmol/l. Moreover, we retrospectively found 7 random values of calciuria between 2016 and 2017. The mean value of 24h calciuria was low 0.43 ± 0.18 mmol/24h/1.73m² along with extremely low UCCR of 0.025 ± 0.005 . She was regularly

admitted in our unit for intravenous treatment with calcium gluconate. Her magnesemia was normal and vitamin D level was low, at 45 nmol/l. Subcutaneous injection of teriparatide (20mcg each, 3-times daily) were started in 2018, however stopped after 1 month as they were inefficient. At that time, her mean calcemia was 1.94 ± 0.07 mmol/l, while mean 24h calciuria and mean UCCR did not significantly change (0.45 ± 0.2 mmol/24h/1.73m² and 0.05 ± 0.007 , respectively). Note that her calciuria remained low likely due to the concurrent intake of thiazide diuretic.

In July 2021, the patient gave her informed consent to be treated with continuous teriparatide infusion by the Omnipod device system. Once the pump was started, calcemia normalized only from day 3, probably due to the fact that we did not apply PTH dose per kilogram and that the patient was overweight (which means that she was likely underdosed). Her mean calcemia was 1.84 ± 0.16 mmol/l on day 1 (6 am to 6 am) and 2.34 ± 0.2 mmol/l from day 3 to day 7. During the first week of hospitalization, mean calciuria was 1.25 ± 1.03 mmol/24h/1.73m² and mean JCCR was 0.1 ± 0.04 , respectively. The patient noticed a very significant improvement in her clinical symptoms, more specifically, her joint and muscle pains fully disappeared. Her BMD, assessed by X-ray absorptiometry (DXA) during her hospital stay, showed osteopenia at the L1-L4 lumbar spine (Tscore -1.3 SD) and femoral neck (Tscore -1.7SD) levels.

After hospital discharge, she asked for continuous paramedical home care during the first month to adapt the flow of the pump and to fill the reservoir and confessed, *a posteriori*, that she intended to modify the pump flow while the protocol required it (from week 3 to week 7 in figure 2B). This fear was due to the fact that she did not want to suffer again from hypocalcemia symptoms, in case she decreased the pump flow. Between weeks 2 and 12, her mean calcemia was 2.37 ± 0.1 mmol/l, her mean 24hrs-calciuria was 4.76 ± 2.17 mmol/24h/1.73m² and mean JCCR $0.42 \pm .07$. It is noteworthy that we stopped thiazide diuretic in this patient after hospital discharge, which can contribute to increase her 24hrs calciuria and UCCR. Otherwise, we paid

attention that she could manage to fill the reservoir by herself, as she was operated of bilateral cataracts. After 3 months, she can refill the pump by herself with the assistance of a nurse, and the flow of the pump is 1.35mcg/h (i.e., 0.32 mcg/kg/d) or 0.9 IU/h. Finally, 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 every month (at the outpatient clinic) and every 6 months at the daily hospital (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, a direct consequence of an increasing incidence of thyroid cancers [28]. In order to replace the lacking hormone, PTH, several therapeutic options are promising, like parathyroid allotransplantation [29], or oral transconPTH [30], while others are already discuss in the clinical field, like subcutaneous injection of PTH. The latter was experimented for the first time in 1929, when bovine extract of PTH was injected to a patient [31]. In 1996, Winer et al. demonstrated in a pilot study, that once-daily [17], and, thereafter, twice-daily [32], subcutaneous injections of PTH(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 [27]. Similar results were observed in children suffering of hypoPTH [33,34] or adults with postoperative hypoPTH [12,35], paving the way for the REPLACE study, a double blind, placebo-controlled, clinical trial, which tested a recombinant form of PTH, namely

rhPTH(1-84), in patients with hypoPTH [36]. This pivotal study supported the fact that PTH therapy results in 1) a decrease of calcium/vitamin D daily intake in treated patients, 2) an improvement of phosphate and vitamin D homeostasis, 3) a decrease of urinary calcium and, 4) a remarkable improvement of patient's quality-of-life [36,37]. Our clinical cases similarly illustrate that treatment with PTH 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 [16], 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 partially elucidated, however, a recent work conducted by Winer et al. suggests that the etiology of hypoPTH could influence the response to PTH therapy [18]. 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 PTH (1-34), marked by a rapid absorption (maximum concentration achieved within 30 min) of the peptide, its rapid elimination (half-life of 1 hour), and therefore a total duration of exposure of approximately 4 h [39]. As such, twice-daily PTH(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 PTH(1-34) with periodic pulses versus twice-daily subcutaneous administration of the peptide [19]. 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 $\mu\text{g/d}$ (0.47 ± 0.13 $\mu\text{g/kg} \cdot \text{d}$), $P < 0.001$) [19]. While encouraging, these data resulted from a formalized clinical study, with pre-determined end points and time-specific clinical visits, such as 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 pump, over a period of 36 months [25]. 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 [22,23,42–45](Table 2). Another group of 8 adults (7 women, 1 man) were included in the clinical trial conducted by Winer et al [19], such as, all of the 15 adult 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 mcg/d, roughly similar to our patients who had respective doses of 23 and 32 mcg/d. 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. However, in our second patient, the baseline value of urinary calcium was low, as a result of diuretic thiazide intake, and therefore, an additional decrease of UCR under PTH (1-34) therapy as unlikely to occur. 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 in patients with refractory hypoPTH, for whom a dedicated protocol, based on serum calcium values, was set up for the adaptation of the pump flow. Patients could have nurse / medical assistance whenever they felt the need for it. 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. We established our protocol according to the guidelines for the management of chronic hypPTH, which recommend to maintain calcemia in the low normal range (no more than 0.125 mmol/l below normal)[5,14]. 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 [46]. 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 [47]. Still, we keep in mind, that the daily dose of teriparatide in our patients, are slightly higher (30mcg versus 20mcg) 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 will not experienced, on the opposite, a relative hyperparathyroidism due to PTH, as it was recently described by others [48]. Finally, through these 2 clinical cases, we also want to underline that medical supervision is highly recommended when treating a patient with teriparatide pump. While we did not observe serious dyscalcemia, we faced to distinct situations that could have resulted in severe dyscalcemia if not cared by the physician. First is the development of lipodystrophies in patient 1, that hamper the delivery of teriparatide and therefore, could have resulted in hypocalcemia if not observed

by the medical staff. Second is the issue of compliance, which is of utmost importance to ensure safety of the therapy and requires repeated information to the patient, like in case 2.

In summary, hypoPTH represents one of the last classical endocrine deficiency diseases for which the missing hormone eventually became available. The long-release, once-daily injectable form of PTH will probably open a new era in the treatment of this chronic debilitating disease [30]. In the meanwhile, we, here, present two patients who benefited of continuous infusion of PTH(1-34) using the Omnipod device, with an adapted protocol for the modulation of the pump flow. While promising, the outcomes of these 2 clinical cases need, obviously, to be further investigated through larger clinical studies.

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.

Legends of figures

Table 1. Clinical and biochemical characteristics of the two patients with refractory hypoparathyroidism (hypoPTH). *Biological values represent pooled data from hospitalization and after hospital discharge.

Figure 1. Algorithmic representation of the protocol delivered to patients after hospital discharge for managing the flow of the Omnipod device.

Figure 2. Graphical representation of the calcemia (solid line, circle) in the two patients (A for patient 1, B for patient 2) and the corresponding flow (IU/h with $0.1 \text{ IU} = 0.15 \text{ mcg}$) of the Omnipod pump (dashed line, triangle). Time is represented in hours, days and weeks. During day 1, modifications of the flow were done ($+0.1 \text{ IU}$ or -0.1 IU) by physicians based on the calcemia measured every 4 hours. From day 2, the flow was adapted according to the protocol. Note that at every time point, the value of the flow reflects adaptation of the flow to the corresponding calcemia. Grey area, limited by dashed lines, represents upper and lower bounds of normal calcemia in serum.

Table 2. Overview of the clinical studies published in the literature using continuous infusion of PTH(1-34) through an insulin pump in cases of hypoparathyroidism. NA: not available. LFU: last follow-up

References

1. M. Mannstadt, J. P. Bilezikian, R. V Thakker, F. M. Hannan, B. L. Clarke, L. Rejnmark, D. M. Mitchell, T. J. Vokes, K. K. Winer, and D. M. Shoback, *Nat. Rev. Dis. Prim.* **3**, 17055 (2017).
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, and R. V Thakker, *J. Clin. Endocrinol. Metab.* **101**, 2284 (2016).
3. J. Powers, K. Joy, A. Ruscio, and 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, and M. B. Wang, *Thyroid* **28**, 830 (2018).
6. P. Han, B. J. Trinidad, and J. Shi, *ASN Neuro* **7**, (2015).
7. C. Cipriani and J. P. Bilezikian, *J. Endocr. Soc.* **5**, bvab003 (2021).
8. L. Underbjerg, T. Sikjaer, L. Mosekilde, and 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, and J. P. Bilezikian, *Osteoporos. Int.* **28**, 463 (2017).
11. W. Arlt, C. Fremerey, F. Callies, M. Reincke, P. Schneider, W. Timmermann, and 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, and Hypoparathyroidism AME Group, *J. Clin. Endocrinol. Metab.* **100**, 3590 (2015).
13. T. Sikjaer, E. Moser, L. Rolighed, L. Underbjerg, L. S. Bislev, L. Mosekilde, and 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, and J. T. Potts, *J. Clin. Endocrinol. Metab.* **101**, 2273 (2016).
15. L. Masi, in (2015), pp. 279–286.
16. A. Palermo, A. Santonati, G. Tabacco, D. Bosco, A. Spada, C. Pedone, B. Raggiunti, T. Doris, D. Maggi, F. Grimaldi, S. Manfrini, and F. Vescini, *J. Clin. Endocrinol. Metab.* **103**, 271 (2018).
17. K. K. Winer, J. A. Yanovski, and G. B. Cutler, *JAMA* **276**, 631 (1996).
18. K. K. Winer, S. Ye, E. M. N. Ferré, M. M. Schmitt, B. Zhang, G. B. Cutler, and M. S. Lionakis, *Bone* **149**, 115977 (2021).
19. K. K. Winer, B. Zhang, J. A. Shrader, D. Peterson, M. Smith, P. S. Albert, and G. B. Cutler, *J. Clin. Endocrinol. Metab.* **97**, 391 (2012).
20. K. K. Winer, K. A. Fulton, P. S. Albert, and G. B. Cutler, *J. Pediatr.* **165**, 556 (2014).
21. M. Puig-Domingo, G. Díaz, J. Nicolau, C. Fernández, S. Rueda, and I. Halperin, *Eur. J. Endocrinol.* **159**, 653 (2008).
22. K. Frey, S. Burger-Stritt, S. Horn, B. Willinger, M. Fassnacht, B. Allolio, and S. Hahner, *Exp. Clin. Endocrinol. Diabetes* **122**, (2015).
23. M. Saraiva, A. C. Chaves, G. Assunção, J. Saraiva, and R. Carvalho, *Am. J. Case Rep.* **22**, e931739 (2021).
24. H. C. Zisser, *Diabetes Ther.* **1**, 10 (2010).
25. A. Linglart, A. Rothenbuhler, I. Gueorgieva, P. Lucchini, C. Silve, and P. Bougnères, *J. Clin. Endocrinol. Metab.* **96**, 3308 (2011).
26. M. Laroche, D. Nigon, I. Gennero, S. Lassoued, J. M. Pouilles, F. Trémolières, M. Vallet, and I. Tack, *Ann. Biol. Clin. (Paris)*. **74**, 465 (2016).
27. K. K. Winer, C. W. Ko, J. C. Reynolds, K. Dowdy, M. Keil, D. Peterson, L. H. Gerber, C. McGarvey, and G. B. Cutler, *J. Clin. Endocrinol. Metab.* **88**, 4214 (2003).

28. G. Pellegriti, F. Frasca, C. Regalbuto, S. Squatrito, and R. Vigneri, *J. Cancer Epidemiol.* **2013**, 965212 (2013).
29. R. Mihai and R. V Thakker, *Eur. J. Endocrinol.* **184**, R165 (2021).
30. A. A. Khan, L. Rejnmark, M. Rubin, P. Schwarz, T. Vokes, B. Clarke, I. Ahmed, L. Hofbauer, C. Marcocci, U. Pagotto, A. Palermo, E. Eriksen, M. Brod, D. Markova, A. Smith, S. Pihl, S. Mourya, D. B. Karpf, and A. D. Shu, *J. Clin. Endocrinol. Metab.* (2021).
31. F. Albright and R. Ellsworth, *J. Clin. Invest.* **7**, 183 (1929).
32. K. K. Winer, J. A. Yanovski, B. Sarani, and G. B. Cutler, *J. Clin. Endocrinol. Metab.* **83**, 3480 (1998).
33. K. K. Winer, N. Sinaii, D. Peterson, B. Sainz, and G. B. Cutler, *J. Clin. Endocrinol. Metab.* **93**, 3389 (2008).
34. K. K. Winer, N. Sinaii, J. Reynolds, D. Peterson, K. Dowdy, and G. B. Cutler, *J. Clin. Endocrinol. Metab.* **95**, 2680 (2010).
35. M. Shah, I. Bancos, G. B. Thompson, M. L. Richards, J. L. Kasperbauer, B. L. Clarke, M. T. Drake, and M. N. Stan, *JAMA Otolaryngol. Head Neck Surg.* **141**, 822 (2015).
36. 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, and J. P. Bilezikian, *Lancet. Diabetes Endocrinol.* **1**, 275 (2013).
37. B. L. Clarke, T. J. Vokes, J. P. Bilezikian, D. M. Shoback, H. Lagast, and M. Mannstadt, *Endocrine* **55**, 273 (2017).
38. B. Cavaco, V. Leite, M. M. Loureiro, M. F. Ferreira, M. C. Pereira, M. A. Santos, and L. G. Sobrinho, *J. Endocrinol. Invest.* **22**, 829 (1999).
39. J. Satterwhite, M. Heathman, P. D. Miller, F. Marín, E. V Glass, and H. Dobnig, *Calcif. Tissue Int.* **87**, 485 (2010).
40. M. H. Samuels, J. Veldhuis, C. Cawley, R. J. Urban, M. Luther, R. Bauer, and G. Mundy,

J. Clin. Endocrinol. Metab. **77**, 399 (1993).

41. H. M. Harms, U. Kaptaina, W. R. Külpmann, G. Brabant, and R. D. Hesch, J. Clin. Endocrinol. Metab. **69**, 843 (1989).

42. Z. Pekkolay, F. Kılınç, H. Soylu, B. Balsak, M. Güven, Ş. Altun Tuzcu, A. V. Kara, and A. K. Tuzcu, Turkish J. Phys. Med. Rehabil. **65**, 198 (2019).

43. J. Ilany, I. Vered, and O. Cohen, Gynecol. Endocrinol. **29**, 807 (2013).

44. G. Díaz-Soto, M. Mora-Porta, J. Nicolau, V. Perea, I. Halperin, and M. Puig-Domingo, Horm. Metab. Res. **44**, 708 (2012).

45. A. Haider, O. Symczyk, Y. Couso, T. Cater, and S. Bryan, Case Rep. Endocrinol. **2021**, 5593653 (2021).

46. J. L. Vahle, G. G. Long, G. Sandusky, M. Westmore, Y. L. Ma, and M. Sato, Toxicol. Pathol. **32**, 426 (2004).

47. E. B. Andrews, A. W. Gilsenan, K. Midkiff, B. Sherrill, Y. Wu, B. H. Mann, and D. Masica, J. Bone Miner. Res. **27**, 2429 (2012).

48. C. Goujard, S. Salenave, K. Briot, P. Chanson, G. Grimon, and P. Kamenický, Lancet (London, England) **395**, 1304 (2020).

Figure 1 and 2

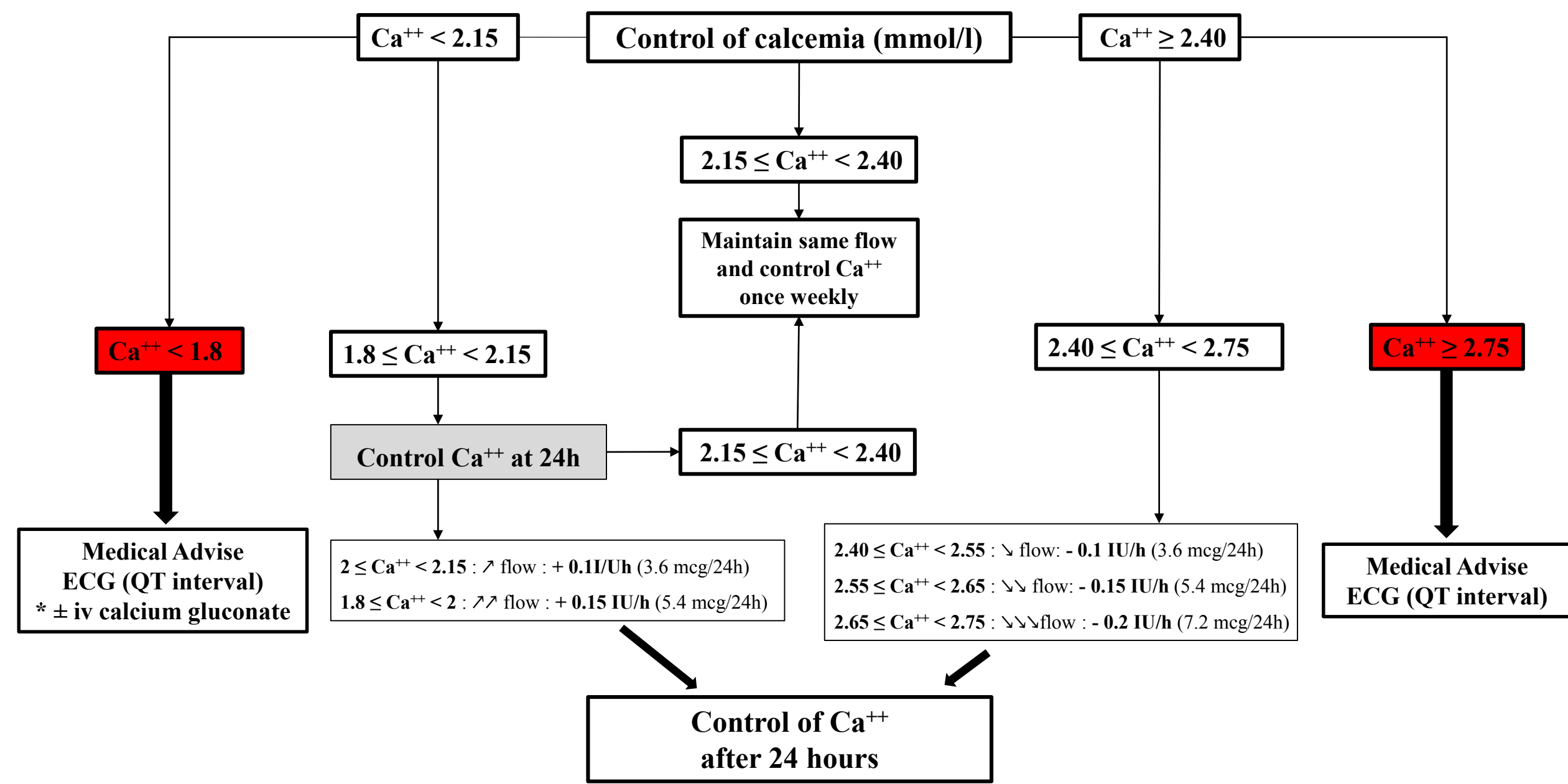


Figure 1

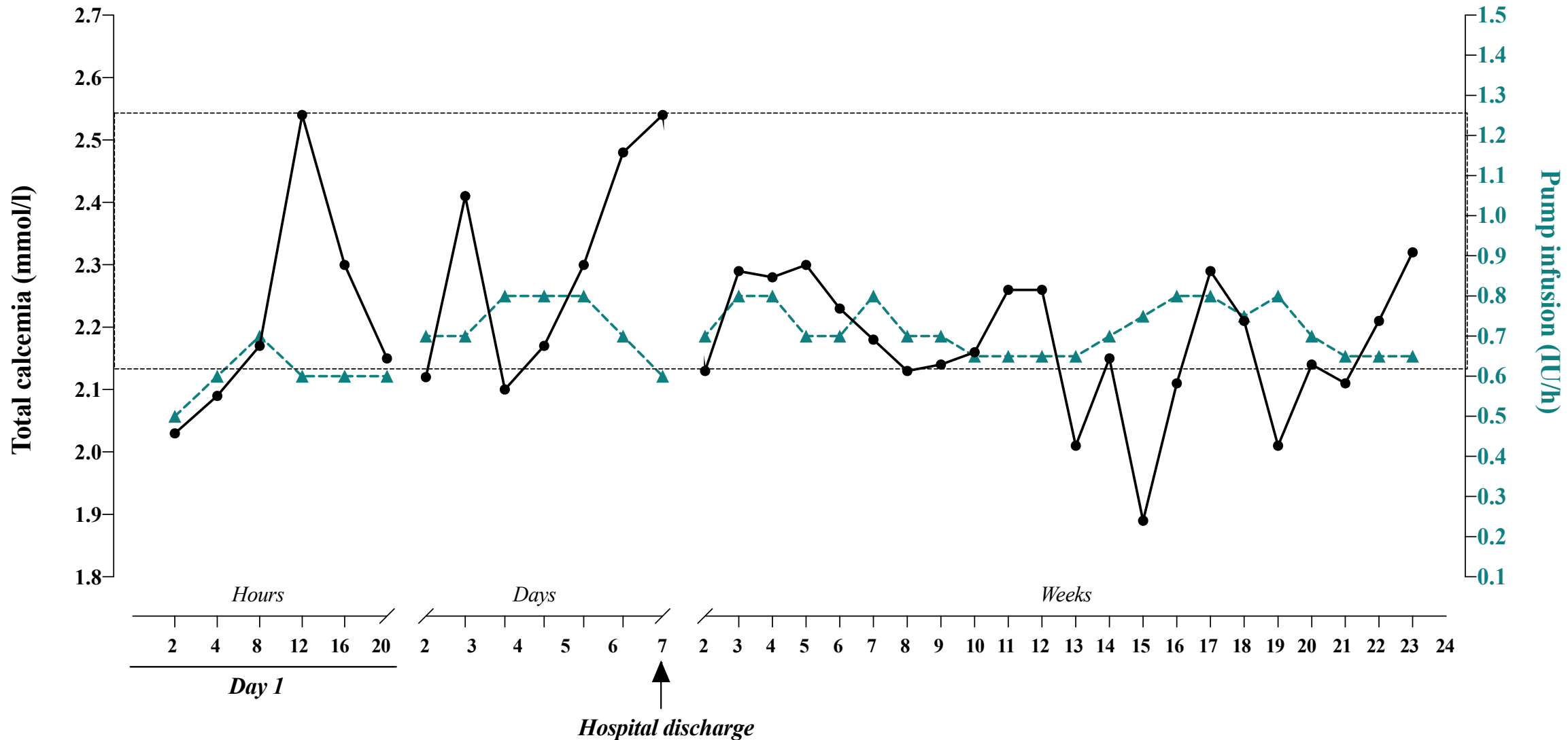


Figure 2A

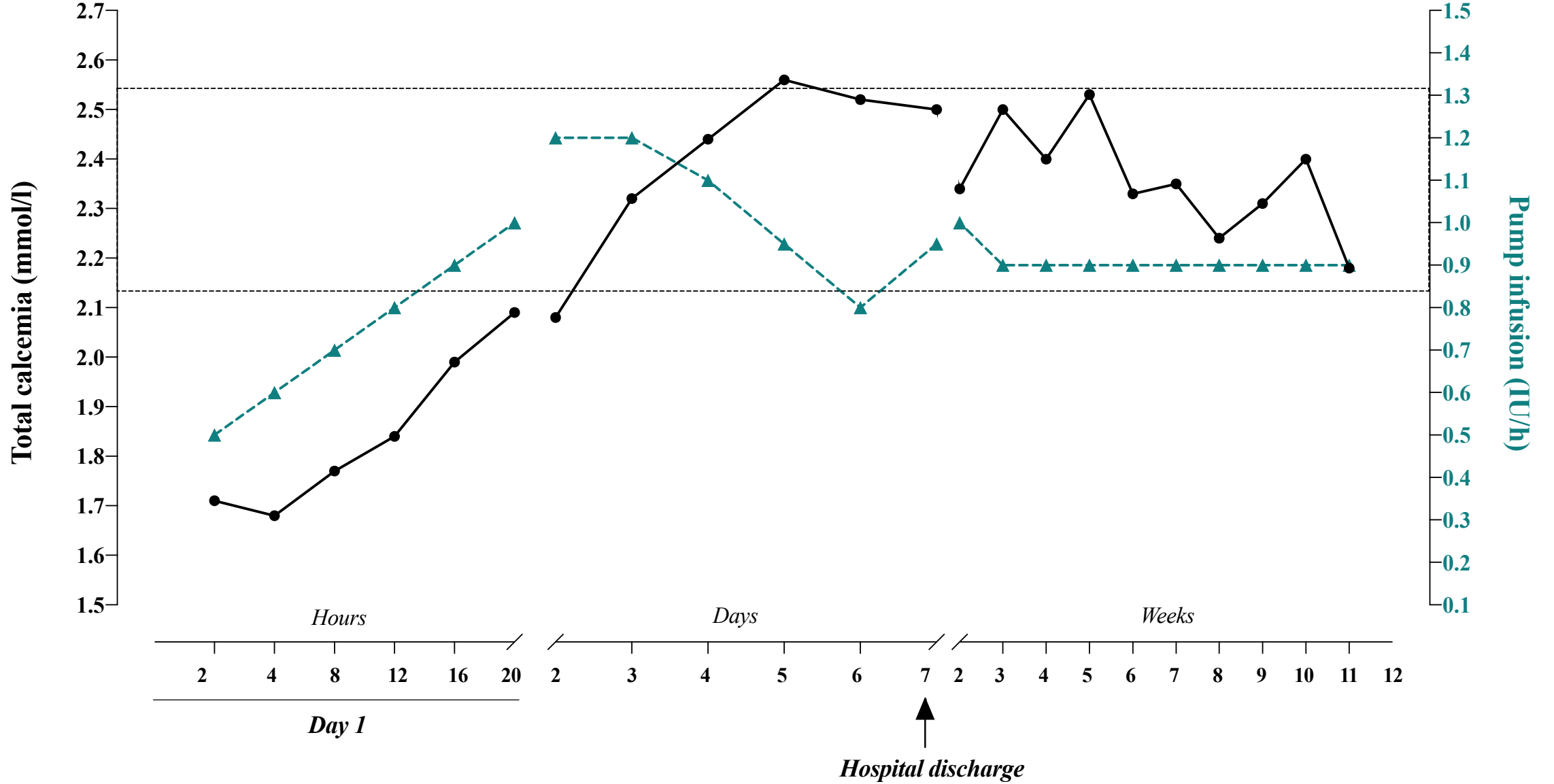


Figure 2B

Table 1

	Patient 1	Patient 2	Normal values
Clinical parameters			
Sex	F	F	/
Age (yo)	46	61	/
Weight (kg)	69	103	/
BMI (kg/m ²)	24.4	41	19-24
HypoPTH (year of diagnosis)	2015	2003	/
Cause of HypoPTH	Postsurgical (Benign goiter)	Postsurgical (Graves disease)	/
Symptoms	General weakness Muscle and joint pain Depression	General weakness Muscle cramps and joint pain	/
Complications of hypoPTH	None	Bilateral posterior subscapular cataract	/
Calcium supplementation before PTH treatment	Calcium carbonate (500mg) 8g/d	Calcium carbonate (500mg): 5g/d iv 10% calcium gluconate every 10 days	/
Calcitriol supplementation before PTH treatment	1µg x3, thrice daily	1µg x4, thrice daily	/
Emergency hospitalizations for hypocalcemia over last 12 months	4	10	/
Biological parameters before PTH (1-34) therapy			
Parathormone (pmol/l)	< 0.64	2.8	1.6 - 6.9
calcemia (mean ± SD, mmol/l)	1.83 ± 0.15	1.78 ± 0.12	2.15 - 2.55
Albuminemia (g/l)	44	42.1	35 - 52
Phosphoremia (mmol/l)	1.96	1.22	0.81 - 1.45
25OH vitamine D (nmol/l)	61	45	75 - 250
Magneseemia (mmol/l)	0.70	0.83	0.66 - 0.99
24h-calciuria (mean ± SD, mmol/24h/1.73m ²)	12.5 ± 2	0.43 ± 0.18	2.5 - 7.5
Urinary calcium-creatinine ratio (UCCR) (mean ± SD)	0.77 ± 0.14	0.025 ± 0.005	< 0.5
CrCl (ml/min/1.73m ²)	102	95	> 90
Biological parameters after PTH (1-34) therapy			
PTH(1-34) injections			
calcemia (mean ± SD, mmol/l)	1.94 ± 0.11	1.94 ± 0.07	2.15 - 2.55
24h-calciuria (mean ± SD, mmol/24h/1.73m ²)	6.16 ± 2.85	0.45 ± 0.2	2.5 - 7.5
Urinary calcium-creatinine ratio (UCCR) (mean ± SD)	0.17 ± 0.18	0.05 ± 0.007	< 0.5
PTH (1-34) pump*			
Calcemia (mmol/l) (mean ± SD)	2.2 ± 0.14	2.22 ± 0.27	2.15 - 2.55
24h-calciuria (mean ± SD, mmol/24h/1.73m ²)	3.56 ± 3	3 ± 2.45	2.5 - 7.5
Urinary calcium-creatinine ratio (UCCR) (mean ± SD)	0.26 ± 0.21	0.23 ± 0.18	< 0.5

Table 1

Table 2 Authors	Year	Number of patient	Gender	Age of patient	Causes of HypoPTH	Type of pump Pattern of administration	Dose of rhPTH(1-34) per day at LFU	Main Results	Calcium / vit D supplementation at LFU	Follow up	Ref
Randomized cross-over clinical trials											
Winer et al.	2012	8	1M/7F	46 ± 5.6 (mean ± sd)	Postsurgical	Omnipod (Insulet®) Basal rate and pulses vs. twice-daily injections	0.17 ± 0.03 mcg/kg	As compared to twice-daily inj. - Less fluctuation of calcium level - Improvement of 24h urine calcium excretion level - Improvement of bone turn-over markers	NA	6 months	[19]
Winer et al.	2014	12	5M/7F	15.7 ± 0.96 (mean ± sem)	Congenital (APS-1 [n=7] and CaSR mutations [n = 5])	Omnipod (Insulet®) Basal rate and pulses vs. twice-daily injection	0.32 ± 0.04 mcg/kg	As compared to twice-daily inj. - Better increase in total calcium level - Better reduction of bone turn-over markers - Higher reduction of magnesium supplements	NA	6 months	[20]
Case reports											
Puig-Domingo et al.	2008 / 2012	1	F	53	Postsurgical (goiter)	MiniMed (Medtronic®) Pulses	25 - 35 mcg	Normalization of ionized calcium level Decrease of ca/cr ratio Gain in BMD	Calcium salt (2g/d) Calcitriol (1.5mcg/d)	5 years	[21,44]
Linglart et al.	2011	3	3M	8, 11 and 13	Congenital (APS-1, n=2) Idiopathic (n =1)	Paradigm 515 (Medtronic®) Basal rate	0.1 - 0.5 mcg/kg	Increase of calcemic level Improvement of ca/cr ratio Decrease in emergency hospitalizations Improvement of QoL	Vitamin D3 (100,000U/month)	3 years	[25]
Ilany et al.	2013	1	F	36 (pregnancy)	Postsurgical (carcinoma)	MiniMed 518 (Medtronic®) Basal rate and pulses	20-30mcg	Stabilization of calcemic level neonate normal calcemic level	Calcium salt (1.2g/d)	1 year	[43]
Frey et al.	2015	2	1M/1F	53 and 47	Postsurgical (ND)	NA	15 and 21mcg	Normalization of serum calcium Normalization of serum phosphate	Discontinued	1 year	[22]
Pekkoly et al.	2019	1	F	47	Postsurgical (Grave's disease)	MiniMed (Medtronic®) Basal rate	33mcg	Normocalcemia achieved Decrease of teriparatide dosing	Discontinued	7 months	[42]
Haider et al.	2021	1	F	34	Postsurgical (Grave's disease)	Pump Omnipod® No precision about method of administration	33mcg	Normocalcemia achieved	Calcium salt discontinued Calcitriol: 0.5mcg/d	9 months	[45]
Saraiva et al.	2021	1	F	31	Postsurgical (carcinoma)	Pump Roche® Basal rate	30mcg	Normocalcemia achieved Improvement of calcium/creatinine ratio Decrease of teriparatide dosing Increase of calcemic level	Discontinued	4 months	[23]
This study	2021	2	2F	46 and 61	Postsurgical (Goiter and Grave's disease)	Omnipod (Insulet®) Basal rate + dedicated protocol	23.4 and 32.4mcg	Normocalcemia achieved Improvement of QoL	Discontinued in both patients	6 and 3 months	NA