PEDIATRIC ENDOCRINOLOGY UPDATE - FOCUS ON

Current treatment of hypoparathyroidism: theory versus reality waiting guidelines for children and adolescents

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Summary. The diagnosis of hypoparathyroidism(HPT)is readily made in the presence of hypocalcemia with markedly reduced or absent parathormone (PTH) levels. Currently available treatments for HPT include high dose vitamin D (ergocalciferol, D2 and cholecalciferol, D3) or, the active metabolite dihydroxy vitamin D (calcitriol), in addition to calcium supplements.This regimen, if not well monitored, can lead to hypercalciuria, as PTH deficiency impairs renal calcium reabsorption. Thus the goal of treatment, is to maintain serum calcium at the low end of the normal range. Undertreatment can cause symptomatic hypocalcemia, while overtreatment hypercalciuria, which may lead to nephrolithiasis, nephrocalcinosis, and renal insufficiency. At present, there is no consensus on the management of HPT in children and adolescents and only few studies are available on the long term outcome of patients with recombinant HPT treatment. The purpose of this article is to review, in a comprehensive manner, the major aspects of HPT management in children and adolescents waiting for authoritative guidelines for the treatment of HPT in this group of patients. Further research, addressing specific questions for this population are urgently needed to improve long-term safety of patients. Educational interventions are also needed for professionals, parents and patients to enable them to improve knowledge, quality of life and effective management care at home. (www.actabiomedica.it)

Key words: hypoparathyroidism, acute and chronic management, hypercalcemia, PTH replacement therapy, monitoring, complications

Introduction

Under physiologic conditions normal calcium homeostasis maintains within a narrow range dependent upon a complex set of regulatory mechanisms that include the effects of parathyroid hormone (PTH), vitamin D metabolites and calcitonin on calcium transport in bone, kidneys, and gastrointestinal tract. Biochemically, hypocalcemia is defined as a total serum calcium level <8.6 mg/dl, corrected for albumin concentration, [Ca corrected= 0.8 × (normal albumin − patient albumin) + serum Calcium] or and ionized serum calcium levels <1.15 mmol/L(1).

Hypoparathyroidism (HPT) is a rare disorder associated with low or no production of PTH. PTH deficiency results in abnormal mineral homeostasis that is characterized by hypocalcemia and hyperphosphatemia. In the kidneys, PTH promotes calcium reabsorption, phosphate excretion, and conversion of 25(OH)D to 1,25(OH)2Dactivating 1a- hydroxylase. In the intestine, 1,25(OH)2D enhances the absorption of calcium and, to a lesser degree, phosphate (Figure 1).

In children, HPT may present in the neonatal period or at any time during childhood and adolescence. It may be transient or permanent. Neonatal hypocal-

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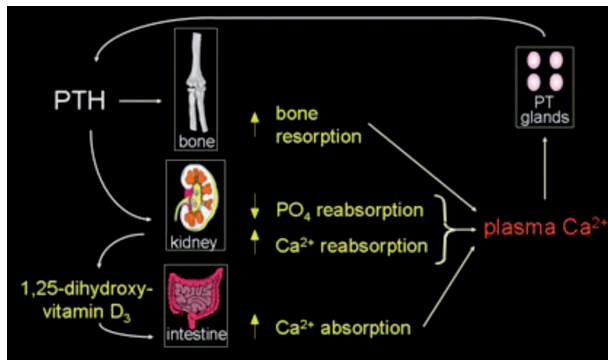
Figure 1. Regulation of systemic calcium homeostasis

cemia (NH) is common in the neonatal period. It is classified into two clinical categories: early NH occurring in the first 24-48 hours of life and late NH at the end of the first week of life. NH due to congenital HPT, either permanent or transient, is rare. The most common form of dysgenesis of the parathyroid glands in newborns and infants is that associated with the DiGeorge syndrome (DSG), a disorder with a frequency of 1:4000 births and is present in approximately 70% of children with isolated hypoparathyroidism. Another more common cause of HPT is an activating mutation of the extracellular calcium-sensing receptor (CASR) gene. A very rare syndrome is the Autoimmune Polyendocrinopathy syndrome type 1, an autosomal recessive disorder with the classic triad of **A**utoimmune **P**olyendocrinopathy, mucocutaneous **C**andidiasis and **E**ctodermal **D**ystrophy (APECED) due to loss-of-function mutations in AIRE gene (transcription factor expressed in medulla of thymus that enables differentiation of self-from foreign antigens). Major disease component of APECED are HPT, adrenal insufficiency and candidiasis (2, 3).

Hypoparathyroidism may also develop as part of chromosomal or mitochondrial disorders such as Kearns-Sayre syndrome or MELAS syndrome, and in association with Wilson disease and congenital or acquired hemosiderosis (2, 4, 5).

Another cause of HPT is the abnormally low levels of serum magnesium. This is often called functional HPT because it resolves when magnesium is restored. Less often, HPT can be caused by abnormally high levels of magnesium in the blood. Magnesium can activate the CASR protein on the hormone-secreting

cells inhibiting the secretion of parathyroid hormone. Patients with the rare disorder pseudoHPT have defects of hormone function with usually elevated levels of PTH prior to therapy (6, 7).

In adults, the cause of HPT is mainly the result of a complication of neck surgery or radiation (8).Transient HPT is relatively common after thyroid surgery, with rates ranging from 6.9 to 46%; permanent HPT is defined when clinical findings persist longer than 12 months (9, 10).

Symptoms of HPT are the result of low serum calcium effect on the internal organs and correlate strongly with the degree of reduction of the absolute levels of calcium and the sharpness of onset. Presenting symptoms are variable. Mild symptoms include numbness and tingling of the extremities and perioral region, muscle cramps, and fatigue. Physical examination often reveals hyperreflexia and positive Trousseau sign (carpal spasm) by 3 minutes of occlusive pressure with a blood pressure cuff (latent tetany). In severe cases, overt tetany, seizure, altered mental status, cardiac rhythm disturbances, refractory congestive heart failure, and laryngospasm are observed (4, 11).

Traditional treatment of chronic HPT includes supplemental calcium along with active vitamin D metabolites. Although the treatment regimen appears simple, management is difficult as it is often associated with wide fluctuations in serum calcium, and risks for hypercalciuria, renal impairment, and hypercalcemia(12). Parathyroid hormone replacement is of great value in improving serum calcium and lowering serum phosphate as well as the doses of calcium and calcitriol supplementation required. Recent developments in basic sciences contributed greatly to our understanding and treatment of hypocalcemic disorders.

The purpose of this article is to review, in a comprehensive manner, the major aspects of HPT management in children and adolescents waiting for guidelines in this group of patients.

Current management of HPT

Management of hypocalcemia of HPT can be considered in two broad categories: symptomatic hypocalcemia and asymptomatic hypocalcemia, acute

and chronic. Indications, adverse reactions and dosage schedules for drugs are provided in the article, but is possible that they may change. The reader is urged to review the drug dosages before starting treatment.

1. Acute management

Symptomatic hypocalcemia (carpal or pedal spasm, seizures, broncho- or laryngospasm), can be a medical emergency requiring acute i.v. administration of calcium. If the symptoms are mild such as paresthesias, oral calcium can be tried; however, in subjects with asymptomatic hypocalcemia and total serum calcium below 7.5 mg/dL, i.v. calcium should still be preferred.

Vitamin D deficiency or hypomagnesaemia should be treated as follows: in vitamin D deficiency commence with vitamin D supplementation; in hypomagnesemia, stop any precipitating drug and administer i.v. Mg^{2+}, 24 mmol/24 h, made up as 6 g of MgSO4 (30 mL of 20%, 800 mmol/L, MgSO4) in 500 mL Normal saline or 5% dextrose. Monitor serum Mg^{2+} to achieve normal serum magnesium level(13).

a. Intravenous administration of calcium

Calcium gluconate 10% contains 93 mg of elemental calcium per 10 ml ampules. It is preferred to calcium chloride, which contains 272 mg elemental calcium per 10 ml ampules, but is irritating and potentially sclerosing the veins. In adults, usually 186 mg of elemental calcium (20 ml of calcium gluconate 10%) diluted in 50 to 100 ml of 5% dextrose is infused over ten minutes by intravenous (i.v.) root. Titrate the rate of infusion to achieve normocalcaemia and continue until treatment with vitamin D or recombinant human PTH (rhPTH) becomes effective.

Calcium should not be given rapidly because of the serious risk of cardiac dysfunction, including systolic arrest. In children and adolescents solution is infused at slow rate not greater than 2 ml (1.86 mg of elemental calcium)/kg over 10 minutes, diluted in 100 ml 5% dextrose/ 0.25 normal saline, with close monitoring of pulse rate and QT interval (4).

This dose of calcium gluconate typically increases serum Ca^{2+} concentration for only several hours. Therefore, the acute i.v. administration of calcium gluconate

should be followed by a slower infusion of calcium. An i.v. solution containing about 1 mg/ml (1,023) of elemental calcium is prepared by adding 11 g of calcium gluconate (equivalent to 1023 mg elemental calcium) to normal saline or 5% dextrose water to provide a final volume of 1000 ml (14).

The i.v. solution should not contain bicarbonate or phosphate because both can form insoluble calcium salts. The solution is administered at an initial infusion rate of 50-100 ml/h (equivalent to 50-100 mg/h). The dose is adjusted to maintain the corrected serum calcium concentration at the lower end of the normal range. A typical infusion rate is 0.5 to 1.5 mg/kg of elemental calcium per hour. Over 8-10 hours, this protocol will deliver as much as 15 mg/kg body weight, raising the serum calcium levels by approximately 2 mg/dL (0.5 mmol/L). Electrocardiogram is used to monitor patients on i.v. calcium therapy when warranted by the situation, as are patients on digoxin therapy.

If hypocalcemia persists, calcium gluconate administration in the form of i.v. boluses or as a continuous i.v. infusion, may be continued for a week to ensure enterocyte recovery and adequate intestinal absorption of oral calcium.

Vitamin D supplementation is often recommended with calcium to promote its absorption. It is also important to address disease-specific problems and correct co-exiting electrolyte disturbances e.g. hypomagnesemia.

2. Chronic management

Standard therapy of HPT is oral calcium and vitamin D supplementation (both active and parent forms) at varying doses, based on clinical judgment (7). The primary goals of chronic management aim in maintaining an acceptable range of the following indexes: (a) serum total calcium (usually in the low-normal range); (b) serum phosphorus (in the high-normal range); (c) 24-h urine calcium excretion (<7.5 mmol/d) and (d) calcium-phosphate product under 55 mg^2/dl^2 (4.4 $mmol^2/L^2$) (1, 15, 16).

a. Oral calcium

The mainstay of conventional treatment of HPT is calcium supplement in combination with vitamin D,

and the therapeutic aim to obtain normocalcemia and reduce long-term complications. Supplemental calcium (1-2 grams of elemental calcium) in two to four divided doses per day, as calcium carbonate (containing 40% elemental calcium) or calcium citrate (containing 21% elemental calcium) are usually recommended in adults (1); for children and adolescents, dosage is 30-75 mg of elemental calcium/kg/day in divided doses (4, 6).When replacing calcium, it is essential to recognize that the actual amount of elemental calcium in the supplement is of major importance. As an example, calcium carbonate comprises 40% elemental calcium, so 1,250 milligrams of calcium carbonate contains 500 mg of elemental calcium. Common calcium supplements may be labelled as: calcium citrate (21% elemental calcium), calcium gluconate (9% elemental calcium), and calcium lactate (13% elemental calcium). All varieties of calcium supplements are better absorbed when taken in small doses (500 mg or less) at mealtimes. Calcium citrate is absorbed equally well with or without food. Calcium phosphate salts should be avoided.

b. Vitamin D and its analogues

Currently available treatments for HPT involve either vitamin D high doses ergocalciferol (D2) or cholecalciferol (D3) or more frequently the active metabolite 1,25-dihydroxyvitamin D3 (calcitriol). The latter is preferred in patients with hypoparathyroidism as PTH is an important facilitator of the renal conversion of 25 hydroxyvitamin D3 to 1,25 dihydroxyvitamin D3; also 1-hydroxyvitamin D3, alphacalcidol, and vitamin D analogues such as dihydrotachisterol (DHT or A.T.10) are used.

The pharmacokinetics of vitamin D analogs have been determined mainly in adults and only in small group of pediatric patients undergoing peritoneal dialysis (17). The present knowledges indicate that in healthy subjects, 25-hydroxyvitamin D3 shows a plasma half-life of about 15 days, whereas the half-life of calcitriol is of only few hours, varying from 4 to 15 hours (18, 19). These differences may be due to differences in metabolism as vitamin D binding affinity (DBP) is based on genetic factors, dose of radio labeled tracers used, timing of sample collection and the analytical method used. More studies, however, are

warranted to determine the disposition of the vitamin D analogues, especially in selected populations such as pediatric patients.

As calcitriol has a rapid action (hours) it is an useful adjunct in the management of acute hypocalcemia, and is frequently used as the initial vitamin therapy. Kanis and Russell (20) showed that the half time of reduction of hypercalcemia after stopping calcitriol was shorter compared to alphacalcidol (mean 1.5 days versus 3.4 days). The highest half times were seen after ergocalciferol (mean: 29.5 days) and after AT10 (mean: 44 days). The authors concluded that, as prolonged hypercalcemia remains a serious risk with all vitamin D derivatives, the rapid reversal of hypercalcemia after calcitriol treatment makes this agent preferable to ergocalciferol and alphacalcidol.

The starting dose of calcitriol in adults is 0.25 to 0.5 μg twice daily to 0,5 μg four times a day (6) and for children and adolescents, 20 to 60 ng/kg/day (4).

Drugs interaction to calcium metabolism

Furosemide and other loop diuretics can increase renal calcium clearance and reduce serum calcium levels. Glucocorticoid antagonizes the action of vitamin D and its analogs and may also precipitate hypocalcemia. Estrogen can increase calcium absorption directly at the level of intestine and, indirectly, through the stimulation of renal 1α-hydroxylase activity, thus estrogen therapy may alter calcium homeostasis requiring dose adjustments (6).

Risks associated to conventional therapy and their monitoring

With current treatment patients may experience wide fluctuations in serum calcium and are at a substantial risk of hypocalcemia and hypercalcemia and of chronic renal failure (21).

1. Hypocalcemia

According to recent data from the USA, only 6% of patients with chronic HPT were treated with

vitamin D2, and the majority, 88%, were prescribed calcitriol (22). As calcitriol is expensive and must be administered daily, other less expensive and long-acting vitamin D preparations are frequently used, once a stable dose is reached. Ergocalciferol (D2) is the least expensive and provides a long duration of action. The usual dose is 50.000 to 100,000 IU per day. When initiating vitamin D2 therapy, calcitriol may be continued for the first 3 weeks, tapering gradually the dose until ergocalciferol becomes effective. Although only a minority of patients with HPT are treated with ergocalciferol, due to the potential toxicity related to its long biological half-life, Streeten EA et al. pointed out that no study has shown high risk of hypercalcemia with usual D2 doses of 50.000 to 100.000 IU/day (23). The authors found significantly less need for emergency care for hypocalcemia in the D2 treated group versus the calcitriol treated group. This is not unexpected due to the short half-life of calcitriol, so patients on calcitriol can become symptomatic if they miss one day of medication. There was significantly less morbidity from hypocalcemia with no evidence of higher serum creatinine in patients who were treated chronically with D2 versus calcitriol. Then treatment with vitamin D should be considered in patients with HPT, particularly those requiring medical care for repeated episodes of hypocalcemia.

2. Hypercalcemia

Hypercalcemia is of particular concern in individuals treated with large doses of parent vitamin D, ergo- or cholecalciferol, which accumulate in large amounts in fat stores and, when released, can result in prolonged parathyroid-independent hypercalcemia. Extremely large doses of vitamin D, in the order of 100,000 units per day, are required to cause hypercalcemia, because the synthesis of 1,25(OH)2 D3 is tightly regulated by serum phosphate levels and parathyroid dependent step of 1-alpha hydroxylation of 25-hydroxyvitamin D. Interestingly, changes in 1-25 (OH)2 D3 levels are modest and result from the down-regulation of the renal 1-alpha- hydroxylase by low levels of PTH, high levels of phosphate and FGF23 and 1-25 (OH)2 D3 itself. The hypercalcemia of vitamin D intoxication results from increased intestinal absorption of calcium

and from the direct effect of 1,25(OH)2 D3 to increase resorption of bone. The cause of hypercalcemia in vitamin D intoxication despite a normal levels of 1-25 (OH)2 D3 is uncertain, but may reflect a) the direct action of 25OH D3 that, at pharmacological concentrations, can overcome vitamin D receptor affinity, and possibly other vitamin D metabolites which are capable of binding the 1,25 (OH)2 D3 receptor weakly; b) the total vitamin D metabolite concentrations, which can displace 1alpha, 25 (OH)2 D from vitamin D binding protein increasing its free concentration and thus increasing gene transcription, which may be locally 1-alpha- hydroxylated by non -renal 1-alpha- hydroxylase (18, 24).

De Sanctis et al. (26) reported an adolescent with thalassemia who developed severe hypercalcemia during regular clinical follow up for HPT treatment with calcitriol and calcium. On the other hand, clinicians should have a high suspicion for malignancy in patients with rapid and high elevation of serum calcium (26).

The rationale of the strategies for lowering serum calcium is based on decreasing intestinal calcium absorption, increasing renal excretion, and decreasing bone reabsorption; in very severe form removal of excess calcium may require dialysis (25). The corner stone of hypercalcemia treatment are: 1. hydration 2. saline diuresis 3. furosemide, after rehydration 4. glucocorticoids, to suppress activity of 25-hydroxy vitamin D- 1-alpha-hydroxylase, and 5. bisphosphonate in case of very elevated calcium (in consultation with endocrinologist) (24, 27).

a. Hydration: the first priority is to correct the extracellular volume depletion that is almost invariably present also in infants, particularly if hypercalcemia is long standing. Usual dose in adult is i.v infusion of 2-4 L of 0.9% Na Cl daily, for 1.5 days. Children should receive fluid volumes in order to correct fluid deficit and to provide daily maintenance requirements (1500 ml/m²) over 24 hours, with half of the total administered in the first 8 hours. If urinary flow has been established, 20 mEq/L of K⁺solution is added. Frequent measurements of serum K⁺, calcium and phosphate are needed to monitor rapid adjustment of fluid and electrolyte

therapy. After dehydration has been corrected and adequate urine flow has been established, furosemide can be used i.v., (1-2 mg/kg, every 12 – 24 hours).

b. Steroids may be used to decrease the intestinal absorption of vitamin D and calcium. The usual dose is i.v. 200-300 mg hydrocortisone/1.73 m², daily for 3-5 days, or prednisone per os 40-60 mg/ 1.73 m² daily for 3-5 days.

c. In case of severe hypercalcemia (>14 mg/dl) or persistently elevated calcium, consider bisphosphonate treatment, in collaboration with endocrinologist. Bisphosphonate blocks calcium resorption correcting hypercalcemia for a longer time compared to the transitory effects of saline and diuretics. Etindronate (5 mg/kg/twice daily orally) or pamidronate (0,5 to 2 mg/kg in 30 ml of normal saline, given intravenously, over 4 hours) have been successfully employed in infants with hypercalcemia due to vitamin D intoxication (28, 29). When calcitriol is not easily available and/or is too expensive, parent vitamin D can be used with a cautionary note regarding vitamin D toxicity (30).

d. Diet management may include advice to avoid food rich in phosphate and salt as carbonated soft drinks, which contain phosphorus in the form of phosphoric acid, as well as other foods rich in phosphate like hard cheeses and whole grains. Intake of food rich in calcium are advised such as the dairy products, green leafy vegetables, broccoli. and foods with added calcium, as are some orange juice products and breakfast cereals.

3. Monitoring serum and urinary calcium, and serum phosphate

Serum calcium and phosphate should be monitored weekly or twice weekly during initial dose adjustment period, and every 3-6 months when serum levels are stable. The absence of PTH reduces the renal tubular reabsorption of calcium and thus patients treated for HPT are at risk of urolithiasis, and renal and soft tissues calcifications. Soft tissue calcification can occur in any tissue; involvement of vital organs in addition to kidney such as blood vessels and brain can result in substantial morbidity or mortality. These risks can be minimized by monitoring therapy to preserve serum calcium level in the low-normal range. Urine calcium should periodically be measured to make sure that patients do not develop hypercalciuria.Calcium 24-hour urine should be determined at least annually, once a stable dose is established (6). In children and adolescents hypercalciuria is defined as calcium excretion greater than 4 mg/kg/24 hours (4). In patient with hypercalciuria a reduction in calcium intake, a sodium restricted diet, and/or treatment with a thiazide diuretic are recommended (1).

Active vitamin D metabolites and analogs also increase intestinal phosphate absorption; when hyperphosphatemia occurs reducing dietary intake of phosphate is indicated (31). In extreme situations, phosphate binders can be used (32). Patients must avoid foods and drinks rich in phosphate; these include milk (despite being a good source of Ca), other dairy products, and canned foods.

The patient should also regularly see an ophthalmologist to screen for cataract.

PTH Replacement Therapy (PTH-RT)

The majority of cases of paediatric HPT are well controlled on conventional treatment with calcium and vitamin D analogues. However, this treatment may be inefficient, especially in patients with autoimmune polyendocrinopathy-candidiasis-ectodermal dystrophy and with activating mutations in the calcium sensing receptor (CaSR) (33).

Over the past two decades, studies of teriparatide [PTH (1-34)] and the full-length natural secretory product of the parathyroid glands, PTH (1-84), ushered a new era in the management of HPT. In January 2015, the FDA approved the use of recombinant human (rh) PTH (1-84) for the management of HPT. Potential advantages of rh PTH over conventional therapy in the management of HPT include: reduction in urinary calcium, reduction in the amounts of calcium and vitamin D requirements, reduction in ectopic soft tissue calcification, and improvement in bone remodeling dynamics and quality of life. Several clinical

studies have evaluated rhPTH as a replacement therapy for HPT (34). However, due to occurrence of osteosarcoma in rat toxicology studies of rhPTH (1-34) there is some concern for long-term use in a pediatric population (35, 36).

Nevertheless, recent studies have demonstrated the advantage of using rhPTH (1-34) to control hypocalcemia in children for periods up to 3 years (35-38).

In five randomized clinical trials in adults and children with rhHPT reviewed by Sikjaer et al. (39) showed that PTH (1-34) therapy stabilizes plasma calcium at an acceptable level and abolish the need for vitamin D analogue treatment. Discrepant results, however, were reported on the urinary excretion of calcium in response to rhPTH, with most studies showing no significant effects (39). These studies included patients with different causes of HPT, including some with activating CaSR mutations. The administration of rhPTH (1-34) twice a day controlled plasma calcium levels better than once-a day (40). Three patients, two of whom were refractory to conventional therapy, were successfully treated with long-term continuous subcutaneous administration of rhPTH (1-34) (41).

Theman et al. and Diaz-Soto et al. (42, 43) treated two patients with rhPTH (a 6-year-old girl with inherited HPT with activating CASR mutation, and a 53-year-old woman with refractory HPT) for 13.5 and 5 years, respectively, with no complications.

rhPTH replacement therapy causes marked increase of bone turnover and a decrease in BMD counteracting the state of over mineralized bone. During long-term treatment, this can lead to a more physiologic bone metabolism (34).

The rationale for using rhPTH (1-84) for HPT is that, in contrast to rhPTH (1-34), it is the native hormone replacing what is truly missing in this disease. For reasons that have not been fully elucidated, the effective half-life of rhPTH (1-84) is longer than rhPTH (1-34) resulting in effective one daily dose (44, 45).

It remains to be determined if a longer acting rhPTH (1-84) molecule with favourable long-term safety and efficacy in adults would benefit children as well (46).

Conclusions

Treatment of HPT remains a challenge and no one treatment has been shown to be satisfactory for all patients. Although the therapy of acute hypocalcemia is usually readily accomplished, chronic hypocalcemia remains a very difficult therapeutic problem. There is wide consensus (1) that the best replacement treatment for HPT consists of calcium salts associated with active vitamin D analogues. However, no formal recommendations have been agreed regarding the most appropriate vitamin D analogue. If activated vitamin D analogues are not available, calciferol (preferentially D3) is recommended. Vitamin D supplementations in a daily dose of 400-800 IU to patients treated with activated vitamin D analogues has been also recommended (1). The rationale of this recommendation is that vitamin D insufficiency has been associated with adverse effects on skeletal as well as extraskeletal health (47).

Treatment of hypoparathyroid patients with calcium and vitamin D analogs increases the risk of hypercalciuria; hypercalciuria is a risk factor for nephrocalcinosis, nephrolithiasis, and impairment of renal function. Thiazide diuretics, which enhance distal renal tubular calcium reabsorption, are sometimes used as an "adjuvant" therapy. Monitoring for renal calcification through renal ultrasound and more formal measurements of creatinine clearance may be warranted. To ameliorate the renal risks, the vitamin D analog and calcium dosages are reduced to maintain serum calcium at the lowest tolerated level (Figure 2) (1).

Consequently, a higher number of hypoparathyroid patients may suffer varying degrees of hypocalcemia as a counterbalance for prevention of hypercalciuria-induced renal damage. Therefore, for optimal management of HPT a specialist should be involved to minimize the risks of hypocalcemia, hypercalciuria, and impairment of renal function.

According to the European Society of Endocrinology (ESE) Clinical Guideline (1) biochemical monitoring of HPT patients should include serum calcium levels, phosphate, magnesium, creatinine and glomerular filtration rate every 3-6 months, and 24-h urinary calcium excretion once a year, once stable doses of supplements are established. The target for urinary
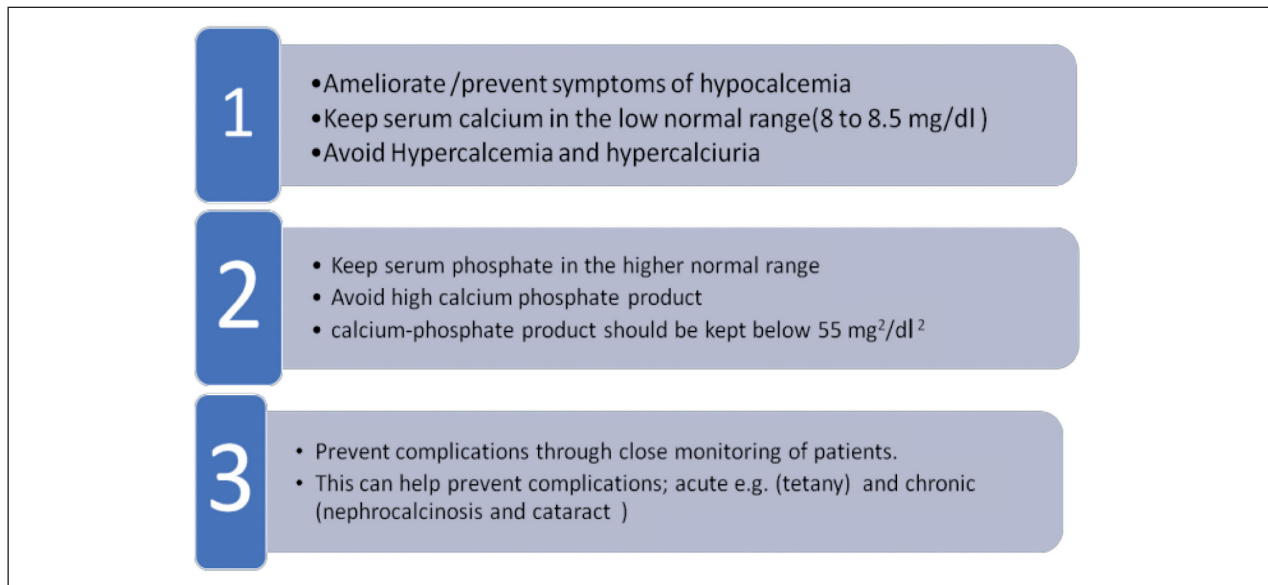
Figure 2. Goals for the management of hypoparathyroidism

calcium excretion is <4 mg/kg/24 hr. Serum levels of calcium are poor indicators of the presence of hypercalciuria and nephrocalcinosis. Thiazide diuretics are used to enhance calcium reabsorption in the distal renal tubules and to reduce calciuria, and allow reductions in the dose of calcium and calcitriol supplementation (48). Patients with HPT have abnormal bone remodeling. Bone mineral density (BMD) values are often above the average for a healthy population and at peak bone mass while serum and urine markers of bone turnover are in the lower half of the normal range or frankly low.

Based on the literature, further research is needed on hyperphosphatemia in HPT, and much more on its treatment and effectiveness. In a patient with hyperphosphatemia and/or an elevated calcium-phosphate product, consider dietary interventions and/or adjustment of treatment with calcium and vitamin D analogues (49).

The treatments showing considerable promise for the HPT patient are those with parathyroid hormone replacement. Replacement therapy with rhPTH could be a therapeutic option for refractory HPT and for patients who are not well controlled on calcium and active forms of vitamin D, and for whom the potential benefits outweigh the potential risks.

Expert opinion of Marcucci G et al. (50) inferred that the research done in the field of rhPTH "has shown that replacement treatment with rhPTH is an attractive option for subjects with HPT who are unable to maintain stable and safe serum and urinary calcium levels. However, since therapy with rhPTH is a long-term management option in HPT, more long-term data are needed".

The diagnosis of HPT is readily made in the presence of hypocalcemia with markedly reduced or absent PTH levels. At present, there is no consensus regarding the management of HPT in children and adolescents and only few studies on the long term outcome of these patients are available in the literature. Therefore, further research, addressing specific questions of this population are urgently needed to improve long-term safety of patients. Educational interventions are also needed for professionals, parents and patients to enable them to improve knowledge, quality of life, and effective management care at home.

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