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New Trends in Calcium and Phosphorus Metabolism Disorders – Hypoparathyroidism

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1. Introduction

Numerous physiological functions are regulated by calcium. In fact, ionized intracellular calcium (Ca²⁺) is the most common signal transduction element, a universal cofactor for various enzymes and a crucial participant in different physiologically relevant pathways at the cell membrane level. Thus, ensuring a stable level of extracellular Ca²⁺ is a priority for preserving many cell functions as automatism of nerve and muscle activity, contraction of cardiac, skeletal and smooth muscle, release of neurotransmitters and secretion of endocrine and exocrine hormones, among others.

The levels of extracellular Ca²⁺ and phosphorus (P) are tightly regulated by complex mechanisms that have evolved from a phylogenetic perspective, in order to maintain their extracellular concentrations within relatively narrow limits. Among key participants in the regulation of Ca²⁺, parathyroid hormone (PTH), calcitonin and 1-25 dihydroxyvitamin D are major hormones involved in mineral ion homeostasis, through their effects on parathyroid glands, bone, kidney and intestine.

Although, injury or removal of the parathyroid glands during neck surgery is by far the most common cause of acute and chronic hypoparathyroidism, there are other no so common causes as parathyroid hormones or vitamin D related disorders that may contribute to an impaired parathyroid function.

Conventional treatment of chronic hypocalcemia, particularly hypoparathyroidism, is based on calcium salts, vitamin D (mainly calcitriol), and drugs that increase renal tubular reabsorption of calcium as thiazides. Recently, new treatments have been developed, increasing the therapeutic armamentarium for hypocalcemic disorders, as synthetic recombinant human parathyroid hormone (rhPTH) 1–34 administered once or twice daily in patients with hypoparathyroidism. This treatment modality has proved to reduce urinary calcium excretion compared with calcitriol therapy and to maintain serum calcium in the normal range, thus avoiding chronic hypercalciuria that may lead to renal function impairment, nephrocalcinosis and renal insufficiency in the long term. What is more, new rhPTH release formulations are currently under investigation, opening a new field to explore for the treatment of hypoparathyroidism.

In this chapter, we will discuss the regulation of the metabolism of calcium and phosphorus and their integrated pathways to maintain their levels within physiological limits with special focus on hypocalcemic disorders and new treatment approaches.

2. Physiological regulation of calcium and phosphorus metabolism

Extracellular Ca^{2+} participates in the regulation of numerous physiological functions, as automatism of nerve and muscle activity, contraction of cardiac, skeletal and smooth muscle, release of neurotransmitters and secretion of endocrine and exocrine hormones among others; thus, physiological concentrations of extracellular ionized Ca^{2+} remain virtually constant at 1.2 mM (5 mg/dL) (Brown, 1991). For these reason, different physiological mechanisms are involved for maintaining extracellular Ca^{2+} level whiting these narrow limits that includes parathyroid hormone (PTH), calcitonin and 1-25 dihydroxyvitamin D as major hormones participating in mineral ion homeostasis, through their effects on parathyroid glands, bone, kidney and intestine.

2.1 General Homeostasis of calcium and phosphorus metabolism

The bone acts as a true storehouse of Ca^{2+} and P, containing nearly the total Ca^{2+} and P of the body in its mineral structure. Only 1% of Ca^{2+} from the bone is in constant exchange with extracellular Ca^{2+} and under tight regulation as this quantitatively minor amounts play a crucial physiological role (Kronenberg et al, 2007).

Extracellular Ca^{2+} not bound to proteins (albumin and globulins mainly), called as ionized Ca^{2+} , acts as the biological active fraction. Its physiological concentration remains virtually constant at 1.2 mM tightly controlled by hormonal mechanisms.

In contrast, resting cytosolic calcium concentration is about 100 nM but fluctuations allow increases up to 1 microM (100 folders) through cellular activation by releasing Ca^{2+} from intracellular stores (endoplasmic reticulum, mitochondria) and through activated channels thanks to a very large chemical gradient (10,000:1). Intracellular Ca^{2+} acts as a key intracellular messenger and cofactor for various enzymes and biological functions (Valero et al, 2008).

On the other hand, organic P is a main constituent and coenzyme for numerous physiological processes as replication, differentiation, development, energy expenditure and storage. Any alteration on P homeostasis cause severe disorders that affect global organ functions (Figure 1).

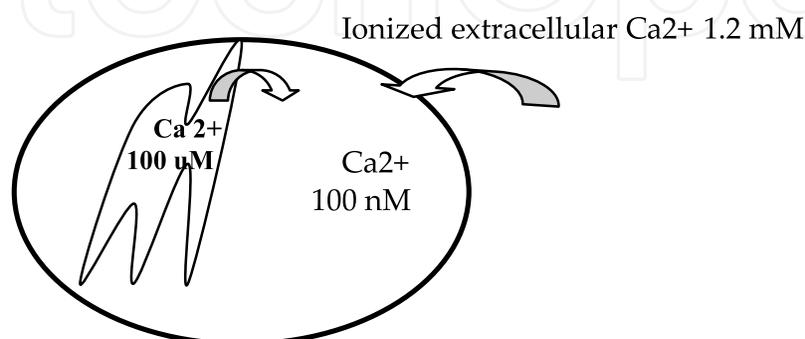


Fig. 1. Calcium concentration in the cell, plasma and intracellular stores and main fluxes (endoplasmic reticulum).

The levels of extracellular Ca^{2+} and P are tightly regulated by complex mechanisms in a coordinated way that has evolved from a phylogenetic perspective in order to maintain their extracellular concentrations within relatively narrow limits.

2.2 Parathyroid hormone

The parathyroid cell is a prototypical extracellular Ca^{2+} sensing cell (Brown, 1998). This characteristic allows the constant monitoring of extracellular ionized Ca^{2+} levels, thus, increasing extracellular Ca^{2+} is sensed by plasma membrane receptor of parathyroid glands cells (the calcium sensing receptor -CaSR-) that mediates the reduction of PTH hormone secretion (Figure 2) (Riccardi & Gamba, 1999).

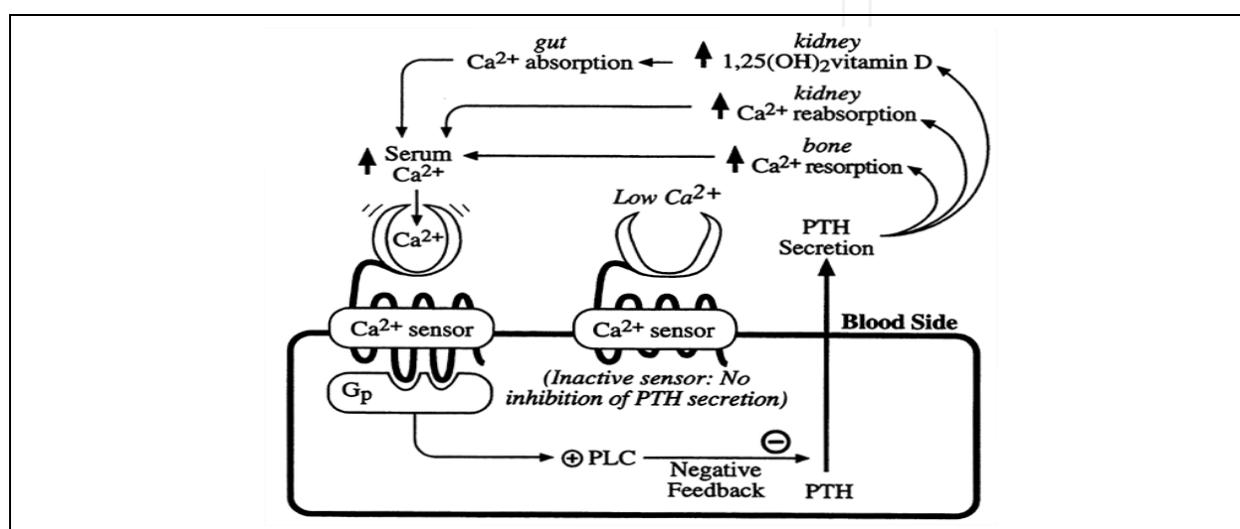


Fig. 2. PTH regulation on parathyroid gland by extracellular Ca^{2+} levels through CaSR
http://chemistry.gravitywaves.com/CHE452/20_Calcium%20Homeostasis16.htm March 15 2011. Dr Noel Sturm

In last years, inherited diseases caused by mutations of the CaSR have been studied (Health et al, 1996). Loss-of-function mutations induce a loose of sensitivity to extracellular Ca^{2+} levels and a disruption of the downregulation mechanism of PTH secretion as in familiar hypocalciuric hypercalcemia and neonatal severe hyperparathyroidism. These inherited diseases are characterized by mild or severe hypercalcemia. Gain of function mutations have been described in recent years, and in these conditions the hypersensitivity to Ca^{2+} levels cause hypocalcemia due to a premature inhibition of PTH secretion by the parathyroid gland as in autosomal dominant hypoparathyroidism (Polak et al, 1994).

Parathyroid hormone (PTH) is secreted by parathyroid glands regulated by ionized extracellular Ca^{2+} through CaSR. PTH is a 84 amino acids peptide hormone synthesized as a large pre-prohormone that exerts its biological effects on its intact configuration or by different amino terminal fragments. A continuous PTH high level as seen in hyperparathyroidism induces stimulation of bone resorption and the release of Ca^{2+} and P to plasma, and consequently leads to a decrease of bone mineral density. On the other hand, intermittent administration of PTH has the opposite effect and it is the basis of its use in the treatment of severe osteoporosis. In the kidney, PTH acts stimulating Ca^{2+} reabsorption and P urinary excretion. Indirectly, PTH provides active vitamin D by hydroxylation of 25(OH)D₃ in position 1 (1,25(OH)₂D₃) which increases calcium absorption at the gut level.

In summary, PTH acts as a Ca^{2+} rising hormone and a major regulatory of Ca^{2+} metabolism; conversely, increasing levels of Ca^{2+} exert a downregulation feed back effect on PTH secretion (Shoback, 2008).

2.3 Calcitonin

Calcitonin is a 32 amino acid peptide hormone secreted by parafollicular cells (C cells) of the thyroid gland. Despite of its important role in few vertebrae animals, in humans its role on Ca^{2+} and P metabolism is less important. However, it is used in the treatment of hypercalcemia due to its decreasing Ca^{2+} renal reabsorption effect and its inhibition Ca^{2+} bone resorption; thus, calcitonin has a net hypocalcemic effect on plasma Ca^{2+} levels in hypercalcemic disorders. Its regulation is mediated by Ca^{2+} ionized extracellular levels in part through the CaSR as in parathyroid glands, although other hormone and vitamin factors could also play an important role. Finally, calcitonin is also secreted by different neuroendocrine tumours, as medullary thyroid carcinoma, and it used as tumour marker (Kudo et al, 2011).

2.4 Vitamin D

Vitamin D acts as a real hormone. Its synthesis and tissue concentration is more dependent of seasonal and sun exposure factors rather than oral intake. Endogenous inactive vitamin D (colecalciferol-Vitamin D₃) is synthesized by ultraviolet radiation, although nutritional alternative sources (supplemented dairy products, fat fish and liver) could eventually provide sufficient quantities for covering daily needs. Vitamin D₃ activation requires hydroxylation of the 25th and 1st positions to get full biological activity (1,25(OH)₂D₃); this process takes place in the liver and kidney where hydroxylation is successively performed and at the kidney level activation of 1-hydroxylase is partially dependent of PTH. Vitamin D can also be hydroxylated at position 24 which renders inactive the molecule.

The main effect of vitamin D on Ca^{2+} and P metabolism is to stimulate calcium absorption in the bowel by means of the binding of its active form 1,25(OH)₂D₃ to the vitamin D nuclear receptor (VDR) (Shiohara et al, 2005). A less pronounced but also an important effect of vitamin D is to promote Ca^{2+} and P apposition in the bone and to stimulate calcium excretion in the kidney. The VDR is a ubiquitous receptor which is expressed in most tissues and cell lines and in fact vitamin D has been implicated in numerous biological actions as activation of the immune system, autoimmune diseases, cardiovascular risk, proliferation and differentiation of cancer cell lines among others (Fernandez et al, 2009; Mathieu & Adorini, 2002; Nagpal et al, 2005).

Calcium and vitamin D intake is currently though to be under normal requirements, especially in old populations due to loss of efficiency of vitamin D synthesis and age-related down regulation of 1 α kidney hydroxylation in relation with kidney function, as well as insufficient sun exposure in aged people. At the moment, a worldwide high prevalence of vitamin D deficiency has been described (Rosen, 2011).

2.5 Integrated homeostasis of calcium metabolism

The levels of extracellular Ca^{2+} and P are tightly regulated by complex interrelation of PTH, calcitonin and 1-25 dihydroxyvitamin D through their balanced effects on parathyroid glands, bone, kidney and intestine target organs (Figure 3).

PTH secretion is regulated by extracellular Ca^{2+} levels and activation of 25(OH)D₃ to 1,25(OH)₂D₃ is regulated by PTH action on kidney. 1,25(OH)₂D₃ enhances calcium

absorption on gut. On the same way, calcitonin regulation is mediated by Ca^{2+} ionized extracellular level. These complex mechanisms work in concert to keep Ca^{2+} and P^+ in a constant concentration for maintaining under optimal conditions some critical physiological functions as automatism of nerve and muscle activity, contraction of cardiac, skeletal and smooth muscle, release of neurotransmitters and secretion of endocrine and exocrine hormones among others.

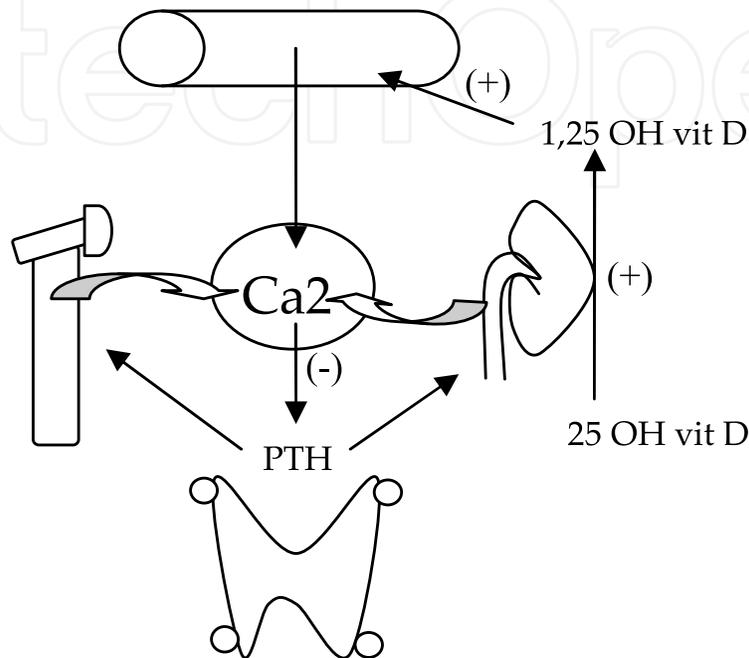


Fig. 3. Integrated physiological homeostasis of calcium metabolism.

Calcium and vitamin D insufficiency leads to an increase in calcium intestinal absorption, renal uptake and calcium bone reabsorption. The first step to reach the new equilibrium is initiated by the low extracellular calcium concentration which is sensed by CaSR and triggers PTH secretion by the parathyroid glands. The increment of PTH level increases the synthesis of the activated form of vitamin D and stimulates absorption of tubular calcium on kidney. On the other hand, 1,25 OH vitamin D acts on the nuclear pathways of the enterocytes to increase absorption of dietary calcium, which is quantitatively the most important response to calcium and vitamin D insufficiency. To summarize, chronic calcium and vitamin D insufficiency provokes a continuous compensatory hyperparathyroidism aimed to maintain Ca^{2+} and P^+ into the physiological levels; this chronic hyperactivation of the parathyroid glands may have deleterious consequences at the long term.

3. Hypocalcemic disorders

Any alteration of this close balance between the hormones involved in calcium metabolism could originate disorders characterized by the presence hypocalcemia.

Although, injury or removal of the parathyroid glands during neck surgery is the most common cause of acute and chronic hypoparathyroidism, other not so common causes should be evaluated and ruled out, mainly caused by alteration in intestinal absorption (vitamin D related) or by decrease reabsorption at the bone and kidney levels (parathyroid hormones related).

3.1 Parathyroid hormones related disorders

Parathyroid hormones related hypocalcaemia could be differentiated from other causes by a low or inappropriately normal PTH level in the presence of low calcium levels, mild hyperphosphatemia and low 1,25(OH)₂D₃.

PTH related causes of hypocalcemia include:

3.1.1 Parathyroid glands destruction

Injury or removal of the parathyroid glands during neck surgery is the most common cause of acute and chronic hypoparathyroidism. Its incidence rate is usually related to surgeon's experience, the type of pathology and the surgical technique performed (Sthepen, 2000). Although postsurgical hypoparathyroidism is usually a transitory problem, occasionally, it persists in 0.4%-33% of cases depending on the series (Page & Strunsky 2007; Torregrosa et al, 2005). It may be caused by vascular interruption or involuntary removal during surgery and it uses to be permanent if there is no remission after 6-9 months after surgery.

After hyperparathyroidism adenoma removal, a transient suppressive hypoparathyroidism can occur in the first 48 hours after surgery of functional nature. In these cases, hungry bone syndrome should be ruled out and could be identified as hypophosphatemia is virtually always an associated feature after surgery of a severe and of long duration hyperparathyroidism.

However, any infiltrative or autoimmune disease that affects all parathyroid glands could cause hypoparathyroidism. Wilson disease, hemochromatosis, metastatic disease can infiltrate parathyroid glands causing their dysfunction (Angelopoulos et al, 2006). Autosomal recessive autoimmunity hypoparathyroidism can be part of autoimmunity polyglandular syndrome type 1, in which Addison disease and mucocutaneous candidiasis are found together with hypocalcemia (Husebye et al, 2009). This syndrome has been related to the autoimmunity regulatory gene AIRE. Autoimmunity antibodies against parathyroid glands and CaSR can support this diagnosis (Dittmar & Kahaly, 2003).

3.1.2 Congenital/inherited parathyroid disorders

Transient neonatal hypocalcaemia is a quite frequent disorder that is usually resolved during the first days after birth. Hyperparathyroidism and diabetes of the mother are the most common causes. However, hypocalcemia disorders that are not resolved during first 4 weeks or life require a more extended diagnosis work-up. Inactivating mutations of some transcription factors as glial cell missing factor (GCM) and SOX3 have been related to neonatal hypoparathyroidism.

In some cases, hypoparathyroidism is part of more complex malformative syndromes arising during the embryonic development, as Di George's syndrome. Di George's syndrome or velo-cardio-facial syndrome is the most frequent severe malformation (1/3000) and it is caused by embryonic disorder of third, fourth and fifth branchial pouches, resulting in the absence of parathyroid glands associated with cardiac malformations, abnormal facies, thymus hypoplasia, and cleft palate. It is caused by deletions in 22q11, and less frequently in 10p (Kobrynski & Sullivan, 2007). Other not so common causes of neonatal/inherited hypoparathyroidism are Kenny-Caffey syndrome and Barakat syndrome among others.

Gain of function mutations of CaSR amino-terminal domain have been published in recent years; in these cases, hypersensitive sensing to Ca²⁺ levels cause hypocalcemia by

premature inhibition of PTH secretion by the parathyroid glands expressed as an autosomal dominant hypoparathyroidism (Pollak et al, 1994). In these patients hypocalcemia is found together with hypercalciuria and normal PTH. In such a situation, treatment with vitamin D results in the development of hypercalcemia which may lead to nephrocalcinosis and renal failure; thus, treatment is aimed to avoid symptoms of hypocalcemia and not to achieve normocalcemia (Pearce et al, 1996).

3.1.3 Pseudohypoparathyroidism

Pseudohypoparathyroidism is characterized by peripheral PTH resistance despite of elevated PTH levels, and hypocalcaemia plus hiperphosphatemia plasma levels similar to what is found in hypoparathyroidism after having ruled out magnesium deficiency and renal failure. It may be associated to a characteristic morphotype called Albright's hereditary osteodystrophy. Its genetic bases and clinical features will be described in detail in another chapter.

3.2 Vitamin D related hypocalcemia

Hypocalcemia syndrome due to vitamin D related disorders is mainly caused by alterations in intestinal absorption of dietary calcium. Hypocalcemic disorders in the context of vitamin D deficiency are characterized by elevated PTH plasma levels and hypophosphatemia with an increased renal phosphate clearance (Figure 4). Increased PTH is of compensatory nature aimed to maintain Ca^{2+} and P^+ within the physiological levels by calcium mobilization from skeleton, increased renal reabsorption of calcium and increased renal 1 α hydroxylation.

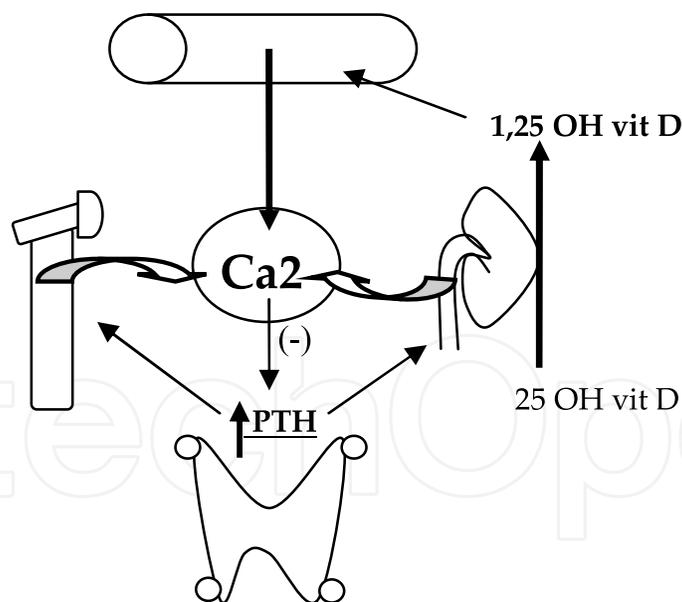


Fig. 4. Adaptation to vitamin D and calcium insufficiency (adaptation pathways on bold type).

Vitamin D related hypocalcaemia could be caused by:

3.2.1 Vitamin D absorption/synthesis deficiency

Vitamin D deficiency is mostly seen in old people, although younger populations may also suffer from this condition. As vitamin D could be sourced by skin synthesis under

ultraviolet irradiation and/or dietary intake, any deficiency on dietary intake or reduction on intestinal fat-soluble vitamin D absorption (gastrectomy, intestinal illness, chronic hepatic insufficiency) and any decrease in skin synthesis due to insufficient solar irradiation or used of high solar protective factor sun blocks, could cause a vitamin D deficiency. It also causes a compensatory hyperparathyroidism and has been correlated with seasonal psychiatric and immune disorders in northern countries (Rosen, 2011).

Modern food industry has supplemented dairy products with vitamin D although it has not been correlated with improvements in general population vitamin D levels.

3.2.2 Impaired 1 or 25 alpha hydroxylation of Vitamin D

Any alteration on hepatic or kidney functions could lead on deficient hydroxylation of vitamin D, as in renal or liver failure. This would cause an intestinal calcium absorption and a compensatory increase in circulating PTH.

It is a common clinical entity especially in chronic renal failure under dialysis. The failure of 1alpha hydroxylation at the kidney level causes a decrease in plasma calcium by malabsorption of dietary calcium intake and a compensatory elevation of PTH (secondary hyperparathyroidism) without an increased phosphate clearance because of kidney failure. Treatment of compensatory hyperparathyroidism is based on the administration of the active form of vitamin D (1-25(OH)₂ Vit D) to cover 1alpha hydroxylase deficit, an increase in calcium intake and phosphate binders (Messa et al, 2010). Regulation of PTH secretion with non hypercalcemic Vitamin D analogs and calcimimetics (parathyroid CaSR sensitizers) has been a revolution in the treatment of secondary hyperparathyroidism associated to renal failure (Borstand et al, 2010).

3.2.3 Impaired entero-hepatic circulation of vitamin D

Vitamin D is a fat-soluble vitamin, so it is under entero-hepatic circulation and adiposity and hepatic deposit. Any alteration on entero-hepatic circulation or accelerated hepatic metabolism and its nature is mainly drug-induced: anticonvulsants, tuberculostatic treatment, and bile acid sequestrants; any of these could cause an accelerated loss of vitamin D.

3.2.4 Calcitriol resistance-Hereditary vitamin D resistant rickets

Some inherited disorders have been described to be associated with vitamin D resistance; their frequency is very low. They are characterized by a biochemical profile concordant with vitamin D deficiency and compensatory hyperparathyroidism with normal or even elevated levels of vitamin D that indicates a resistance vitamin D status. Most mutations described in vitamin D resistant rickets involve intranuclear vitamin D receptor (VDR) at the DNA binding domain and it affects the regulation of gene expression (Mallory et al, 2004).

Clinical features are variable but it uses to appear during childhood with hypocalcaemia and hypophosphatemia, associated with alopecia, bone deformations and short stature. Treatment with high doses of calcitriol do not use to be successful, although it depends on the specific mutations on VDR. Vitamin D analogues have opened new therapeutic possibilities on this rare illness. Treatment with sequestrant compounds could cause an accelerated loss of vitamin D.

3.3 Other causes

Other hypocalcaemia causes include: bone apposition in osteoblastic metastasis; sequestration by intravascular drugs or by acute hyperphosphatemic states (rhabdomyolysis,

chemotherapy); treatment or ion alterations and vitamin D insufficiency in HIV infected patients; critical illness as acute pancreatitis.

4. Acute hypocalcaemia treatment

Acute hypocalcaemia is a medical emergency that requires a quick diagnosis and treatment. However, chronic hypocalcaemia is frequently asymptomatic and treatment must be aiming to normalization of calcium levels without increasing complications (Cooper & Gottoes, 2008).

Acute hypocalcaemia can be diagnosed by measuring total calcium levels using protein correction to calculate free extracellular calcium (a decrease in calcium of 0.8 mg/dl for every 1 g/dL decrease in albumin) or by direct monitoring of ionized Ca^{2+} (Kronenberg et al, 2007).

Symptoms are correlated with acute instauration and magnitude of the deficiency, especially in relation to neuromuscular excitability as carpopedal spasm. In acute and severe cases of hypocalcemia general tetany, bronchospasm and serious cardiac arrhythmias have been described, thus serum calcium levels must be measured frequently in this period, and electrocardiographic monitoring must be done during initial replacement therapy.

Acute hypocalcemia treatment requires prompt normalisation of calcium plasma levels using intravenous calcium infusion; other ions alterations are particularly important, i.e. the correction of hypomagnesaemia that causes impaired secretion of PTH from parathyroid glands and precludes the correction of hypocalcemia.

5. Chronic hypocalcemia treatment

The conventional treatment of chronic hypocalcemia and hypoparathyroidism is based on calcium salts, vitamin D (mainly calcitriol), and drugs that increase renal tubular reabsorption of calcium as thiazides. However, over the past few years, the administration of synthetic recombinant human parathyroid hormone (rhPTH) 1-34 once or twice daily, even with more physiological releasing devices in patients with hypoparathyroidism has proved to reduce urinary calcium excretion compared with calcitriol therapy, and to maintain serum calcium in the normal range, thus avoiding chronic hypercalciuria that may lead to renal function impairment, nephrocalcinosis and renal insufficiency in the long term. On the other hand, new vitamin D analogues have been investigated to maintain calcium levels on normal range without hypercalciuria complications.

In this section we will describe conventional and new treatment approaches of chronic hypocalcemia mainly focused on post surgical hypoparathyroidism, due to the important innovations appeared in last years.

5.1 Conventional treatments

The conventional treatment of chronic hypocalcaemia and hypoparathyroidism is based on calcium salts, vitamin D (mainly calcitriol), and drugs that increase renal tubular reabsorption of calcium as thiazides.

Treatment objectives are to maintain free ionized calcium levels within the normal interval or plasma calcium in the lower half or slightly below the normal range (8.0-8.5 mg/dL), and to avoid hypercalciuria (< 250 mg urine calcium/24 hours) and other treatment complications. It should be directed at the underlying disorder (Shoback, 2008).

5.2 Calcium salts

Long-term treatment of patients with chronic hypocalcemia is warranted with 1 to 3 g of elementary calcium per day in the various forms of salts available (table 1) because of the increased excretion of calcium. Interrupting the supplement can rapidly lower an elevated calcium value. It should be must be scheduled in 3-4 doses with meals to facilitates its absorption. Calcium carbonate is by far the most used calcium salts due to its low cost, despite of gastrointestinal adverse effects and that it requires gastric acidification to assure its absorption; thus achlorhydric patients or under proton-pump inhibitors treatment should be avoid unlike citrate calcium and should be taken with food or citrus drinks to promote maximal absorption. Besides, calcium citrate is preferable because it increases urinary citrate thus helping calcium to stay in solution (Harvey et al, 1988). Of the calcium preparations available, only the carbonate and citrate salts contain sufficient elemental calcium (per tablet) for the efficient treatment of most patients with hypoparathyroidism. Other preparations may be used in patients who cannot tolerate citrate and carbonate salts. The percentage of elemental calcium is lower in these other preparations, and do not adds any benefit (Maeda et al, 2006; Shoback, 2008).

| Calcium Salts | Ca element content | Milligrams of salt needed 1 g preparation elementary calcium |
|--------------------------|--------------------|--------------------------------------------------------------|
| Calcium Carbonate | 40% | 2500 |
| Calcium Phosphate | 38% | 2631 |
| Calcium Chloride | 27% | 3700 |
| Calcium Citrate | 21% | 4762 |
| Calcium Lactate | 13% | 7700 |
| Calcium Gluconate | 9% | 11100 |

Table 1. Calcium salts available. Calcium carbonate: constipation is a common side effect; calcium carbonate is best absorbed with meals and with acid present in the stomach. Calcium citrate: Recommended in patients who have achlorhydria or who are taking a proton-pump inhibitor, in order to achieve sufficient absorption of calcium (Maeda et al, 2006).

5.3 Vitamin D

All patients with hypoparathyroidism must be treated with vitamin D or analogues in addition to calcium. Vitamin D chosen must be selected depending on the underlying disorder, thus impaired renal 1 α hydroxylation should be treated with 1 α hydroxylated analogues, but vitamin D insufficiency could be treated with non hydroxylated vitamin D metabolites (Cooper & Gittoes, 2008).

Compared to PTH, replacement with calciferol steroids leads to a higher urinary excretion of Ca with an increased risk of nephrocalcinosis. Vitamin D toxicity is an important concern and may occur at any time. Manifestations may include altered mental status, fatigue, thirst, dehydration, reduced renal function, nephrolithiasis, and constipation. Treatment involves discontinuation of the vitamin D preparation and the calcium salt intake. Depending on the severity, and especially if the toxic effects are related to treatment with vitamin D metabolites with long half-lives, intravenous saline infusion and possibly oral glucocorticoids may quickly antagonize vitamin D action and restore normocalcemia in a

short period of time. Levels of 25-hydroxyvitamin D must be monitored, even in patients receiving calcitriol and alfacalcidol to assess vitamin D dosage adequacy. The target 25-hydroxyvitamin D level is 30 ng/ml.

The current most used drugs are dihydrotachysterol (average half-time 7 days), alphacalcidol (average half life-2 days) and calcitriol (average half life-1 day) depending on underlying pathology (table 2). Not all drugs are available in all countries and short half-life compound are more recommendable due to its higher security. Theoretically, for patients with labile calcemia, dihydrotachysterol may be preferable because it provides better stability but a higher risk of intoxication. When an additional rapid effect is needed or security is the priority short-acting drugs can be added. (Maeda et al, 2006).

On hypoparathyroidism, calcitriol is preferred over vitamin D2/D3 because of its potency, rapid onset and offset of action. The vast majority of patients require calcitriol in dosages of 0.25 µg, taken twice daily, and extremely rare cases up to 0.5 µg four times daily. However, vitamin D and calcium dosage show a remarkable variability so straight monitoring and titration is warranted at the beginning of the treatment.

| Vitamin D metabolites | 25/1a hydroxylation required | Dosage per day | Onset of action | Offset of action |
|--------------------------------------------------------------|------------------------------|------------------------------|-----------------|------------------|
| Vitamin D2 (ergocalciferol)/ Vitamin D3 (cholecalciferol) | +/+ | 25,000-100,000 UI once daily | 10-14 days | 14-25 days |
| 1, 25 OH Vitamin D (Calcitriol) | -/- | 0.25-1 ug twice daily | 1-2 days | 2-3 days |
| 1a hydroxyvitamin D (alfacalcidol) | +/- | 0.5-3.0 ug daily | 1-2 days | 5-7 days |
| Dihydrotachysterol | -/- | 0.2-1.0 mg once daily | 4-7 days | 7-21 days |
| 25 (OH) vitamin D (Calcidiol) | -/+ | 0.625-5 mg | 4-8 weeks | 6-12 weeks |

Table 2: Vitamin D metabolites and actions (Maeda et al, 2006; Shoback, 2008).

5.4 Enhanced calcium renal tubular reabsorption: Thiazides

Hypoparathyroidism causes increased excretion of urinary calcium in relation to serum calcium and chronic vitamin D treatment predisposes to hypercalciuria, nephrolithiasis, and nephrocalcinosis. The use of drugs that increase renal tubular reabsorption of calcium as thiazides could be useful in hypocalcemia as complementary treatment and may help to control hypercalciuria (Porter et al, 1978). In fact, patients should be evaluated annually to rule out complications of vitamin D chronic treatment as nephrocalcinosis by imaging techniques and cataracts with an ophthalmic revision (Levine , 2001), besides high water intake is recommended, at least 1.5-2.5 L/day.

5.5 New treatment approaches

Treatment of hypoparathyroidism/hypocalcemia with vitamin D metabolites and calcium salts are usually well tolerated. However, quality of life studies suggest that despite

optimization or normalization of biochemical values, patients with treated hypoparathyroidism show scores of depression, anxiety and somatisation higher than matched controls (Arlt et al, 2002). What is more, vitamin D and calcium salts are not an absolutely safe treatment. In fact, treatment is aimed to target low-normal calcium levels in order to prevent hypercalciuria and deterioration of renal function at long term.

In last years, the administration of synthetic human PTH 1-34 once or twice-daily in patients having hypoparathyroidism has proved to reduce the level of urinary calcium excretion compared with calcitriol therapy as well as maintaining serum calcium in the normal range, avoiding chronic hypercalciuria that may lead to impairment of renal function, nephrocalcinosis and renal insufficiency. Cost and inconvenience of injection treatment in the case of rPTH are the reasons why currently classic treatment with vitamin D plus calcium is preferred, despite the risk of hypercalciuria and long term impairment of renal function. However, in recent years, successful rhPTH treatment has been reported in cases of hypocalcemia and hypoparathyroidism not controlled by conventional therapy, thus indicating its usefulness in such a resistant cases (Angelopolulos et al, 2007; Mahajan et al, 2009; Puig-Domingo et al, 2008, Sanda et al, 2008, Shiohara et al, 2006; Winer et al, 2008).

On the other hand, research on calcium sensing receptor and vitamin D analogues have opened new and promising investigation in future treatments. In fact, in last years clinical availability of cinacalcet, the agonist of Calcium Sensing Receptor has proved to be effective for the treatment of hyperparathyroidism (Marcocci et al, 2009). Research on antagonists of calcium sensing receptor (calcilytic agents) may be used to promote inactivation of the receptor in the parathyroid glands and increase PTH secretion, specially in those hypocalcemic patients with activated CaSR mutations (Nemeth et al, 2001; Leth et al, 2010).

5.6 Recombinant human PTH

Hypoparathyroidism is one of the few endocrine diseases for which hormone-replacement therapy is not the treatment approach. Over the last 10 years, some clinical assays using synthetic recombinant human parathyroid hormone 1-34 (rhPTH) administered once or twice daily in adults and children with hypoparathyroidism, have proved to maintain serum calcium in the normal range as well as reducing urinary calcium excretion compared with conventional treatment with vitamin D (Winer et al, 1993, 1996, 1998, 2003, 2008, 2010). This treatment modality may prevent renal function impairment, nephrocalcinosis and renal insufficiency in the long term as it avoids the chronic hypercalciuric state associated to vitamin D administration. On the other hand, many studies have shown that rhPTH treatment in adult subjects with osteoporosis produces a rapid rise in bone mineralization, which may contribute to a faster recovery of lost bone mineral content of these patients (Farocki et al, 2007).

Despite these advantages, rhPTH has not become the treatment of choice for hypoparathyroidism, because conventional treatment with vitamin D and calcium salts is usually well tolerated, and rhPTH injection is more expensive. However, in recent years, successful rhPTH treatment has been reported in cases of hypocalcaemia and hypoparathyroidism not controlled by conventional therapy as an off-label treatment.

Only a few small, randomized trials have assessed the use of injectable PTH (1-34) and supplemental calcium in patients with this condition in a relative short period of follow-up of 3 years. In those trials, rhPTH has proved to maintain calcium levels between normal or slightly below normal range but with a significantly reduction of urinary calcium excretion. Twice-daily rhPTH versus once allowed a marked reduction in the total daily PTH 1-34

dose, with less fluctuations in serum calcium, normalization of urine calcium and significantly improved metabolic control both in adults and children. Also, rhPTH efficacy has been extensively published in case reports dealing with hypocalcemic disorders not controlled under conventional treatment, some of them trying to mimic more physiological delivery as using multipulse subcutaneous pump PTH delivery (Puig-Domingo et al, 2008). Major concerns of rhPTH use are related to safety; those data have been obtained mainly from osteoporosis treatment studies. Animal toxicity studies have raised concerns regarding dose-dependent PTH effects on the bone (Sato et al, 2002). Long-term, supraphysiological doses of recombinant human PTH 1-34 (rhPTH), given under continuous delivery rather than in a pulsatile way to rats with normal functioning parathyroid glands, was associated to an increased risk of osteosarcoma development. However, this higher risk has been associated to a particular effect on rat bones and does not seem relevant to PTH-deficient patients receiving physiological replacement doses. In fact, post commercialisation follow-up has not detected an increase in human osteosarcoma diagnosis until now (Harper et al, 2007). Anyway, more physiological release of PTH as using subcutaneous pumps delivery or patch could be even a safer alternative (Horwitz & Stewart, 2008).

5.7 Calcium sensing receptor antagonists

PTH secretion is regulated by a cell surface receptor that detects small changes in the level of plasma calcium, the calcium sensing receptor (figure 2). This receptor provides a particularly interesting and new molecular target for drugs useful for treating calcium and bone disorders. At the moment, a calcimimetic (compounds that mimic or potentiate the effects of extracellular calcium at the CaSR) is commercialized as cinacalcet (Mimpara®) and it is approved and used in non surgical or tertiary hyperparathyroidism (Marcocci et al, 2009).

In the same way, molecules that blocked CaSR activity will stimulate PTH secretion. Although, there is no calcilytic compound available yet for therapeutic human use, some of them are under research with promising preliminary results, especially for the treatment of patients with CaSR activating mutations whose treatment with vitamin D and calcium does not correct the underlying pathophysiological defect, and they often worsen hypercalciuria and accelerate kidney stone formation or nephrocalcinosis resulting in impaired renal function under conventional treatment (Letz et al, 2010).

6. Conclusion

Numerous physiological functions are regulated by calcium metabolism, thus, ensuring a stable level of extracellular Ca^{2+} is a priority for preserving normal homeostasis. In this respect, levels of extracellular Ca^{2+} and phosphorus are tightly regulated by complex mechanisms in which key participants are parathyroid hormone, calcitonin and 1-25 dihydroxyvitamin D through their effects over parathyroid glands, bone, kidney and intestine. Any alteration of this close balance between the hormones involved in calcium metabolism could originate hypocalcemia.

Although post surgical hypoparathyroidism is the most common cause, diagnosis and treatment of hypocalcemic disorders require a detailed study and infrequent causes should also be evaluated and ruled out. Hypoparathyroidism could be classified into two main groups: vitamin D related causes and parathyroid hormone related causes. Although, conventional treatment of chronic hypocalcaemia and hypoparathyroidism is based on

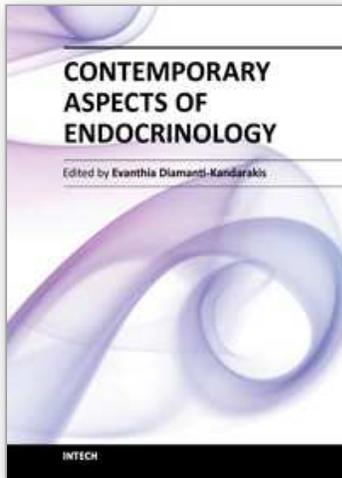
calcium salts, vitamin D (mainly calcitriol) and drugs that enhance renal tubular reabsorption of calcium, the administration of synthetic recombinant human parathyroid hormone (rhPTH) 1-34 and research in calcium sensing receptor have opened new promising fields in the last few years.

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