REVIEW ARTICLE

Secondary hyperparathyroidism and target organs in chronic kidney disease

Nikodimopoulou M, Liakos S

1st Propedeutic Medical Department, AHEPA Hospital, Aristotles University of Thessaloniki,Greece

Abstract

Secondary hyperparathyroidism (SHPT) is a common disorder in patients with chronic kidney disease (CKD) and is characterized by excessive serum parathyroid hormone (PTH) levels, parathyroid hyperplasia and an imbalance in calcium and phosphorus metabolism. Secondary hyperparathyroidism develops early in the course of CKD and becomes more prominent as kidney function declines.

PTH is a major uremic toxin and may be responsible for long-term consequences that include renal osteodystrophy, severe vascular calcifications, alterations in cardiovascular structure and function, immune dysfunction, and anemia. These adverse effects may contribute to an increased risk of cardiovascular morbidity and mortality among end-stage renal failure patients. Hippokratia 2011; 15 (Suppl 1): 33-38

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Corresponding author: Nikodimopoulou M, 2 Verias str., 55535 Pilea,Thessaloniki, Greece, Tel: +30 2310 330 558, e-mail: nikodimopoulou@yahoo.gr

Secondary hyperparathyroidism and bone mineral metabolism

There is increasing interest in understanding and treating the consequences of chronic renal insufficiency (CRI), defined here as reduced glomerular filtration rate (GFR) not requiring renal replacement therapy[1]. End-stage renal disease (ESRD) dialysis patients have reduced bone mineral density (BMD) and increased hip fracture rates[2,3]. Patients with CRI may also have reduced BMD as a result of abnormalities in acid-base and vitamin D-parathyroid hormone (PTH) homeostasis.

Metabolic acidosis, as indicated by decreased serum bicarbonate, has been detected by some investigators with even modest reductions in GFR[4]. Chronic metabolic acidosis may lead to bone buffering and slow dissolution of bone mineral[5]. Short-term oral administration of bicarbonate in postmenopausal women improves calcium and phosphorus balance and reduces bone resorption.

Many patients with mild to moderate CRI also have decreased serum $1,25(OH)_2$ vitamin D and increased PTH levels[6] and their bone biopsies show evidence of PTH excess and increased bone turnover[7]. Biochemical markers of bone turnover have been found to correlate with PTH levels and GFR[8]. Low 1, $25(OH)_2$ vitamin D level is an independent risk factor for hip fractures[9].

Several studies have found that patients with CRI have decreased BMD. These studies have been limited by small sample sizes, lack of racial or ethnic diversity and, perhaps most importantly, failure to adjust adequately for some key confounders such as sex, age and weight[10]. The generalization of these findings to patients with CRI in the general population (that is, those not necessarily seen by nephrologists or endocrinologists) is also unclear. It is important to test rigorously the hypothesis that reduced renal function is an independent risk factor for decreased BMD given that 6.2 million Americans are estimated to have serum creatinine >1.5 mg/d[11] and osteoporosis and hip fractures are major clinical and public health problems.

The Third National Health and Nutrition Examination Survey (NHAHES-III) Study show that although subjects with worse renal function have significantly lower femoral BMD, this association can be explained by confounding, principally by sex, age and weight. After taking into account the facts that women, older individuals and smaller individuals have less renal function and lower BMD, renal function itself is not independently associated with BMD[11].

The term renal osteodystrophy represents a variety of bone disorders caused by chronic renal failure (CRF). The most common abnormality is the osteitis fibrosa cystica, with extensive bone marrow fibrosis and increased osteoclastic bone resorption[12]. Osteitis fibrosa cystica (OFC) is characterized by several types of radiographic findings. Bone resorption occurs because of increased osteoclastic activity and affects all bone surfaces at different skeletal sites. It may be subperiosteal, intracortical, endosteal, trabecular, subchondral, subligamentous or subtendinous[13]. Subperiosteal bone resorption is the most characteristic radiographic feature of hyperparathyroidism and is found in the phalanges, humerus and distal epiphysis of the clavicles[14]. When resorption is subchondral, like in the sacroiliac joints, it can mimic the widening of the pubic symphysis, leading to "pseudo-widening" of the joint. It occurs in different joints, particularly the sacroiliac, sternoclavicular and acromioclavicular joints. Intracortical and endosteal resorption can cause scalloped defects of the inner cortical contour. Association of trabecular resorption (which causes loss of definition) and granular texture leads to a "salt and pepper" appearance on the

skull. Subligamentous and subtendinous bone resorption also occurs at many sites, such as the ischial tuberosities, femoral trochanters and insertions of the coracoclavicular ligaments. Losses of lamina dura of the teeth are also usually due to bone resorption[13].

Osteosclerosis can also occur in SHPT. Such changes are frequently found despite the presence and predominance of resorption. They are related either to excessive osteoblastic cell function in response to bone resorption, or to increased production of mineralized osteoid[13]. Increased amounts of trabecular bone predominate in the axial skeleton, such as in the pelvis, ribs, spine and skull. One of the typical findings is broad osteosclerosis located below the endplates of the vertebral bodies, representing accumulations of excess osteoid, with normal density in the middle parts. This finding is called "rugger jersey spine sign"[15]. Another typical example is sclerosis of the cortical surface of the cranium.

In severe cases of OFC, some bone deformities and fragility fractures may appear. Excessive resorption of the terminal phalanges may cause a deformity named acroosteolysis[13]. Severe resorption in the sacroiliac joint may cause great damage to the pelvis, thus leading to deformities that can impair the ability to walk. Thoracic vertebral fractures increase the anteroposterior diameter and enlarge the base, and thus the thorax can take on a "bell mouth" shape. In cases of thoracic kyphoscoliosis, abnormal curvature and vertebral rotation may lead to chest deformity.

Fragility fractures sometimes occur at the sites of brown tumors. These lesions are caused by rapid osteoclastic activity and peritrabecular fibrosis, and are usually well-defined purely lytic lesions with the cortex thinned and expanded but not penetrated. Since they are usually painless, the clinical diagnosis is commonly made when the patient presents a fracture. However, a brown tumor may cause spinal cord compression when it involves the column, or it may cause breathing or eating difficulties when it deforms the face. Brown tumors appear mostly at the pelvis, ribs, clavicles, mandible and extremities[16,17].

Metastatic calcification occurs when the calcium/phosphate solubility product in extracellular fluid is exceeded[18]. Its presence has become a very important sign since Block et al. demonstrated the positive correlation between mortality risk and plasma calcium-phosphate product[19], especially due to vascular calcification, including the coronary arteries. Other types of soft-tissue calcifications, such as visceral and periarticular calcifications, are also frequently seen in patients undergoing long-term hemodialysis. Tumoral calcinosis is the calcification of periarticular subcutaneous tissues around the major joints. Typically, the hips and shoulders are affected, although additional joints such as the elbows, feet, hands and wrists can become involved[20,21].

Although bone histology remains the best method for differentiating between the forms of renal osteodystrophy, serum levels of parathyroid hormone (PTH) are commonly used for diagnosing secondary hyperparathyroidism and OFC. In patients with end stage renal disease (ESRD) and chronic hemodialysis, PTH serum levels are considered adequate between 150 and 300 pg/ml. Four to eight-fold elevations of PTH are predictive for high-turnover bone disease and levels above this are strongly correlated with OFC[22,23].

Secondary hyperparathyroidism and cardiovascular disease

End-stage renal disease has been associated with changes in the structure and function of the myocardium[24]. A significant percentage of patients who start dialysis treatment have cardiac abnormalities, particularly left ventricular hypertrophy (LVH). Likewise, approximately 70% of the patients under chronic hemodialysis treatment present LVH[25]. Different conditions have been implicated in the pathogenesis of ESRD-related LVH, such as hypertension, chronic anemia, arteriovenous fistulas, concurrent ischemic heart disease, and hypoalbuminemia. These factors have independent effects, which possibly act synergistically leading to LVH and its related morbidity and mortality[26]. Verma et al (2007) demonstrated that Renal impairment was associated with smaller LV and larger LA volumes and increased LVMI. Systolic function was similar when compared with patients with normal renal function. Thus, reduced systolic function cannot account for worse outcomes in patients with renal impairment after MI. Indirect measures of diastolic function suggest that diastolic dysfunction might be an important mediator of increased risk in this population[27].

Parathyroid hormone has been identified as an important cardiotoxin in ESRD. Previous studies have supported the view that high PTH serum levels in uremic patients may cause deleterious effects in myocardium metabolism and function. The association between PTH levels and LVH has been reported by some investigators, with inconsistent results[28].

The circulating level of parathyroid hormone is regulated by the calcium concentration in the plasma. Thus, a falling plasma calcium level elicits synthesis and release of the hormone whereas an increase in plasma calcium has an inhibitory effect on the PTH secretion[29]. In turn, PTH raises the plasma calcium level by causing release of calcium from the bones, increases the absorption of calcium from the small intestine, and reduces the renal excretion of calcium. Accordingly, PTH receptors have been demonstrated in the heart, and in vitro, PTH induces hypertrophy of cardiomyocytes[30]. From clinical studies there are also indications that PTH may contribute to development of left ventricular hypertrophy. Thus, in patients with end-stage renal disease and secondary hyperparathyroidism as well as in patients with primary hyperparathyroidism, there is a strong correlation between left ventricular mass and the level of serum PTH[31].

Chronic hemodialysis patients with increased plasma concentrations of PTH and end-stage renal disease develop left ventricular hypertrophy and approximately 50% of the annual mortality in patients with end-stage

renal disease is attributed to cardiovascular events. In order to identify potential target cells of PTH in the cardiovascular system, several investigators studied the effects of PTH on cardiomyocytes, endothelial cells, and vascular smooth muscle cells. In 1988 it was found that parathyroid hormone-related peptide-PTH-rP, a peptide hormone structurally related to PTH, is expressed in the heart. PTH-rP was initially identified as a secretion product of squamous tumors[30]. It is now known that PTH-rP is constitutively expressed in various tissues including the heart. On various target cells PTH-rP can bind to and stimulate the same receptor as PTH. From these findings it has been argued that PTH-rP acts as a paracrine or endocrine modulator in cardiovascular organs. PTH-rP is supposed to influence the hemodynamic behaviour of the heart as well as angiogenesis and arteriosclerosis[31].

It is generally assumed that peptide hormones like PTH and PTH-rP bear regions that are configured for high affinity to a receptor binding region and regions that interact with the receptor to initiate a cascade of intracellular signals functional do mains. Additional orders of complexity are added by findings that one peptide hormone may interact with more than one class of receptors. Expression of different receptors and involvement of different functional domains of a given peptide hormone may vary among target cells. This review summarizes the present knowledge about the action of PTH and PTH-rP on cardiovascular target cells with a focus on cellular aspects. PTH activates protein kinase C in adult cardiomyocytes[32]. On isolated adult ventricular cardiomyocytes several humoral factors have been identified that induce signs of myocardial hypertrophy, i.e. increase in protein synthesis, cellular protein mass, and re-expression of fetal type proteins like creatine kinase BB[33]. Among these, several factors act, like PTH, via an activation of protein kinase C.

The question arises is, whether elevated plasma concentrations of PTH contribute to the genesis of myocardial hypertrophy in vivo. Clinical data support this hypothesis: Severe left ventricular hypertrophy was found in 70% of patients with end-stage renal disease, who exhibit elevated plasma PTH levels[34]. In two clinical studies patients with extremely high serum PTH levels, caused by secondary hyperparathyroidism, and accelerated left ventricular mass underwent parathyroidectomy. This resulted in a marked reduction of both plasma PTH levels and left ventricular mass[35,36]. Direct evidence for a hypertrophic effect of PTH on cardiomyocytes has been shown by the use of ventricular cardiomyocytes isolated from adult rats. On isolated ventricular cardiomyocytes a hypertrophic response can be characterized by increased protein synthesis, protein mass, and re-expression of fetal type proteins. On these cells the PTH peptides PTH 1–34 and PTH 28–48 stimulated 14C-phenylalanine incorporation, used to determine protein synthesis, whereas PTH 39–69 did not. This was accompanied by an increase in total cellular protein mass. PTH 1–34 and PTH 28–48, but not PTH 39–69, was similarly potent in induction of cytosolic creatine kinase. Induction of cytosolic creatine kinase was mainly due to a re-expression of the fetal type creatine kinase isoform, CK-B[37]. An increase of CK-BB activity by PTH could be mimicked by addition of phorbol myristate acetate, a protein kinase C activator, and attenuated by staurosporine, a protein kinase C inhibitor. It is concluded, that PTH exerts a direct hypertrophic effect on cardiomyocytes via activation of protein kinase C and that a functional domain covering the amino acids 28–34 is responsible for this effect.

Park et al demonstrated that the partial correction of SHPT with intravenous calcitriol causes a regression in myocardial hypertrophy without biochemical or hemodynamic changes, such as heart rate, BP, and TPR. The changes in plasma levels of iPTH and, secondarily, plasma levels of neurohormones (especially AT II) after calcitriol therapy may have a key role in attenuating ventricular hypertrophy in SHPT[33].

Therapy with activated vitamin D to chronic hemodialysis patients is associated with reduction in cardiovascular-related mortalit. Conversion of nutritional vitamin D ($25(OH)D_3$) to the hormonally active form of vitamin D ($1,25(OH)_2D_3$) occurs primarily in the kidney; thus, patients with kidney failure commonly present with altered vitamin D status. There is growing evidence that vitamin D either directly or indirectly affects cardiac structure and function. The vitamin D receptor knockout mouse model demonstrates increased cardiac rennin expression and marked cardiomyocyte hypertrophy, and $1,25(OH)_2D_3$ attenuates cardiomyocyte proliferation and hypertrophy in vitro. Here, we demonstrate that treatment with an activated vitamin D compound attenuates the development of cardiac hypertrophy and dysfunction in a recognized animal model of such abnormalities and that comparable findings are evident in humans[38,39].

Secondary hyperthyroidism and metabolic syndrome

Impaired carbohydrate metabolism is a common finding in patients with chronic renal failure. Studies in humans have demonstrated that both insulin resistance[40,41] and impaired insulin secretion contribute to the pathogenesis of the carbohydrate intolerance. The insulin resistance is almost always present in patients with uremia whereas insulin secretion could be normal, increased, or decreased. The normal response of the β-cells to the presence of insulin resistance is to enhance their secretion of insulin. If, for any reason, the β-cells are unable to augment their secretion of insulin appropriately, an impaired glucose tolerance would ensue. Indeed, previous studies have shown that glucose intolerance is usually encountered in uremic patients in whom both impaired tissue sensitivity to insulin and impaired β-cell secretion of insulin coexist[39]. During the past several years, data have been accumulated implicating parathyroid hormone (PTH) as a uremic toxin. Excess PTH has been shown to exert deleterious effects on the central[42] and peripheral nervous system[43], hematopoietic system[42], and skeletal muscle metabolism[44].

Advanced glycation end products (AGEs) are involved in the development of atherosclerosis and in the occurrence of uremic, ageing, and diabetic vascular disease[46,47]. In uremia, the blood levels of AGEs are elevated and endothelial RAGE is overexpressed[48]. RAGE mediates the binding of AGEs to endothelial and mononuclear phagocytes and this stimulates the cell activities[46]. IL-6 is considered to be one of the main mediators of inflammation as reflected by an enhanced production of fibrinogen and C-reactive protein in the liver and strongly affects the inflammatory process involved in the development of atherosclerosis through the stimulation of acute phase protein synthesis[49]. On the basis of these data, we evaluated the possible action of PTH on gene and protein expression of RAGE and IL-6.

A possible effect of PTH on endothelial cells has been suggested recently by showing that human PTH and human PTH-related protein (hPTHrP) stimulate the release of NO by bovine pulmonary artery endothelial cells, measuring NO using microsensor technology[50]. The aim of the present study was to determine the effect of PTH on the endothelial NOS (eNOS) system in cultured human umbilical cord vein endothelial cells (HUVEC) and the pathways which may be involved.

Chronic excess of PTH exerts its deleterious effect on cell function and metabolism through the hormone-mediated rise in the basal levels of[$Ca^{+2}i$ [51]. The chronic elevation of PTH, as in CRF, has been shown to cause a sustained elevation in $Ca^{+2}i$ of hepatocytes[48]; it is therefore plausible to suggest that such an increase in $Ca^{+2}i$ is responsible for the derangements in hepatic lipase metabolism. Support for this notion is found in the observations obtained in CRF-V rats which have normal $Ca^{+2}i$ of hepatocytes and normal hepatic lipase metabolism despite CRF and elevated levels of PTH.

Chronic renal failure (CRF) is associated with hyperlipidemia due in major part to impaired removal of triglycerides from plasma[50]. Both lipoprotein lipase and hepatic lipase are involved in the removal of triglyceride from plasma. Hepatic lipase activity after injection of heparin is reduced in CRF. This defect was apparently due to the rise in calcium content of the liver mediated by the state of secondary hyperparathyroidism of CRF. An increase in calcium content of the liver may reflect an elevation in cytosolic calcium ($Ca^{+2}i$) of hepatocytes. Indeed, CRF is associated with sustained elevation in $Ca^{+2}i$ of many cells, including hepatocytes, and the high $Ca^{+2}i$ is a major factor underlying cell dysfunction in CRF[52,53]. A decrease in the activity of hepatic lipase in CRF could be due to a decrease in the production of the enzyme, an inhibition of the enzyme activity, an impairment in its release from the liver, or to any combination of such potential derangements. These possibilities have not been fully elucidated. The elevation in $Ca^{+2}i$ downregulates the mRNA of many proteins such as the receptors of parathyroid hormone (PTH)-PTHrP, angiotensin II, or vasopressin in hepatocytes and of PTH-PTHrP in kidney and heart[54-56]. It is theoretically possible that the elevation in $Ca^{+2}i$ of hepatocytes in CRF exerts a similar effect on the mRNA of hepatic lipase. Such a potential action could cause a decrease in the production of the enzyme.

Secondary hyperparathyroidism and vitamin D

Parathyroid hormone and 1,25-dihydroxyvitamin D3 [$1,25(OH)_2D_3$], the vitamin D hormone, are responsible for maintaining serum calcium values at sufficient levels for many physiological events, including proper neuromuscular function and bone mineralization. Their coordinated activities depend on several metabolic and functional interactions. In conditions of low serum calcium, the calcium-sensing receptor of the parathyroid gland stimulates PTH secretion. PTH increases circulating levels of $1,25(OH)_2D_3$ by increasing expression of the renal 25-hydroxyvitamin D3-1 -hydroxylase (1-hydroxylase) gene[57] which encodes the enzyme responsible for the production of the vitamin D hormone. $1,25(OH)_2D_3$ exerts the biological actions of vitamin D by binding to the vitamin D receptor (VDR), a steroid_thyroid hormone nuclear receptor, and regulating the transcription of target genes. Through this mechanism, $1,25(OH)_2D_3$ stimulates the intestinal absorption of calcium while $1,25(OH)_2D_3$ and PTH act in concert to increase bone resorption and renal reabsorption of calcium. As a form of negative feedback regulation, $1,25(OH)_2D_3$ decreases PTH expression by negatively regulating the PTH gene[58,59].

The biological response to $1,25(OH)_2D_3$ is directly related to the VDR content of target tissues. Thus, the regulation of receptor expression is a critical determinant of hormone activity. The VDR has been shown to be developmentally regulated, expressed in a tissue-specific manner, and regulated by a variety of physiological factors and hormones. It is well established that $1,25(OH)_2D_3$ can stimulate receptor expression in the kidney and parathyroid gland while having minimal influence on intestinal VDR expression[60]. Several studies have noted a positive correlation between calcium and VDR expression. Hypocalcemia induced by dietary calcium restriction dramatically reduces renal VDR levels and prevents $1,25(OH)_2D_3$ from increasing VDR expression[61].

Reduced dietary calcium also has been associated with diminished VDR mRNA in avian and rat parathyroid gland. If left untreated, renal failure with subsequent vitamin D deficiency and hypocalcemia will lead to a decrease in parathyroid gland VDR content and the development of vitamin D resistance[62]. The molecular trigger responsible for the hypocalcemia-mediated decline in renal and parathyroid gland VDR content is heretofore unknown. PTH expression is inversely related to serum calcium values. Because hypocalcemic animals have high circulating levels of PTH and reduced renal and parathyroid gland VDR expression, we hypothesized that PTH may down-regulate VDR expression. Previous investigations into PTH-mediated regulation of VDR expression yielded mixed results. A PTH-mediated increase of VDR and VDR mRNA was reported in osteoblast-like UMR-106 cells[63], whereas a PTH-mediated

decrease in VDR and its transcript was reported in ROS osteoblast cells. In vivo, osmotic PTH administration to rats nearly doubled renal VDR levels[64]. However, these in vivo results were complicated by the PTH-mediated activation of the 1a-hydroxylase gene and the increase in circulating levels of $1,25(OH)_2D_3$. Recently, our laboratory and others have generated 1a-hydroxylase-null (1a-hydroxylase-/-) mice that are incapable of endogenously producing $1,25(OH)_2D_3$[65]. We have used these null mice to directly assess the effect of PTH on VDR expression, and from these studies, we have uncovered an additional functional interaction between PTH and the vitamin D endocrine system that is of both physiological and clinical significance.

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