Original Research Article

Secondary hyperparathyroidism in chronic kidney disease

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Abstract

Chronic kidney failure is much more common than people realize, and often goes undetected and undiagnosed until the disease is well advanced and kidney failure is fairly imminent. As the kidney function decreases it affects many other systems of the body mainly the calcium phosphorous metabolism as the metabolism is mainly controlled by kidney in terms of absorption and reabsorption of calcium phosphorus. Secondary hyperparathyroidism is usually found in patients with kidney failure and involves all four parathyroid glands. The kidney problems trigger the parathyroid glands into making excess parathyroid hormone (PTH). Here we have reconfirmed the findings and evidence of secondary hyperparathyroidism in chronic kidney disease patient.

Key words

Hyperparathyroidism, End stage renal disease, Hypocalcemia, Pituitary.

Introduction

Chronic kidney failure, also known as chronic renal failure, chronic renal disease, or chronic kidney disease, is a slow progressive loss of kidney function over a period of several years. Eventually the patient has permanent kidney failure. Chronic kidney failure is much more common than people realize, and often goes undetected and undiagnosed until the disease is well advanced and kidney failure is fairly imminent. It is not unusual for people to realize they have chronic kidney failure only when their kidney function is down to 25% of normal. It has been known for many years that ESRD is associated with very high mortality. CKD is initially without specific symptoms and is generally only detected as an increase in serum creatinine or protein in the urine. As the kidney function decreases it affects many other systems of the body mainly the calcium phosphorous metabolism as the metabolism is mainly controlled by kidney in terms of absorption and

reabsorption of calcium phosphorus. Secondary hyperparathyroidism is usually found in patients with kidney failure and involves all four parathyroid glands. The kidney problems trigger the parathyroid glands into making excess parathyroid hormone (PTH). Calcium levels are usually in the normal or low range and PTH levels can be markedly elevated.

Secondary hyperparathyroidism (SHPT) is a common consequence of chronic kidney disease (CKD) [1, 2]. Major traditional concerns about the disorder include metabolic bone disease that occurs as a consequence of excess parathyroid hormone (PTH) synthesis and secretion and disturbances in calcium and phosphorus metabolism that may contribute to the development of soft tissue and vascular calcification. Recent observational studies have linked certain biochemical abnormalities such as elevated levels of calcium and phosphorus in serum to adverse clinical outcomes among patients with stage 5 CKD who require treatment with dialysis [3–5]. These disturbances may arise either from the disease itself or from the therapeutic interventions used to manage it [2]. The current review focuses more narrowly, however, on the key determinants of parathyroid gland function in CKD and the factors that influence the development and progression of SHPT. Recent scientific advances provide a much better understanding of the molecular mechanisms and signal transduction pathways involved in the pathogenesis of SHPT due to CKD and in the regulation of PTH synthesis and secretion in this important clinical disorder.

Here in this study, we have correlated the biochemical parameters iPTH, Calcium, phosphorus, urea, potassium in chronic kidney disease.

Material and methods

68 chronic kidney patients from all the age groups were included in the study along with 25 age and sex match healthy subject. Complete clinical history was obtained from the patients. Blood samples were collected for analysis of iPTH, calcium, phosphorus, urea, potassium. Samples from the patients were obtained before performing the dialysis.

iPTH samples were collected and immediately processed on Access 2 Immunoassay analyzer from Beckman Coultor to avoid disintegration of intact PTH molecule. Calcium, phosphorus, urea, potassium analysis was done on integrated DXC860i analyzer form Beckman Coultor. The statistical analysis was done using micro soft excel 2007.

Results

The results obtained in the study were tabulated as follows. Sex wise distribution of study subject was as per **Table – 1**. Distribution of patients according to age group was as per **Table – 2** and **Graph - 1**. Trend of increasing iPTH value as disease duration increases was as per **Table – 3**. Calcium, Phosphorus, iPTH values in patients and healthy subjects was as per **Table – 4** and **Graph – 2, 3, 4**.

Table - 1: Sex wise distribution of study subject.

	Male	**Female**	**Total**
Subjects	47	21	68
Healthy subjects	15	10	25

Table - 2: Distribution of patients according to age group.

Age group	**Total number of cases**	**Male**	**Female**
21-25	2		2
26-30	1	1	
31-35	7	4	3
35-40	9	8	1
41-45	12	10	2
46-50	28	18	10
51-55	6	3	3
56-60	5	4	1

Graph - 1: Age wise distribution of patients.

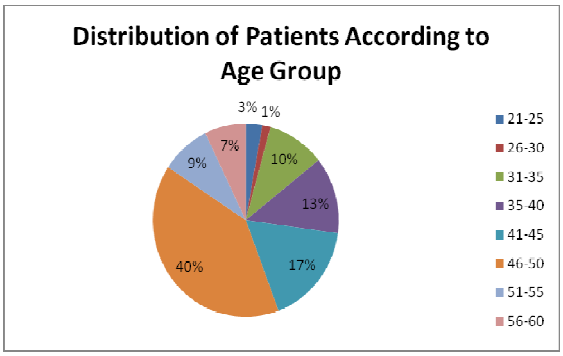


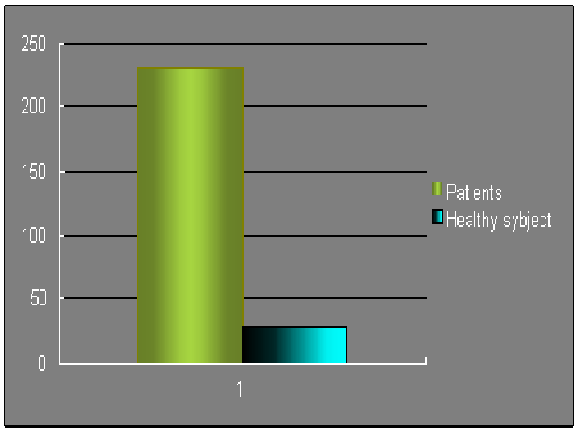
Table - 3: Trend of increasing iPTH value as disease duration increases.

Duration of disease	No of Cases	Mean iPTH Value
< 5 year	3	49.68 pg/ml
5-8 year	19	138.9 pg/ml
8-12 year	39	254.6 pg/ml
>12 year	7	407.5 pg/ml

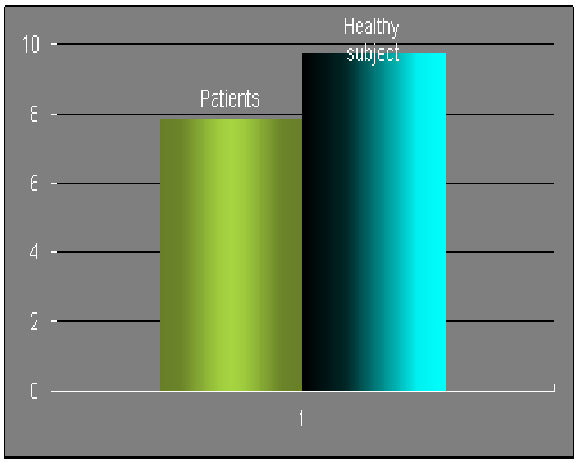
Table - 4: Calcium, Phosphorus, iPTH values in patients and healthy subjects.

	Mean iPTH pg/ml	Mean Calcium mg/dl	Mean Phosphorus mg/dl
Patients	231.3±5.7	7.9 ± 0.78	5.2 ± 0.68
Healthy Subject	27.8 ± 1.9	9.8 ± 1.1	3.2 ± 0.28

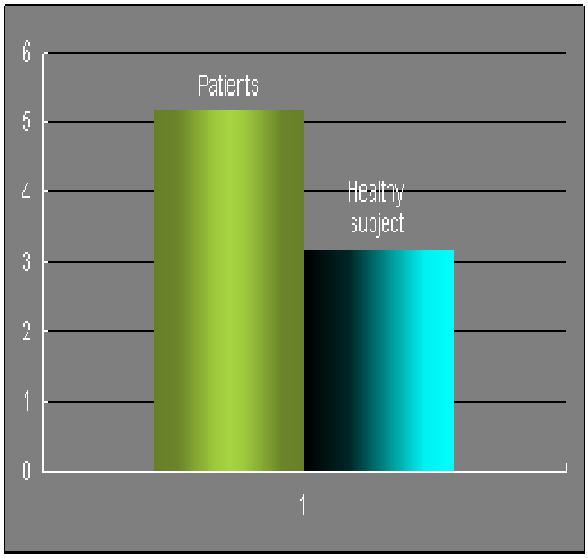
Graph - 2: iPTH values in patients and healthy subjects.



Graph - 3: Calcium values in patients and healthy subjects.



Graph - 4: Phosphorus values in patients and healthy subjects.



Discussion

The results obtained in our study are consistent with other researcher. The findings showed that patients with chronic kidney disease have higher levels of phosphorus and iPTH whereas lower levels of calcium. The mean phosphorus value for the chronic kidney patient is 5.2 mg/dl as compared to 3.2 mg/dl in healthy subjects. Also the mean iPTH value for patients is 231.3 pg/ml as compared to 27.8 pg/ml in healthy subjects. The mean calcium value for the patients was 7.9 mg/dl as compare to 9.8 mg/dl in healthy subject. The study also shows the trend of increasing

iPTH value as the duration of disease goes on increasing. Secondary hyperparathyroidism is associated with chronic kidney disease. And the severity increase as the duration of disease increases.

Unlike other endocrine organs, the parathyroid gland is not controlled by the pituitary. It secretes parathyroid hormone in response to serum calcium levels. That's it. No pituitary/hypothalamic input. The function of parathyroid hormone is to raise serum calcium; so when the calcium level drops below normal, that's the signal for the parathyroid to start secreting parathyroid hormone.

Secondary hyperparathyroidism occurs when the parathyroids are over functioning because something is causing chronic hypocalcemia usually chronic renal failure.

In chronic renal failure, phosphate is not excreted well, and vitamin D is not converted to its active form very readily. Calcium phosphate forms in the circulation, leading to a decrease in free serum calcium. The hypocalcemia then stimulates the parathyroids to grow and secrete parathyroid hormone, and voila, you have hyperparathyroidism.

The development of secondary HPT results from many factors, including deficiency of calcitriol, retention of phosphorus, a decrease in the activation of the calcium-sensing receptor (CaR) in the parathyroid gland, and skeletal resistance to the calcemic effect of PTH. As kidney function declines, so does phosphorus excretion, thus causing plasma phosphorus levels to rise while plasma calcium and calcitriol levels decrease. A reduction in calcitriol also contributes to a reduction in intestinal calcium absorption. All of these factors contribute to the development of hypocalcemia, which is the impetus for an increased production of PTH [6]. More recently, fibroblast growth factor-23 (FGF-23), which increases early in the course of CKD possibly as a consequence of phosphorus retention, has been found to suppress calcitriol synthesis, in turn leading to increased PTH [7]. PTH is the principal calcium-regulating hormone in man. Parathyroid tissue evolved originally to allow animals to adapt to life in the relatively calcium-deficient surroundings of terrestrial compared with marine aquatic environments. The parathyroid glands secrete PTH in a pulsatile manner that is regulated by a calcium-sensing G-protein-coupled receptor, or the CaSR, located on the surface of parathyroid cells [8, 9, 10]. The actions of PTH to regulate serum calcium concentrations are mediated both directly and indirectly. Minute-to minute changes in PTH release into the circulation affect serum calcium levels directly by modifying calcium transport in the distal nephron and by affecting the exchange of calcium between plasma and a rapidly exchangeable pool in bone [8, 9, 11, 12]. The actions of PTH on calcium transport in the distal nephron and on the miscible calcium pool in bone occur within minutes to hours [13, 14, 15]. Moreover, the very steep slope of the inverse sigmoidal curve that describes the relationship between blood-ionized calcium and plasma PTH levels assures that small variations in ionized calcium concentration elicit large reciprocal changes in PTH secretion to modulate these fluxes appropriately [15]. Ongoing short-term variations in PTH secretion that are mediated by the CaSR thus provide a robust mechanism for maintaining a constant level of ionized calcium in blood by regulating continuously the amounts of calcium that enter or leave the plasma compartment via the kidney and bone [11, 12, 13, 14] only minor changes in blood ionized calcium concentration increase PTH secretion promptly and markedly [15, 16, 17, 18].

Calcium and Phosphorus metabolism in renal failure

When GFR falls, the phosphorus clearance decreases significantly, leading to phosphorus retention. This hyperphosphatemia, subclinical when estimated GFR is 30 mL/min, is thought to be the principal cause of secondary hyperparathyroidism. Phosphorus induces PTH secretion by 3 mechanisms.

- Direct stimulatory effect on the

parathyroid glands as previously mentioned.

- Induction of mild hypocalcemia by precipitating with calcium as CaHPO4. Hypocalcemia also results from decreased calcium release from bone pools.
- Stimulation of FGF-23, which leads to severe inhibition of 1- hydroxylase and depressed level of 1,25 dihydroxyvitamin D [9]. The down regulation of the vitamin D receptors on the parathyroid glands leads to vitamin D resistance. The loss of negative feedback on the parathyroid glands causes a high PTH level.

Early stages of CKD, both in dogs with experimental uraemia induced by renal-artery ligation, and in humans, are associated with an increase in phosphaturia, which correlates with increasing levels of serum PTH [16]. The stimulus for the increased PTH secretion was once thought to be the complexing of serum calcium with retained phosphorus and the deposition of this complex in soft tissues. Deposition of calcium–phosphorous complexes results in small decreases in levels of Ca2+, and this decrease was thought to stimulate PTH secretion [19]. More recent studies over the past 20 years, however, show a direct effect of phosphate on the parathyroid gland. Notably, these direct effects require the tissue architecture of the parathyroid gland to be maintained by a signaling pathway that involves phospholipase A2 metabolism [20, 21, 22, 23].

The mechanism by which phosphate levels in the extracellular fluid are sensed is unknown. One possibility is that phosphate retention signals to the parathyroid gland through a small decrease in Ca2+ level, which would be sensed by the parathyroid calcium receptor and lead to increased PTH secretion. In bone, phosphate retention would increase FGF-23 expression by altering hydroxyapatite synthesis and bone matrix metabolism [24]. A high phosphate level also has direct effects on cellular processes. For example, use of medium with a high phosphate concentration increased the expression of osteogenic genes in cultured mouse smooth muscle cells [25]. This effect was caused by the formation of calcium–phosphate nanocrystals of 150 nm in diameter and was prevented by the mineralization inhibitor, pyrophosphate [25]. In addition, mice given increasing loads of dietary phosphorus have shown clear incremental increases in serum Fgf-23 levels [26].

If very short-term increases in PTH secretion are insufficient to prevent a decline in blood ionized calcium concentration and restore basal levels of the CaSR activation, additional PTH is made available for secretion by upregulating pre-pro-PTH gene transcription and PTH synthesis.

Conclusion

Secondary hyperparathyroidism is common in long standing kidney diseases. The severity of hyperparathyroidism increases as the duration of disease increase. Low calcium and high phosphorus levels are commonly associated with chronic kidney diseases.

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