

# The Relavence of Serum Total Calcium and Ionized Calcium to Intact PTH ratios in Secondary Hyperparathyroidism patients with CKD during Haemodialysis

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## ABSTRACT :

**Background:** The Secondary hyperparathyroidism (SHPT) describes a complex alteration in bone and mineral metabolism that occurs as a direct result of chronic kidney disease (CKD). During early secondary hyperparathyroidism, the blood calcium levels are normal or low, but the PTH level is high. The parathyroid gland plays a central role in controlling serum calcium concentrations by regulating secretion of parathyroid hormone (PTH).

**Materials and Method:** In the prospective case-control study, 50 samples of blood from haemodialysis patients with SHPT attending to Department of Biochemistry, Chalmeda Anand Rao Institute of Medical Sciences, Nephrology OP & IP in a multi-specialty Hospital in, Karimnagar, Telangana and 11 healthy control samples were also collected after proper consent were taken, the samples were processed for iPTH, total calcium and ionized calcium. Intact PTH assay were done by Chemiluminescence method in Snibe Maglumi 1000 and Total calcium estimation by colorimetric method were done in Randox Daytona analyser. The ratios of Serum Calcium to Intact PTH and ionized Calcium to Intact PTH were done by calculative method using data of parameters in this study and statistical significance for P value were done by using student t-test.

**Results:** The mean and SD values of patient group of intact PTH were  $321.81 \pm 225.92$  and control group were  $49.35 \pm 15.45$  with p value less than 0.0001 extremely significant. The mean and SD values of ionized calcium were  $3.84 \pm 0.52$  and control group are  $4.34 \pm 0.28$  with p value less than 0.0001 which were also extremely significant.

**Conclusion:** The relavence of ratios for serum calcium-intact PTH and ionized Calcium intact PTH highlights the significance of activities among haemodialysis patients in the diagnosis of secondary hyperparathyroidism. There by it should be included along with reference panel determinations as a parameter for early detection of complication of the SHPT.

**Keywords:** Relavence of ratios of serum total Calcium-intact PTH and ionized Calcium – intact PTH in SHPT

## INTRODUCTION

The Secondary hyperparathyroidism (SHPT) occurs as a direct result of chronic kidney disease (CKD) and is a well-recognized complication of CKD, Patients with mild CKD may be asymptomatic and therefore may not be identified until the pathology of SHPT has begun. Identifying patients at risk and evaluating for SHPT is imperative because early intervention may slow or arrest the progression of both bone and cardiac disease. There

are five stages of CKD patients based on the degree of renal function and act as markers to predict the development of comorbidities of CKD leading to SHPT.

In the previous studies had shown that CKD patients classified as Stage 3, Stage 4, or Stage 5 are at risk for, or may already have developed the complications. As it is known that the SHPT is shown to increase as the CKD progresses from 40% in stage 3 to more than 80% in stage 5 CKD.<sup>[1]</sup>

The early identification and treatment of SHPT is crucial to prevent or control the consequences of this complication.<sup>[2]</sup> The PTH is involved in the homeostasis of bone metabolism by regulating the level of calcium in the blood. The entire PTH molecule is composed of a sequence of 84 amino acids referred to as the intact hormone (iPTH).

The smaller fragments of this molecule may have unique actions in the body, generally, the iPTH is measured to diagnose the status of parathyroid gland function and used to assess bone metabolism and bone disease. It has a short half-life (2 to 4 minutes) before being degraded to various inactive fragments. PTH acts mainly on 2 organs: the bone and the kidney, Calcium has a negative feedback effect on the parathyroid glands through the calcium sensing receptor.

Vitamin D is an essential factor in the regulation of calcium and phosphorus balance. The active form is 1,25 dihydroxy vitamin D. Isakova et al, provided evidence that serum FGF23 increased earlier than serum iPTH in patients with CKD, through the Klotho receptor it acts mainly on the kidney to increase phosphorus clearance. The FGF-23 also inhibits the 1- $\alpha$  hydroxylase activity, causing a low 1, 25 dihydroxyvitamin D level.

Hyperphosphatemia is the principal stimulator for FGF-23. As the dynamics of parathyroid hormone has bifunctional and bidirectional effect on PTH-Calcium. The serum Calcium levels controls PTH secretion and in humans. The PTH-Calcium curve, is the Calcium – PTH curve because there is variable dependency between them. The serum Calcium response to PTH shows linear when between 5 to 10 mg/dl but then PTH levels decrease due to Calcemic response when Calcium exceeds 10 mg/dl. There are few reasons which appears to the Calcemic response .

An attempt is made to justify these factors as to how the PTH secretion is modified by rate and directional changes towards the Calcium levels which prevails in progress of the disease. It is stated by Levin et al as the early status of the disease and diagnosis with treatment is critical in the management of patients suffering with CKD of SHPT. It is noted that a 34% increased risk of mortality shown to be known for Ca & P product more than 72 mg/dl as the Ca & P increases risk is shown as elevation of 11% for every 10 points increases.

This is why the current Kidney Disease Outcomes Quality Initiative (K/DOQI) recommendation is to keep PTH between 150 and 300 pg/mL to avoid a complete suppression of the osteoclasts and prevent a dynamic bone disease. During early secondary hyperparathyroidism, the blood calcium levels are normal or low, but the PTH level is high. The parathyroid gland plays a

central role in controlling serum calcium concentration by regulating secretion of parathyroid hormone (PTH). The increased or decreased secretions of PTH are dependent on the levels of serum calcium. The Secondary hyperparathyroidism (SHPT) is a common complication of end stage renal disease (ESRD). The iPTH levels can be used as a criterion in treating ESRD. There by following universal reference panel determination of ratios of intact PTH combined with plasma/serum ionized calcium is a reliable means of studying the hyperparathyroidism associated with chronic renal disease. As in previous studies it is noted that physiologically, the relation between PTH secretion and calcium concentration is defined by a sigmoid curve.

The set point of PTH secretion is defined as the concentration of calcium required to reduce maximum PTH secretion by 50% or it can also be defined as the serum calcium concentration required to reduce PTH secretion to half the difference between the maximum and minimum levels. The set point of PTH secretion defines the sensitivity of the parathyroid glands to calcium concentration, Ionized Calcium is normally better for accurately monitoring calcium status in renal diseases.<sup>[3]</sup>

There are advantages of measuring ionized calcium over total calcium, the ionized calcium is more reliable indicator of calcium status of patients in certain clinical conditions, when the physiologically active form of calcium is 50% of total calcium. The relationship between iPTH and calcium levels or iPTH and ionized calcium can be expressed as sigmoid curve.<sup>[4]</sup>

The SHPT secondary to CKD is an overproduction of PTH caused by several changes that occur in bone and mineral metabolism as a result of decreased kidney function . The first changes that usually occur with declining kidney function involve the deficiency of activated vitamin D and an increase in phosphorus excretion by the remaining functional nephrons. Both of these changes stimulate an increase in PTH synthesis and secretion. The intact PTH levels shows the increase as early as start of 3<sup>rd</sup> stage of CKD along with serum Calcium and Phosphorus being normal. The mortality by effect of SHPT was known to occur due to hyperphosphatemia.

Thus, in the present study, by following universal reference panel determination of plasma /serum in the form of ratios of serum Calcium to ionized Calcium and especially ratio of Intact PTH to ionized Calcium shows as a reliable means of studying the hyperparathyroidism associated with chronic renal disease. Hence the ratios calculation may impose the importance in criteria for assessment of the disease in ESRD stage for early diagnosis and treatment in secondary hyperparathy-

roidism leading to renal failure causing deep concern in status of morbidity and mortality.

**MATERIALS AND METHOD**

*Study Design*

In prospective case-control study, 50 samples of blood from haemodialysis patients with SHPT attending to Nephrology OP & IP patients in CAIMS, a multi-specialty Hospital, Karimnagar, Telangana and 11 healthy control samples were also collected from faculty members aged 20 to 75 years of both sexes from March 2018 to February 2019. After standard performa of consent from both controls and patients in the study were taken. The samples were collected in fasting conditions under aseptic procedure. The serum obtained is used for the analysis.

*Method*

- Intact PTH assay were done by Chemiluminiscence method in Snibe Maglumi 1000.
- Total calcium estimation were done in Randox Daytona analyzer by Colorimetric Method.
- Arsenazo 111 specifically binds to Calcium forming a colored complex, which is directly proportional to the intensity of the colored complex measured at 660 nm.
- Serum /plasma used for estimation
- Normal values in serum - 8.10 to 10.4 mg/dl [5].
- The ionized Calcium is calculated from Serum Calcium values.
- The ratios of Serum Calcium to Intact PTH and ionized Calcium to Intact PTH were done by calculative method using data of parameters in this study.

*Inclusion Criteria:*

- Chronic Kidney Disease leading to SHPT patients were included in the study.

*Exclusion Criteria:*

- Hormonal Imbalance
- Diabetes mellitus
- Liver disease and Vitamin D deficiency were excluded from study.

*Ethical Approval*

This study is started after getting ethical approval from Institute Ethics Committee, Chalmeda Anand Rao Institute of Medical Sciences, Karimnagar.

**STATISTICAL ANALYSIS**

Statistical analysis is done by using inferential statistics (statistical test of significance, t-test) for quantitative data

and ratio for qualitative data with the help of Microsoft Excel 2010 and Statistical Package for Social Science (SPSS) Version 25.

**RESULTS**

The mean and SD values of patient group of intact PTH are 321.81 ± 225.92 and control group are 49.35 ± 15.45 with p value 0.0001 extremely significant.

The mean and SD values of ionized calcium are 3.84 ± 0.52 and control group are 4.34 ± 0.28 with p value 0.0001 extremely significant showing decrease in the data to that of Controls, so also the total serum calcium the Mean, SD were 7.63 ± 1.24 for patients and 8.68 ± 0.56 for control showing the decrease in patients to that of controls as documented in (Table1).

**Table 1: The statistical data of intact PTH, Total calcium and ionised calcium**

| Parameters      | Mean & SD controls | Mean & SD of tests | P value  |
|-----------------|--------------------|--------------------|----------|
| Intact PTH      | 49.35 ± 15.45      | 321.81 ± 225.9     | < 0.001* |
| Total Calcium   | 8.68 ± 0.56        | 7.63 ± 1.24        | < 0.001* |
| Ionized Calcium | 4.35 ± 0.28        | 3.84 ± 0.52        | < 0.001* |

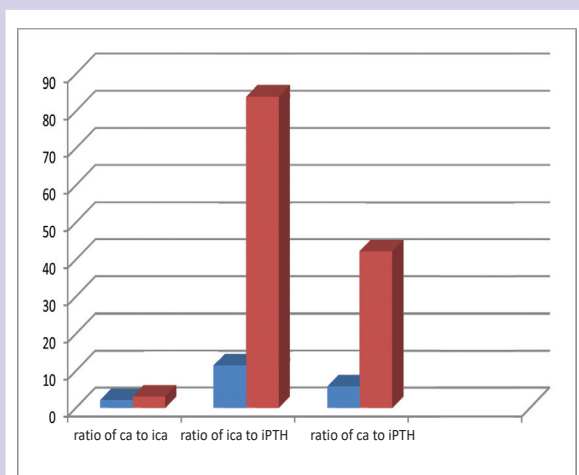
*\*p-value is highly significant at 1% level of significance.*

The statistical analysis was done using student t test. By calculative method the ratios were assessed to show the significance of serum Calcium to ionized Calcium and with the ratio of intact PTH to ionized Calcium ratio are as shown in Table 2.

It is noted as the ratios of Calcium to ionized Calcium in patients and the controls as 2.8 and 2.0, the Ipth to ionized Calcium as 83.80 and 11.37 and intact iPTH to serum Calcium as 42.17 and 5.68 respectively.<sup>[1]</sup> The comparison of ratios for intact PTH to ionized Calcium shows 7.3 folds increase to the patient data to controls. 2. Whereas intact PTH to serum Calcium shows 7.4 folds increase.<sup>[3]</sup> In comparison to the serum Calcium to ionized Calcium showed 1.49 folds increase in patients data to controls of SHPT patients in this study.

**Table 2: Shows the Ratios of Controls with Patients and increase in folds**

| Parameters                          | Ratio in Controls | Ratio in patients and Folds increase |
|-------------------------------------|-------------------|--------------------------------------|
| Serum Calcium to Ionised Calcium    | 2.0               | 2.98 and 1.49                        |
| Serum Intact PTH to Ionised Calcium | 11.37             | 83.80 and 7.3                        |
| Serum Intact PTH to Calcium         | 5.68              | 42.17 and 7.4                        |



**Figure 1: Shows the ratios of serum Calcium to ionized Calcium, intact PTH to ionised Calcium and Calcium to intact PTH**

There is increase of ratios in patients to the control group as shown in table 2 & figure 1 for serum Calcium to ionized Calcium, intact PTH to ionized Calcium and intact PTH to Calcium of which, ratio of intact PTH to ionized Calcium were showing the importance of increase in folds with intact PTH to serum Calcium. The Ratio of intact PTH to ionized calcium is relevant in predicting the severity of the disease and leading to complications.

## DISCUSSION

The parathyroid gland plays a central role in controlling serum calcium concentrations by regulating secretion of parathyroid hormone (PTH). As it is known that increased or decreased secretions of PTH are dependent on the levels of serum calcium and the Secondary hyperparathyroidism (SHPT) is a common complication of end stage renal disease (ESRD). The PTH hormone is a mature molecule, which contains 84 amino acids and is biologically active at 1- 34 amino acids region.

The region of PTH from 1-84 amino acids is the intact PTH, which is predominantly cleaved in liver and kidney. The PTH raises serum ionized calcium levels through direct action on bone and the kidneys. The intact PTH levels are elevated in SHPT usually associated with renal failure as a result of constant stimulation of parathyroid gland by low calcium levels and inversely the Hypocalcaemia accompanied by low PTH level seen in hypoparathyroidism either post surgical or idiopathic.

The Ionized Calcium is normally better for accurately monitoring calcium status in renal diseases. Ionized calcium is high in neonates at birth in blood then decreases by 10 – 20% after 1-3 days, after a week ionized

calcium concentration in the neonates stabilize at concentrations slightly higher than adults. Ionized calcium represents physiologically active form of total calcium in the plasma. The normal levels of ionized calcium, which varies in adults and children. In adults, a level of 4.64 to 5.28 mg/dl is normal. In children, a normal ionized calcium level is 4.8 to 5.52 mg/dL. But when seen in table -1 in the present study, the mean, SD showed  $4.35 \pm 0.28$  in controls and  $3.84 \pm 0.52$  in patients showing the decrease in them to controls though in normal ranges. Ionized calcium values are higher in children and young adults.

In healthy, plasma ionized calcium concentration is maintained between approximately 1.15(4.6mg/dl) and 1.30 mmol/L (5.2 mg/dl). Ionized calcium binds to negatively charged sites on protein molecules, competing with hydrogen ions for the same binding sites on albumin and other calcium-binding proteins. This binding is pH dependent and alters the level of ionized calcium in the blood. An increase in pH, alkalosis, promotes increased protein binding, which decreases free calcium levels. Acidosis, on the other hand, decreases protein binding, resulting in increased free calcium levels.

As seen in table-1, the Mean, SD showed for intact iPTH were  $49.35 \pm 15.45$  in controls and  $321.81 \pm 225.9$  in patients showing increase in them to that of controls, where as in Mean, SD for Total serum Calcium in controls and patients showed as  $8.68 \pm 0.56$  and  $7.63 \pm 1.24$  which denotes that Total Calcium decrease in patients to that of controls. As Serum ionized calcium concentrations is 50% below normal will result in severely reduced cardiac stroke and with moderate to severe hypocalcemia, left ventricular function may be profoundly depressed.

The Ionized calcium, which accounts for 50% to 55% of total calcium, is the physiologically active form of calcium. Low ionized calcium values are often seen in renal disease, critically ill patients, or patients receiving rapid transfusion of citrated whole blood or blood products. Nomograms have been used to calculate ionized calcium from total calcium, albumin, and pH values. However, calculated ionized calcium results have proven to be unsatisfactory. Hence the accuracy of measured parameters needs to be evaluated in these patients with a new method in interpretation as in the present study reveals the relevance of ratios of these parameters will prove worthy.

The Nephrology guidelines recommend targets and treatment strategies to correct serum levels of phosphorus, calcium and parathyroid hormone because observational data suggest that there is an association between these biomarkers and vascular disease which leads to death<sup>[6,7]</sup>, shows the significance in mortality and



morbidity of the disease. The burden of cardiovascular morbidity in individuals with chronic kidney disease necessitates the potential for serum levels of phosphorus, PTH and calcium to act as important modifiable risk factors.<sup>[8]</sup> Among patients of ESRD beginning dialysis, initial PTH levels above 200pg/ml was associated with half the mortality of similar patients with PTH levels below 65pg/ml controlling ionized calcium by monitoring its concentration can avoid complications such as renal stones, other soft tissue calcification. According to previous studies, if the iPTH value are less than 100 pg/ml there is 83% probability that the renal patient has a dynamic low bone turnover disease.<sup>[9]</sup>

The PTH and serum calcium curves are sigmoid in primary and secondary hyperparathyroidism due to renal failure.<sup>[10]</sup> Similarly the intact PTH and ionized calcium curves are sigmoid.<sup>[11]</sup> It can be imperative to note that the PTH levels increase to that of serum Calcium or with serum levels of PTH to that of ionized Calcium showed as sigmoid curve at maximum levels upto 5mg/dl for serum Calcium and 600 mg/dl for intact PTH levels and minimum iPTH level of sigmoid curve is 200 pg/ml with total calcium levels of 9.5 mg/dl. Similarly, the highest ionized calcium levels observed from sigmoid curve were 2.3 mg/dl with iPTH level 480 pg/ml and lowest iPTH was 90 pg/ml corresponding to ionized calcium of 4.8 mg/dl. Thus, the iPTH level below 90 pg/ml, total calcium below 5 mg/dl, and ionized calcium below 2.3 mg/dl deteriorates the conditions associated with SHPT of chronic kidney disease.

Thus, the parathyroid gland activity is mediated by a direct interaction of calcium ions with the calcium sensitive receptors. Where in the hyperparathyroidism either primary or secondary or pseudo or idiopathic there is decreased calcium receptors.

Accordingly in previous studies indicate that the ionized calcium is the set point for the patients undergoing haemodialysis with chronic kidney disease and the range of this set point lies between 2.3-4.8 mg/dl (0.57-1.2 mmol/L) to be aberrant and also it has been noted in the in-vitro experiments which showed an increased set point in SHPT.

There are also some studies which states that the set point of the PTH- calcium curve changes with variation in extracellular calcium i.e., decreases with hypocalcaemia and increases with hypercalcaemia.

There is a lack of comparability in the iPTH levels and it remained as a problem for the management of ESRD. This lack of comparability in iPTH levels is due to two entities: In ESRD patients due to decreased kidney function there is accumulation of large and small fragments of PTH, which interfere with two antibodies that are intended to

bind iPTH.<sup>[12,13,14]</sup> The standards or calibrators used to determine iPTH vary from company to company which would have potential to cause assay interference.

The iPTH levels can be used as a criterion in treating ESRD if there is a development of a universal reference panel to use in standardization of commercial iPTH assay. Though the set point for the patients on hemodialysis is the measure of ionized Calcium, the influence of SHPT on the set point of the PTH-calcium curve is controversial. It is thus evident by the facts of intact PTH - Calcium curve, there is a need for accurate method for early diagnosis for patients of SHPT in stages 3-5 and it can be done by calculating ratios of serum Calcium-intact PTH and ionized Calcium intact PTH-as shown in table-2 & figure-1, as ionized Calcium is a better parameter for Calcium status in renal causes of concern, which also happens to be physiologically active form of Calcium in plasma, when associated with intact PTH as shown as elevated parameter in SHPT and inversely proportional to Calcium levels.

If we follow a universal reference panel in standardization of iPTH assay then the iPTH value <90 pg/ml, ionized calcium <2.3 mg/dl, total calcium <5 mg/dl can be used as cut off in determining the severity of SHPT in patients undergoing hemodialysis and is associated with chronic kidney disease. Evaluation of such parameters regularly may result in effective management of individuals with chronic kidney disease.

Thus, by following universal reference panel determination of plasma in the form of ratios of iPTH to serum Calcium and ionized Calcium, where in present study the intact PTH to Calcium shows 7.4 folds increase & especially the ratio of Intact PTH to ionized Calcium which shows the 7.3 folds increase is a reliable means of studying the hyperparathyroidism associated with chronic renal disease. Hence the ratios calculation may impose the importance of criteria for assessment of the disease in ESRD stage for early diagnosis and treatment and the containment of the morbidity and mortality of the disease, the potential need of these biomarkers plays a key role in the severity of the disease.

There by using the ratios in universal reference panel determination, in plasma/serum for intact iPTH to serum ionized calcium and intact PTH to serum Calcium will show a useful means of studying the hyperparathyroidism associated with chronic renal disease<sup>[15]</sup> leading to complication of SHPT, as revealed in previous studies that complications appear 40% in stage -3 and 80% in stage-5, it could be better to impact these with the use of a method with accuracy for prevention of adverse complications.

Hence, the present study on ratios of parameters will be

useful in containment of ESRD progression shows relevance to patients with SHPT undergoing hemodialysis and relates to increase of intact PTH response to decrease of ionized Calcium in patients with SHPT.

## CONCLUSION

As Ionized calcium, which accounts for 50% to 55% of total calcium, is the physiologically active form of calcium. Low ionized calcium values are often seen in renal disease, critically ill patients, or patients receiving rapid transfusion of citrated whole blood or blood products and also in the present study though it showed that 50% of ionized calcium to that of Total Calcium, the relevance of Ratios of serum calcium-intact PTH and ionized Calcium-intact PTH highlights the significance of activities among haemodialysis patients in the diagnosis of secondary hyperparathyroidism at a early stage of ESRD and It should be used as reference panel determinations as a parameter for early detection of complication of the disease.

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## CONFLICT OF INTEREST:

The authors declared no conflict of interest.

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## REFERENCES

- Wei Y, Lin J, Yang F, Li X, Hou Y, et al. Risk factors associated with secondary hyperparathyroidism in patients with chronic kidney disease. *Exp and Therapeutic Med.* 2016; 12:1206-121-2.
- Sarah Tomasello. Secondary Hyperparathyroidism and chronic kidney disease. *Diabetes Spectrum.* 2008; 21(1):19-25.
- Buritt MF, Picrides AM. Comparative studies of total and ionized calcium in serum in normal subjects and patients with renal disorders. *Mayo Clin Prac.* 1980; 55:606-13.
- Sudhakar T et al , The Set Point of Intact Parathyroid Hormone-Ionized Calcium Curve during the Progression of Secondary Hyperparathyroidism among Patients Undergoing Haemodialysis. *Am J Med Biol Res.* 2014; 2(4):87-90.
- Barnett RN. The medical usefulness of stat tests. *Am J Clin Pathol.* 1973; 69:520.
- National Kidney Foundation. K/DOQI Clinical practice guidelines for bone metabolism and disease in chronic kidney disease. *Am J Kidney Dis.* 2003; 42(4):S1-S201.
- Kidney disease: Improving Global Outcomes (KDIGO) CKD-MBD Work group. KDIGO clinical practice guidelines for the diagnosis evaluation, prevention, and treatment of chronic kidney disease-mineral & bone disorder (CKD-MBD). *Kidney Int.* 2009; 76 (113):S1-S130.
- Suetonia C Palmer, Andrew Hayen, Petra Macaskill, Fabio Pellegrini, Jonathan C Crig, et al. Serum levels of Phosphorus, Parathyroid hormone, and calcium and risks of death and cardiovascular disease in individuals with chronic kidney disease. *JAMA.* 2011; 305(11):1119-1127.
- Monier Faugere MC, Geng Z, Mawad H et al. Improved assessment of bone turnover by the PTH (1-84)/ large C-PTH fragments ratio in ESRD patients. *Kidney Int.* 2001; 60(4):1460-8.
- Mizunashi K, Furukawa Y, Goto MM, Abe K. Sigmoidal curve shift in idiopathic hypoparathyroidism and pseudohypoparathyroidism. *Am Soc Nephrol.* 1998; 62(4):290-4.
- Francis S. Greenspan, David G. Gardner. Basis and clinical Endocrinology: Mineral Metabolism and metabolic bone disease chapter 8; 6th edition, Mc Graw Hill Publishers; 2000; 277-278.
- Brossard, CM, Roy L, Lepage R, Gascon Barre MD Amor P. Accumulation of a non (1-84) molecular form of parathyroid hormone (PTH) detected b intact PTH assay in renal failure: importance in the interpretation of PTH values. *J Clin Endocrino Metab.* 1996; 81:3923-9.
- Brossard JH, Lepage R, Cardinal H, Roy L, Dorais, et al. Influence of glomerular filtration rate on non (1-84) Parathyroid hormone(PTH) detected by intact PTH assays. *Clin Chem.* 2000; 46:697-703.
- Lepage R, Roy L, Brossard JH, Rousseau L, Dorais C, Lazure C, et al. A non (1-84) circulating parathyroid hormone (PTH) fragment interferes significantly with intact PTH commercial assay measurements in uremic samples. *Clin Chem.* 1998; 44:805-9.
- Pietila K, Morsky P, Pastemack A, Mustonen J, Koivula T. Intact PTH, ionized calcium and calcium infusion test in the evaluation of hyperparathyroidism in chronic renal failure. *Nephron.* 1987; 47(4):284-9.