# *Comparison Between Ionized Calcium and Corrected Calcium in Relation to iPTH in Patients on Regular Hemodialysis*

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# مقارنة بين الكالسيوم المتأين والمصحح المرتبط بهرمون الباراثيرمون فى مرضى الغسيل الكلوى الدموى

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توطئة للحصول على درجة الماجستير فى الباطنة العامة

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" وقل رب زدنی علماً "

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*To my family*

# Introduction

*S*econdary hyperparathyroidsm is frequently observed in patients with chronic renal failure ***(Locatelli et al., 2002).***

*S*econdary hyperparathyroidism is a result of hypocalcaemia, hyperphosphataemia, and reduced levels of 1,25 dihydroxyvitamin D3***(Horl, 2004).***

*H*yperparathyroidism is not only associated with renal bone disease but also with excess cardiovascular morbidity and mortality in these patients ***(Young et al., 2004)***.

*Cl*inical guidelines for the treatment of disturbances in mineral and bone metabolism in patients with chronic kidney disease have recently been published .The target concentrations for calcium,phosphorus and calcium phosphorus product are close to the normal range even in patients with chronic kidney disease stage 5 ***(Am J Kidney Dis, 2003).***

*T*he main factor for regulation of parathyroid hormone (PTH)secretion is the extra cellular ionized calcium concentration ***(Slatopolsky et al., 1998)***

*I*n clinical guidelines, the target level for serum calcium is given as albumin-corrected total calcium concentration and no target level is given for the concentration of ionized calcium ***(Am J Kidney Dis, 2003).***

*A* variety of formulae have been proposed to permit calculation of the albumin-corrected total calcium or ionized calcium from the total calcium and protein concentration,but no data support the use of such algorithms ***(Catherine et al., 2000).***

The sample collection and handling are crucial for an accurate measurement of ionized calcium ***(Catherine et al., 2000).***

# AIM OF THE WORK

The aim of this work is to evaluate the use of ionized calcium as opposed to albumin-corrected total calcium in assessment of calcium status in haemodialysis patients with the same dialysate calcium level and to correlate the results of both, albumin corrected calcium and ionized calcium to the iPTH level

# Chronic Renal Failure and 2ry Hyperparathyroidism

**Historical background**

The parathyroid glands were first described in 1850 at the autopsy of an Indian rhinoceros by Sir Richard Owen, conservator of the Hunterian Museum of the Royal College of Surgeons of England ***(Owen, 1862)***.

Thirty years later, an illustrated anatomical and histological description in animals and humans was given by Ivar Sandstrom, a medical student from Uppsala ***(Sandstrom, 1890)***.

Felix Mandl in Vienna was the first to undertake parathyroid surgery in 1925, successfully removing a parathyroid adenoma in a patient with osteitis fibrosa cystica ***(Lucubrate, 1994).***

In the same period, the first American patient diagnosed with hyperparathyroidism needed seven operations before an adenoma was found in the mediastinum ***(Bauer and Federman, 1962)***.

Parathyroid hormone (PTH) extracts were first prepared in the early 1920s ***(Collip, 1925).***

In the 1980s, PTH was sequenced, its gene ***(Weaver et al., 1984)*** and its receptor were cloned and improved

chemiluminescent immunoassays for intact PTH were developed ***(Schneider et al., 1993)***.

The recent cloning of the calcium receptor in 1993 opened new perspectives for understanding the regulation of parathyroid function ***(Brown et al., 1993)***.

## Introduction

Chronic kidney disease (CKD) is almost constantly associated with disturbances of calcium and phosphate metabolism. These disturbances occur early in the course of CKD. Initially, they are characterised by a tendency towards hypocalcemia, fasting hypophosphatemia, and diminished plasma calcitriol concentration, together with a progressive increase in plasma intact parathyroid hormone (iPTH) and the development of osteitis fibrosa. The latter is the consequence of a longstanding stimulation of bone turnover by excessive PTH secretion. In the last decade, however, the increasing recognition of this complication led to frequent oversuppression of PTH by the administration of excessive calcium and/or vitamin D supplements, with its skeletal consequence of iatrogenic low-turnover bone disease. In recent years, nephrologists became progressively aware of the fact that the abnormally high calcium and phosphate levels associated with both hyper and hypoparathyroidism are detrimental to CKD patients, not only in terms of abnormal bone structure and strength, but also in terms of soft-tissue calcification and

cardiovascular as well as all-cause mortality ***(Moe and drueke, 2003)*.**

Secondary hyperparathyroidism is common in patients with severe chronic kidney disease requiring dialysis therapy. In this disorder of bone, there is decrease in renal production of 1,25-dihydroxyvitamin D3, and hypocalcaemia that develop during the course of progressive kidney disease ***(Martinez et al., 1997)***.

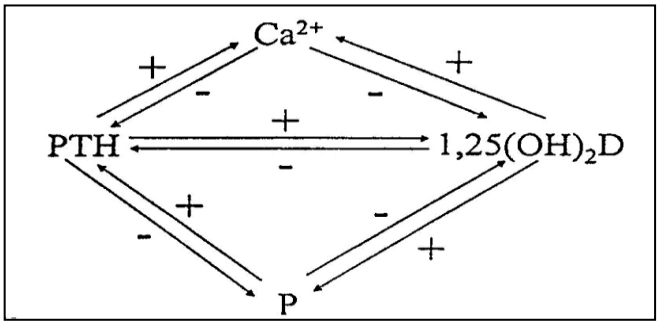



***Fig. (I):*** *Interrelationships between* $Ca^{+2}$, phosphate, PTH and 1,25 $(HO)_2$ $D_3$ *concentrations* ***(Silver,2000).***

There is uncertainty about the initial steps. The processes that lead to increased PTH secretion probably become operative in the early stages of renal insufficiency and continue throughout the life of the patient. So, the blood levels of PTH become elevated early in the course of renal insufficiency even in patients with mildly abnormal renal function ***(Massry, 1989).***

***Sequence of events in early renal failure***

The precise sequence of metabolic anomalies in incipient CKD leading to secondary (2ry) hyperparathyroidism remains a matter of debate. Many years ago, it was postulated that a retention of phosphate in the extracellular space due to the decrease in glomerular filtration rate and the accompanying reduction in plasma ionized calcium concentration was the primary event in the pathogenesis of 2ry hyperparathyroidism. These anomalies would only be transient and a new steady state would rapidly occur, with normalized plasma calcium and phosphorus in response to excessive PTH secretion and the well-known effect of this hormone on tubular reabsorption of phosphate ("trade-off hypothesis" of Bricker and Slatopolsky) ***(Slatopolsky et al., 1972)***.

However, this hypothesis has become less attractive since it was demonstrated that plasma phosphorus is not often elevated in early CKD. It is generally normal and may be even moderately diminished in some cases, and the urinary elimination of phosphate after an oral overload is actually accelerated ***(Llach et al., 1977)***.

Nonetheless, one could argue that in early renal failure normal or even subnormal concentrations of plasma phosphorus might be observed subsequent to a slight, initial increase, causing an enhanced release of PTH which in turn corrects plasma phosphorus immediately, due to a permanent inhibition of tubular phosphate reabsorption ***(Saito et al., 2004).***

Another, recently identified factor involved in the control of serum phosphorus may also play a role, namely fibroblast growth factor-23 (FGF-23) ***(Saito et al., 2004)***.

This factor decreases plasma phosphorus by reducing tubular phosphate reabsorption similar to, but independent of PTH, and decreases the renal synthesis of calcitriol, in contrast to the action of PTH ***(Imanishi et al., 2004)***.

In turn, calcitriol and PTH appear to increase serum FGF-23 whereas phosphate loading or deprivation do not change its serum levels ***(Larsson et al., 2003)***.

Circulating FGF-23 levels increase with the progression of chronic renal failure and may contribute to the development of 2ry hyperparathyroidism ***(Shigematsu et al., 2004).***

In early CKD stages, disturbances of calcium metabolism may already be present. They include a calcium deficiency state due to a decrease in oral calcium intake and an impairment of active intestinal calcium absorption, a tendency towards hypocalcemia due to skeletal resistance to the action of PTH, and a reduced expression of the calcium-sensing receptor (CaR) in the parathyroid cell. All these factors may contribute to the development of parathyroid overfunction. Their relative importance increases with the progression of CKD. It also depends on individual patient characteristics such as the underlying type of nephropathy, comorbidities, dietary habits, and appetite ***(Moallem et al., 1998).***

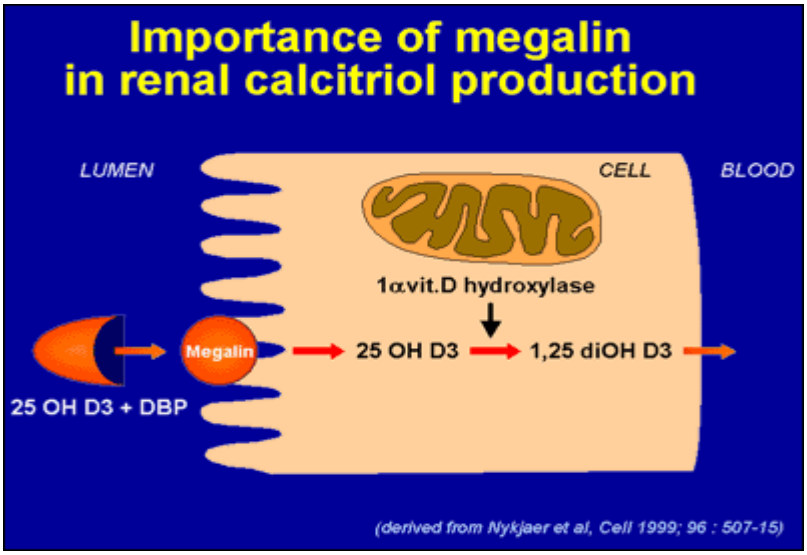
***Role Inhibition of calcitriol synthesis in early CRF*.**

A primary role of the disturbed renal synthesis of calcitriol in incipient CKD has become the preferred hypothesis in the last decade. A relative or absolute impairment of renal calcitriol production could well be the most important player in the initial sequence of events leading to secondary 2ry hyperparathyroidism. The major underlying cause would be a reduced tubular transformation of 25OH vitamin D (calcidiol) to calcitriol, due to an intracellular accumulation of phosphate. In addition, the progressive loss of nephron mass and the well-known tendency towards metabolic acidosis could also play a role ***(Dunlay et al., 1989)***.

Another hypothesis can be proposed, based on the observation that calcidiol does not penetrate into proximal tubular epithelium from the basolateral side, but only from the luminal side. Thus it has been shown that the complex formed by calcidiol and its binding protein (DBP) has to be ultrafiltered by the glomerulus before it enters this epithelium from the apical side and serves as substrate for the renal enzyme, 1-α-OH vitamin D hydroxylase ***(Nykjaer et al., 1999)***.

This obligate entry pathway was actually discovered in mice by serependicity, namely after the knock-out of the *megalin* gene, whose protein product is a multifunctional brush border membrane receptor. The deletion of this gene induced a state of vitamin D deficiency/rickets. It could then be shown that binding of the calcidiol/DBP complex to megalin was

followed by endocytosis across the proximal tubule brush border membrane, thereby making the vitamin D metabolite available as a substrate for 1-α-OH vitamin D hydroxylase and its transformation into calcitriol (**Figure2**). In case of a reduction of glomerular filtration rate a decreased transfer of the calcidiol-DBP complex into the proximal tubular fluid would occur and hence a reduced availability of calcidiol substrate for luminal reabsorption and ultimately calcitriol formation. However, the validity for the human situation of this mechanism established in the mouse has subsequently been questioned since 1-α-OH vitamin D hydroxylase expression was found not only in proximal, but also in distal tubular epithelium of human kidney, that is in tubular areas in which megalin apparently is not expressed ***(Zehnder et al., 1999).***




**Figure(2)** *Importance of megalin in renal calcitriol production*