INTRODUCTION

Disturbances of bone and mineral metabolism are a hallmark of chronic kidney disease (CKD). ***(Moe et al., 2006)***

At the onset of chronic kidney disease, the systemic mineral metabolism and bone composition start to change. This alteration is known as chronic kidney disease - mineral bone disease (CKD-MBD). The greater the decrease in renal function, the worse the progression of CKD-MBD. CKD-MBD involves serum calcium, serum phosphate, parathyroid hormone (PTH), and vitamin D metabolism derangement, and its main endpoints are altered bone turnover, bone mineralization, bone volume, bone linear growth, bone strength, and vascular/other soft tissue calcification. ***(Liu et al., 2013)***

CKD-MBD develops early in the course of CKD as an adaptive response to altered hormonal status, reduced production of calcitriol (1, 25-dihydroxyvitamin D3, or 1, 25[OH]2D), and increased secretion of the fibroblast growth factor- 23 (FGF-23) and PTH to maintain a normal serum concentration of calcium and phosphorus. These events start when the glomerular filtration rate (GFR) falls below 60 mL/min per 1.73 m2 (CKD stage 3) and are almost universally present in advanced CKD stages (CKD stages 5 and 5D) ***(Cunningham et al., 2011).***

According to KDIGO guidelines, the traditional types of renal osteodystrophy (ROD) classified by bone biopsies have been defined on the basis of turnover and mineralization as follows: mild, slight increase in turnover and normal mineralization; osteitis fibrosa, increased turnover and normal mineralization; osteomalacia, decreased turnover and abnormal mineralization; adynamic, decreased turnover and acellularity; mixed, increased turnover with abnormal mineralization. ***(KDIGO guidelines, 2009)***

Early recognition and management of the CKD-MBD is believed to be an essential step to avoid future complications ultimately impacting outcome. The KDIGO clinical practice guidelines of CKD-MBD recommend monitoring and treating abnormal serum levels of calcium, phosphorus, and PTH as early as stage 3 CKD. ***(Karohl and Raggi, 2012)***

Fracture is a significant cause of morbidity and mortality and the incidence of fractures is also increasing with the increasing average age of dialysis patients. ***(Maeno et al., 2009)***

Bone mineral density (BMD) as measured by dual-energy X-ray absorptiometry (DEXA) relates to fracture risk in subjects with normal renal function, in patients with CKD and patients on haemodialysis, although not evident from all studies or in all patient populations. ***(Jamal et al., 2006)***

DEXA measures attenuation through the body tissues of low doses of x-ray, allowing the determination of both bone mineral content and bone area, from which BMD is calculated. In patients on hemodialysis therapy, DEXA of the lumbar spine often overestimates BMD, perhaps because of extraosseous densities, such as calcified blood vessels, or decreases in cortical and increases in trabecular bone in response to increased PTH levels, suggesting that the hip or forearm may be better sites for measuring BMD. ***(National Kidney Foundation, 2010)***

Assessment of bone turnover markers (BTMs) has lately been recommended for CKD patients and dialysis patients. ***(KDIGO guidelines, 2009)***

The recommended BTMs include total alkaline phosphatases (t-ALP) and bone-specific alkaline phosphatases (b-ALP), which in combination with serum parathyroid hormone (PTH) have been found useful for assessment of bone loss. ***(Park et al., 2010)***

Specific immunoassays for bone ALP have been available for nearly 20 years, but their use has not become widespread in nephrology, probably reflecting perceived difficulties of measurement and the primary role assigned to PTH in the management of CKD-MBD. Bone ALP has a relatively long half-life of 1–2 days, and its plasma concentration

depends only on its rate of release from the osteoblasts and on its hepatic degradation. Unlike PTH, bone ALP does not accumulate with progressive loss of GFR. ***(Urena and De Vernejoul., 1999)***

Further, bone ALP has a good relationship with bone histology and bone mineral density and is also a good predictor, with DEXA-derived bone mineral density, of future fracture risk in dialysis patients. ***(Iimori et al., 2012)***

AIM OF THE WORK

The aim of this study is to study the possible correlation of DEXA scan to bone specific alkaline phosphatase in prevalent hemodialysis patients.

RENAL OSTEODYSTROPHY

Disorders of mineral and bone metabolism are common in patients with CKD. Traditionally, these disorders have collectively been called renal osteodystrophy.

However, in 2006, an international work group convened by Kidney Disease: Improving Global Outcomes (KDIGO) recommended that the term "renal osteodystrophy" be exclusively used to define bone pathology associated with CKD. Moreover, given that mineral and bone disorders contribute to CKD-associated cardiovascular disease and high mortality rates, KDIGO recommended that the new term chronic kidney disease-mineral and bone disorder (CKD-MBD) be used to describe the broader systemic disorder that occurs as a result of CKD. ***(KDIGO 2009)***

CKD-MBD is defined as a systemic disorder of mineral and bone metabolism due to CKD, manifested by either one or a combination of the following three components:

- Abnormalities of calcium, phosphorus, parathyroid hormone (PTH), or vitamin D metabolism.
- Abnormalities in bone turnover, mineralization, volume linear growth, or strength.
- Extra-skeletal calcification.

The pathophysiology of the disorder is complex and involves a number of feedback loops between the kidney, bone, intestine, and the vasculature. The main goal of this system is maintenance of calcium and phosphorus balance, often at the expense of abnormalities in other components of the system.

While most elements of CKD–MBD are usually present when the glomerular filtration rate (GFR) falls below 40 mL/min, some components may be observed earlier in the course of CKD and precede the onset of clinically detectable abnormalities in serum phosphorus, calcium, PTH, and vitamin D. ***(Fang Y et al., 2014)***

Abnormalities of Calcium, Phosphorus, PTH, or Vitamin D Metabolism

Phosphate retention and secondary hyperparathyroidism underlie the biochemical abnormalities that characterize CKD-MBD. Secondary hyperparathyroidism begins early in the course of CKD, and the prevalence increases as kidney function declines (particularly to estimated glomerular filtration rate [eGFR] <60 mL/min per 1.73 m2). Secondary hyperparathyroidism occurs in response to a series of abnormalities that initiate and maintain increased parathyroid hormone (PTH) secretion. ***(Cunningham J et al., 2011)***

The main abnormalities that contribute to the pathogenesis of secondary hyperparathyroidism are:

- Phosphate retention.
- Decreased free ionized calcium concentration.
- Decreased 1, 25-dihydroxyvitamin D (calcitriol) concentration.
- Increased fibroblast growth factor 23 (FGF-23) concentration.
- The reduced expression of vitamin D receptors (VDRs), calcium-sensing receptors (CaSRs), fibroblast growth factor receptors, and klotho in the parathyroid glands.

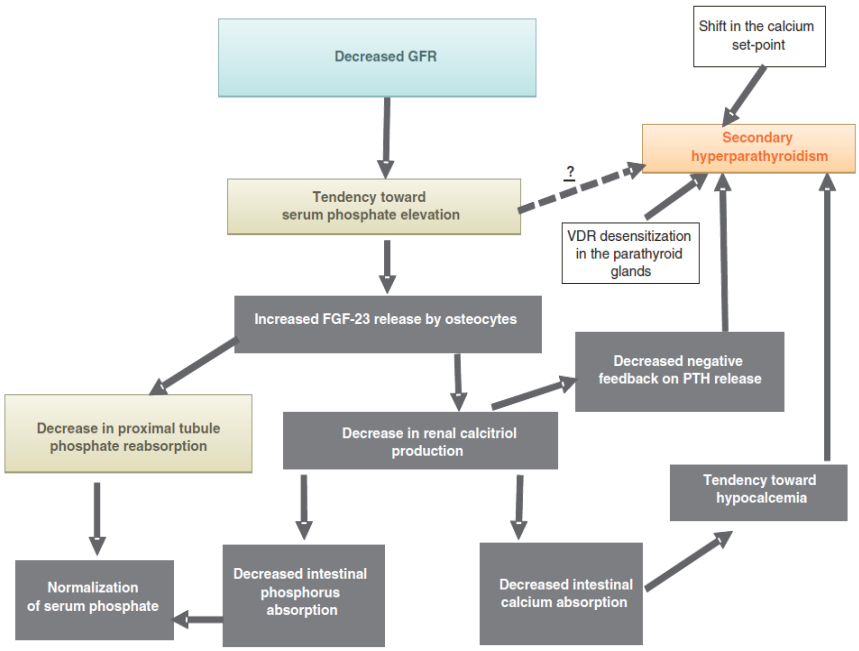

Figure 1: Pathophysiological mechanism of secondary hyperparathyroidism related to chronic kidney disease.

The relative importance of these abnormalities in triggering PTH production can be understood by examining the changes in their concentrations in relation to the increase in PTH during the course of CKD. Increased PTH concentrations first become evident when the eGFR drops below 60 mL/min per 1.73 m2. At that time, serum calcium and phosphate concentrations are normal and remain within normal ranges until the eGFR decreases to approximately 20 mL/min per 1.73 m2. ***(Levin A et al., 2007)***

Circulating calcitriol concentrations begin to fall much earlier, when the GFR is <60 mL/min per 1.73 m2 (occasionally even at higher eGFRs and are typically markedly reduced in subjects with end-stage renal disease (ESRD) ***(Kestenbaum et al 2005)***

The primary reason for the decline in calcitriol concentration is likely an increase in FGF-23 concentration, rather than the loss of functioning renal tissue ***(Gutierrez O et al., 2005)***

Hyperphosphatemia (a relatively late phenomenon in CKD) may also contribute to the decline in calcitriol synthesis by suppression of 1-alpha-hydroxylase enzyme.

Thus, progressive kidney dysfunction results in calcitriol deficiency and hyperphosphatemia, both of which result in

hypocalcemia. These abnormalities directly increase PTH concentrations via different mechanisms.

Phosphate retention has long been thought to be the initial trigger for many of the components of CKD-MBD, particularly the increased PTH secretion. A tendency to phosphate retention, beginning early in CKD as the decline in GFR decreases the filtered phosphate load, is thought to play a central role in the development of secondary hyperparathyroidism ***(Martin KJ et al., 2007)***

Three major and not mutually exclusive theories have been proposed to explain how phosphate retention initially promotes PTH release ***(Block et al 2004)***:

- The induction of hypocalcemia
- Decreased formation or activity of calcitriol (1, 25-dihydroxyvitamin D, the active form of vitamin D that is produced by the kidney)
- Increased PTH gene expression
- Phosphate retention contributes to secondary hyperparathyroidism in early CKD at least in part by decreasing serum free calcium concentration and calcitriol synthesis ***(Koh et al 2001)***.

If phosphate retention is prevented by restricting phosphate intake in proportion to the reduction in GFR, the rise in plasma PTH concentration can be prevented ***(Llach F.., 1995)***

Even in patients who have moderate renal insufficiency and already established secondary hyperparathyroidism, lowering the plasma phosphate concentration with oral phosphate binders can partially reverse the hypocalcemia, hyperparathyroidism, and calcitriol deficiency ***(Elder & Grahame 2002)***

From the viewpoint of phosphate homeostasis, the initial elevation in PTH secretion is appropriate since the ensuing increase in phosphate excretion lowers the plasma phosphate concentration toward normal. Among patients with severely reduced GFR, PTH inhibits proximal tubule phosphate reabsorption from the normal 80 to 95 percent to as low as 15 percent of the filtered phosphate ***(Cunningham J et al., 2011)***

Hyperparathyroidism also tends to correct both the hypocalcemia (by increasing bone resorption) and the calcitriol deficiency (by stimulating the 1-hydroxylation of calcidiol [25-hydroxyvitamin D] in the proximal tubule).

However, the hyperparathyroidism is maladaptive over the long-term. Furthermore, the effect of PTH on phosphate

balance changes as GFR declines. Since phosphate reabsorption by the renal tubules cannot be lowered below a minimum threshold, continued PTH-induced release of phosphate from bone can actually exacerbate the hyperphosphatemia ***(Elder & Grahame 2002)***.

Hyperphosphatemia may also have a direct effect on PTH synthesis and secretion that is independent of the plasma concentrations of calcium and calcitriol in advanced CKD ***(Silver J, Levi R. 2005)***

Hyperphosphatemia also stimulates the secretion of FGF-23, which acts to suppress PTH secretion ***(Wetmore et al 2010)***.

Decreased calcitriol activity — Plasma calcitriol concentrations generally fall below normal when the GFR is <60 mL/min per 1.73 m2, although low concentrations have also been found in some patients with higher eGFR (ie, <80 mL/min per 1.73 m2) ***(Gutierrez et al 2008)***.

Initially, the decline in calcitriol concentration is likely to be due to the increase in FGF-23 concentration rather than the loss of functioning renal mass. The FGF-23-induced decrease in calcitriol begins early, when the GFR drops to <70 mL/min per 1.73 m2. However, in advanced CKD, hyperphosphatemia and loss of renal mass may also contribute to the decline in calcitriol synthesis.

Phosphate retention (or perhaps increased phosphate concentrations in the proximal tubule) can directly suppress the renal synthesis of calcitriol by inhibiting 1-alpha-hydroxylase activity ***(Llach F. 1995)***

FGF-23 decreases the synthesis of calcitriol by suppressing the activity of 1-alpha-hydroxylase ***(Gutierrez O et al., 2005)***

Increased dietary phosphate load and increased calcitriol stimulate the secretion of FGF-23, predominantly by bone osteocytes, which act on target tissues by binding to and activating the FGF-23 receptor in the presence of its co-receptor, klotho. ***(Urakawa I et al., 2006)***

Indirect effects on PTH are achieved through decreased intestinal absorption of calcium and calcium release from bone, both of which promote the development of hypocalcemia, which stimulates PTH secretion. ***(Malluche HH et al., 2002)***

Calcitriol normally acts on the VDR in the parathyroid gland to suppress PTH transcription, but not PTH secretion A decrease in calcitriol concentrations also lowers the number of VDRs in the parathyroid cells ***(Denda M et al., 1996***)

The lack of calcitriol and the decreased number of receptors may both promote parathyroid chief cell hyperplasia and nodule formation through potential nongenomic effects.

Even normal plasma calcitriol concentrations do not necessarily preclude a role for initial calcitriol deficiency since the ensuing secondary hyperparathyroidism will increase calcitriol synthesis. ***(Usatii M et al., 2007)***

More importantly, low calcitriol concentration can increase PTH secretion by removing the inhibitory effect of calcitriol on the parathyroid gland ***(Hasegawa et al 2010)***.

The administration of calcitriol, on the other hand, can partially reverse the hyperparathyroidism both in early and advanced disease. Calcitriol and other vitamin D analogs can reduce parathyroid cell proliferation in vitro, in part by blocking the increase in the growth-promoting factor transforming growth factor-alpha (TGF-alpha) ***(Dusso et al 2001)***.

Hypocalcemia and Calcium-Sensing Receptor

Calcium is a major regulator of PTH secretion. Minute changes in the serum ionized calcium are sensed by a specific membrane receptor, the CaSR, which is highly expressed on the surface of the chief cells of the parathyroid glands ***(Rodriguez et al 2005)***.

Changes in PTH secretion in response to serum calcium are tightly regulated by the CaSR.

The fall in serum calcium concentration in CKD, as sensed by the CaSR, is a potent stimulus to the release of PTH. This is best shown in mouse and human genetic studies, in which extracellular calcium, acting through the CaSR, was the major regulator of PTH transcription, secretion, and parathyroid gland hyperplasia ***(Panda et al 2004)***.

Total serum calcium concentration decreases during the course of CKD due to phosphate retention, decreased calcitriol concentration, and resistance to the calcemic actions of PTH on bone. PTH secretion varies inversely with serum calcium concentration. ***(Silver J et al., 2005)***

Persistently low serum calcium concentrations also appear to directly increase PTH mRNA concentrations via posttranscriptional actions and stimulate the proliferation of parathyroid cells over days or weeks. ***(Silver J et al., 2005)***

In CKD, the number of CaSRs may be reduced in hypertrophied parathyroid glands, particularly in areas of nodular hypertrophy. ***(Cañadillas S et al., 2005)***

Decreased expression of the CaSR appears to be related to the proliferation of parathyroid tissue, and both may be related to increased phosphorus. The change in receptor number can lead to inadequate suppression of PTH secretion by calcium,