Hormonal and Mineral Changes in Early Stages of Chronic Kidney Diseases

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Abstract- This study evaluates divalent ion abnormalities (DIA) and the hormonal changes throughout the spectrum of early CKD stages (1-4) as defined by K/DOQI. A total of 96 patients (48.96% males, mean age 62±13 yrs) with CKD 1 to 4, were prospectively evaluated and followed-up. There were (20, 27, 32, and 17 patients in CKD-1, 2, 3, and 4 respectively). The diagnosis was confirmed by renal biopsy, Table-1. Mean serum creatinine (62±32 umol/L). Plasma levels of calcium, phosphorus, calcitriol (CTRL), and parathyroid hormone (PTH) were evaluated among the groups. A 24-hour urinary creatinine, calcium (Uca), phosphorus (Up), creatinine clearance and fractional excretion of calcium (FeCa), and phosphorus (FeP) were also compared. PTH was measured using the standard IRMA test (normal values 10-50 pg/dl), and calcitriol was measured by RIA test (normal values are 74.5 – 169 pmol/l). The exclusion criteria are nephrolithiasis, hypercalcemia, proteinuria >3g/24 hrs, previous renal transplant, and therapy with steroids or anticonvulsants (Phenytoin).

Keywords: divalent ion abnormality, CKD, calcitriol, secondary hyperparathyroidism, hyperphosphatemia, hypocalcemia, parathyroid hormone (PTH).

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Hormonal and Mineral Changes in Early Stages of Chronic Kidney Diseases

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Abstract- This study evaluates divalent ion abnormalities (DIA) and the hormonal changes throughout the spectrum of early CKD stages (1-4) as defined by K/DOQI. A total of 96 patients (48.96% males, mean age 62±13 yrs) with CKD 1 to 4, were prospectively evaluated and followed-up. There were (20, 27, 32, and 17 patients in CKD-1, 2, 3, and 4 respectively). The diagnosis was confirmed by renal biopsy, Table-1. Mean serum creatinine (62±32 umol/L). Plasma levels of calcium, phosphorus, calcitriol (CTRL), and parathyroid hormone (PTH) were evaluated among the groups. A 24-hour urinary creatinine, calcium (Uca), phosphorus (Up), creatinine clearance and fractional excretion of calcium (FeCa), and phosphorus (FeP) were also compared. PTH was measured using the standard IRMA test (normal values 10-50 pg/dl), and calcitriol was measured by RIA test (normal values are 74.5 – 169 pmol/l). The exclusion criteria are nephrolithiasis, hypercalcemia, proteinuria >3g/24 hrs, previous renal transplant, and therapy with steroids or anticonvulsants (Phenytoin).

The serum Ca levels were not different among the four groups (Fig-1), however, urinary calcium decreased progressively from 207±11 (CKD-1) to 56±44 (CKD-4, P<0.01), (Fig-2). The urinary calcium excretion was directly correlated with CTRL; and inversely correlated with PTH, (p<0.001 and p<0.01, respectively), (Fig-3). Even though, serum phosphorus increased only in CKD-4 (p<0.01), (Fig-4), it was significantly correlated with the overall decrement of GFR (p<0.0001), (Fig-5). Likewise, the overall decrement in GFR was correlated with UP (p<0.0001), (Fig-6). Serum phosphorus has a positive linear correlation with CTRL and inversely correlated with PTH levels (p<0.0001, and p<0.001), respectively, (Fig-7, and Table-2). The Ca x P product was also positively correlated with PTH and negatively with CTRL, (p<0.001 and p<0.001, respectively), (Fig-8). As expected, there was a positive increase in PTH levels with increased CKD stage, this was significant in CKD-3 (p<0.001), (Fig-9). There was a significant correlation between GFR and PTH levels (p<0.0001), (Fig-10). Finally, CTRL levels decreased in CKD-3 (p<0.001), (Fig-11, Fig-12 and Table-3), and were overall, correlated with the decrement in GFR (p<0.0001).

Conclusion: A significant positive calcium and phosphate balance together with a deficit of CTRL develop early in CKD patients. Secondary hyperparathyroidism with divalent ion and CTRL abnormalities are important events in CKD patients requiring the development and implementation of preventive and therapeutic interventions to improve prognosis in CKD patients.

Keywords: divalent ion abnormality, CKD, calcitriol, secondary hyperparathyroidism, hyperphosphatemia, hypocalcemia, parathyroid hormone (PTH).

I. INTRODUCTION

Chronic kidney disease afflicts between 2.5 and 18 million Americans with millions more at increased risk for the disorder (Jones 1998, NKF 2002). The national kidney foundation (K/DOQI) classified kidney disease into 5 stages based on the estimated glomerular filtration rate (eGFR) before patients go on dialysis or for transplantation. As the GFR declines, the incidence of co-morbid conditions such as hypertension, anemia, left ventricular hypertrophy, mineral and bone disorders (CKD-MBD) increase.

Disturbances of bone and mineral metabolism are common in CKD. Increase in serum phosphate and decrease in 1, 25-dihydroxyvitamin D3 occur early in the course of the disease (GFR<60 ml/min/1.73m²), whereas hypocalcemia is a relatively late finding (GFR<20 mL/min/1.73 m²).

The pathophysiology of CKD-MBD involves many feedback loops between the intestine, the kidney, and the vasculature to maintain calcium and phosphorus balance. 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 2014, Pereira 2009, Sabbagh 2012, Oliveira 2010, Isakova 2011).

II. SUBJECTS AND METHODS

This study evaluates divalent ion abnormalities (DIA) and the hormonal changes throughout the spectrum of early CKD stages (1-4) as defined by K/DOQI. A total of 96 patients (48.96% males, mean age 62±13 yrs) with CKD 1 to 4, were prospectively evaluated and followed-up. There were (20, 27, 32, and 17 patients in CKD-1, 2, 3, and 4 respectively). The diagnosis was confirmed by renal biopsy, Table-1.

Mean serum creatinine (62±32 umol/L). Plasma levels of calcium, phosphorus, calcitriol (CTRL), and
Parathyroid hormone (PTH) were evaluated among the groups.

A 24-hour urinary creatinine, calcium (Uca), phosphorus (Up), creatinine clearance and fractional excretion of calcium (FeCa), and phosphorus (FeP) were also compared.

PTH was measured using the standard IRMA test (normal values 10-50 pg/dl), and calcitriol was measured by RIA test (normal values are 74.5 – 169 pmol/l).

The exclusion criteria are nephrolithiasis, hypercalcemia, proteinuria >3g/24 hrs, previous renal transplant, and therapy with steroids or anticonvulsants (Phenytoin).

a) Statistical analysis

SPSS software version 9.0 was used to analyse the data. ANOVA or analysis of variance was used to compare group means when applicable.

III. Results

The serum Ca levels were not different among the four groups (Fig-1), however, urinary calcium decreased progressively from 207±11 (CKD-1) to 56±44 (CKD-4, P<0.01), (Fig-2).

The urinary calcium excretion was directly correlated with CTRL; and inversely correlated with PTH, (p<0.001 and p<0.01, respectively), (Fig-3).

Even though, serum phosphorous increased only in CKD-4 (p<0.01), (Fig-4), it was significantly correlated with the overall decrement of GFR (p<0.0001), (Fig-5).

Likewise, the overall decrement in GFR was correlated with Up (p<0.0001), (Fig-6).

Serum phosphorus has a positive linear correlation with CTRL and inversely correlated with PTH levels (p<0.0001, and p<0.001), respectively, (Fig-7, and Table -2).

The Ca x P product was also positively correlated with PTH and negatively with CTRL, (p<0.001 and p<0.001, respectively), (Fig-8).

As expected, there was a positive increase in PTH levels with increased CKD stage, this was significant in CKD-3 (p<0.001), (Fig-9).

There was a significant correlation between GFR and PTH levels (p<0.0001), (Fig-10).

Finally, CTRL levels decreased in CKD-3 (p<0.001). (Fig-11, Fig-12 and Table-3), and were overall, correlated with the decrement in GFR (p<0.0001).

IV. Discussion

Phosphate retention and secondary hyperparathyroidism (SHPT) are the main biochemical abnormalities in CKD-MBD. Secondary hyperparathyroidism begins early in the course of CKD as clearly demonstrated in this study, and the prevalence increases as kidney function declines (particularly to estimated glomerular filtration rate [eGFR] <60 mL/min/1.73 m²). Secondary hyperparathyroidism occurs in response to a series of abnormalities that initiate and maintain increased PTH secretion (Cunningham 2011).

The main abnormalities that contribute to the pathogenesis of SHPT are; i- phosphate retention, ii- decreased free ionized calcium concentration, iii- decreased 1,25-dihydroxyvitamin D (CTRL) concentration, vi- increased fibroblast growth factor 23 (FGF-23) concentration, v- the reduced vitamin receptor expression and calcium sensing receptors in the parathyroid gland.

The increased PTH concentrations becomes evident when the eGFR drops <60 mL/min/1.73 m², CKD-3. At that time, serum calcium and phosphate concentrations are normal and remain within normal ranges until the eGFR decreases to approximately 20 mL/min/1.73 m² (Levin 2007). Circulating CTRL concentrations begin to fall much earlier, when the GFR is <60 mL/min per 1.73 m² (Levin 2007), CKD-3, Fig-12, and are markedly reduced in patients with end-stage renal disease (ESRD) (Pitts 1988). The primary reason for the decline in CTRL concentration is likely an increase in FGF-23 concentration. Even though, FGF-23 was not measured in this study but its role has been demonstrated in other studies (Gutierrez 2005).

Reduced functioning nephrons and hyperphosphatemia are accessory factors for the decline in CTRL (Gutierrez 2005). Hyperphosphatemia is a relatively late phenomenon (CKD-4) and may also contribute to the decline in CTRL synthesis by suppression of 1-alpha-hydroxylase enzyme, Fig-4.

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 2007, NKF 2002, Kates 1997). This could not be supported by this study, Fig-4. Hypocalcemia, decreased activity of CTRL, and increased PTH gene expression have been proposed to explain how phosphate retention initially promotes PTH release (Hruska 1995, Fournier 1992, Liach 1995).

If phosphate is reduced by restricting phosphate intake in proportion to the reduction in GFR, or the use of phosphate binders in established hyperphosphatemia, these measures could prevent the rise in plasma PTH concentration, partially reverse the hypocalcemia, hyperparathyroidism, and CTRL deficiency (Liach 1995).

The secondary hyperparathyroidism is maladaptive over the long-term (Liach 1995), and 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 rise induces release of phosphate from bone can actually exacerbate the hyperphosphatemia which probably happened late in the disease process. Hyperphosphatemia also stimulates the secretion of FGF-23, which acts to suppress PTH secretion (Wetmore 2010, Saito 2005).

Plasma CTRL concentrations generally fall below normal when the GFR is <60 mL/min per 1.73 m², (CKD-3), Fig-12. Low concentrations of CTRL have also been found in some patients with higher eGFR (ie, <80 mL/min per 1.73 m²) (Levin 2007, Liach 1995, Koenig 1992, Wilson 1985, Gutierrez 2008).

The decline in CTRL is first due to increased FGF-23 followed later by reduced functioning renal mass, when GFR drops to <70 ml/min/1.73m². In advance CKD, hyperphosphatemia may play a significant role (Gutierrez 2005). The hyperphosphatemia and low CTRL will have direct and indirect effect on PTH concentration. The indirect effect is achieved via decreased intestinal absorption of calcium as well as release of calcium from bone. These effects propagate hypocalcemia which stimulate PTH secretion (Hsu 1994, Silver 1986, Malluche 2002).

Through vitamin D receptors, CTRL suppress PTH transcription by the parathyroid gland (Brumbaugh 1975). By time, the VDRs concentration in the parathyroid gland decrease and along with low levels of CTRL will promote parathyroid cell hyperplasia and nodular hyperparathyroidism (Denda 1996).

More importantly, low CTRL concentration can increase PTH secretion by removing the inhibitory effect of CTRL on the parathyroid gland (Liach 1995, Slatopolsky 1984), Table-3. The administration of CTRL, on the other hand, can partially reverse SHPT both in early (Wilson 1985) and advanced kidney disease (Slatopolsky 1984).

There is also evidence that decreased responsiveness to CTRL contributes to the development of hyperparathyroidism. In particular, physiologic concentrations of CTRL may be unable to normally suppress PTH secretion, perhaps due to a reduction in the number of VDRs in the parathyroid gland (Denda 1996, Fukuda 1993). Studies in patients on maintenance dialysis reveal that the decrease in receptor density is most prominent in areas of nodular, rather than diffuse, hyperplasia (Fukuda 1993). Therefore, a reduced number of VDRs may contribute both to the progression of SHPT and to the proliferation of parathyroid cells, leading to nodular hyperplasia.

Minute changes in ionized calcium are sensed by the CaSRs in the parathyroid gland which regulate PTH secretion (Rodriguez 2005). The fall in serum calcium concentration in CKD, as sensed by the CaSR, is a potent stimulus to the release of PTH (Li 1998, Panda 2004). Decreased CTRL levels, hyperphosphatemia, and PTH resistance on the bone cause the hypocalcemia of SHP in advanced CKD. This could not be demonstrated in this study, as the level of total calcium is almost normal in all the stages of CKD (1-4).

This apparent controversy could be explained by low ionized calcium level even in the face of normal total calcium level. PTH secretion varies inversely with serum calcium concentration (Silver 2005). Persistently low serum calcium concentrations also appear to directly increase PTH mRNA concentrations via post-transcriptional actions and stimulate the proliferation of parathyroid cells over days or weeks (Silver 2005, Wilson1985).

The shortcoming of this study is the small sample size of patients studied and the fact that it has been carried out in one center which may not be applied widely on different ethnic groups. The measurement of CTRL, PTH, and serum calcium and phosphate are done on snap shot which may not be representative of their dynamic state in living individuals.

V. CONCLUSION

A significant positive calcium and phosphate balance together with a deficit of CTRL develop early in CKD patients. Secondary hyperparathyroidism with divalent ion and CTRL abnormalities are important events in CKD patients requiring the development and implementation of preventive and therapeutic interventions to improve prognosis in CKD patients.

Disclosure: The authors have nothing to disclose.

REFERENCES Références Referencias


