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Evaluation parathyroid hormone function and some minerals in chronic renal failure

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Abstract:
Parathyroid hormone (PTH) in secondary hypoparathyroidism is a very potent uraemic toxin, which affects calcium/phosphate homeostasis and vitamin D in patients with end-stage renal disease (ESRD).The aim of this study to evaluate bone disease and some minerals in chronic renal failure.
Patients and methods: The study was designed on 106 Iraqi subjects age range (20-69 years) with chronic renal failure. The subjects involved in this study 40 conservative patients (21 Males and 19 Females) and 66 hemodialysis patients (44 Males and 22 Females).
Results: PTH increased in chronic renal failure patients and vitamin D decreased in chronic renal failure patients, and more deterioration directly related to the degree of renal failure. Electrolytes (phosphorus, calcium and magnesium) were within the limit of the normal range in conservative and hemodialysis patients but chloride and potassium little rise in stage4 and also phosphorus little rise in stage5 while calcium little decrease in stage5.
Conclusions: PTH increased in CRF and vitamin D decreased in CRF, and more deterioration directly related to the degree of renal failure. Progress deteriorates of PTH begin in stage4 but more deterioration in stage5 and improved in hemodialysis patients, while electrolytes less effected in this study.

INTRODUCTION

The term ‘‘CKD-associated mineral and bone disorders’’ comprises abnormalities in bone and mineral metabolism and/or extra skeletal calcification secondary to CKD pathophysiology [1,2]. Renal osteodystrophy is the spectrum of histologic changes that occur in bone architecture of patients with CKD. Together, both processes cause serum calcium levels to fall resulting in increased secretion of parathyroid hormone (secondary hyperparathyroidism). Parathyroid hormone has a phosphaturic effect. It also increases the calcium levels by increasing bone resorption and promoting 1-a-hydroxylation of 25-hydroxy vitamin D synthesized by the liver (limited effect because of reduced kidney reserve from scarring) [3,4]. Parathyroid hormone (PTH) in secondary hypoparathyroidism is a very potent uraemic toxin, which affects calcium/phosphate homeostasis and vitamin D in patients with ESRD [5].

PTH acts to reduce calcium clearance and stimulates synthesis of 1,25-dihydroxyvitamin D, which stimulates calcium absorption in the gastrointestinal tract [3]. In their normal state, the glands function to keep serum calcium levels within a consistent and tightly controlled range. The glands synthesize and store the PTH, allowing it to respond within minutes of hypocalcemia. Sustained hypocalcemia leads to cellular replication and increased mass of the glands. Calcium and 1,25-dihydroxyvitamin D provide negative feedback at the parathyroid glands to inhibit PTH release. One normal gland is sufficient for adequate secretion of PTH to maintain normal calcium levels [4,6,7].

MATERIALS AND METHODS

The study was designed on 106 Iraqi subjects age range (20-69 years) with chronic renal failure in Baqubah teaching hospital in Ibn Sina Center for Dialysis during the period from 28 February to 23 May 2017. The subjects involved in this study 40 conservative patients (21 Males and 19 Females) and 66 hemodialysis patients (44 Males and 22 Females). The Conservative patients divided in three Subgroups according to the stages of chronic kidney disease:- Stage 3: consisted of (12) patients (5 Male and 7 Female), Stage 4: consisted of (13) patients (8 Male and 5 Female), and Stage 5: consisted of (15) patients (8 Male and 7 Female). The hemodialysis (HD) patients divided in to two Subgroups according to the duration of dialysis: Group A: consisted of (21) patients (16 Male and 5 Female) less than Six months on dialysis and Group B: consisted of (45) patients (28 Male and 17 Female) more than Six months on dialysis. PTH and Vitamin D were estimated in serum of all subjects by using an automated quantitative COBAS e411 test (from Roche, Germany). Electrolytes were estimated in serum of all subjects by using an automated quantitative COBAS 111 (from Roche, Germany).

Statistical Analysis

Data procession software package was used SPSS 20 for windows. Data were expressed as mean ± standard error (M ± SE). Differences between means of two major groups were analyzed by using t-test and the significance was tested at two-tail P value. However, differences among Subgroups were analyzed by using one-way analysis of variance (ANOVA), then if there are significant differences, they were analyzed by least significant difference (LSD) test. The P value of differences < 0.05 was considered significant.

RESULTS

Table (1) shows that the levels of parathyroid hormone in the conservative group (19.91±2.65pmol/L) and in hemodialysis group (22.4±3.32pmol/L) were higher than the upper limit of the normal range (1.6-6.9pmol/L), but without any significant ($p>0.05$) differences between two groups. Vitamin D levels in the conservative group (6.61±0.90ng/mL) and in hemodialysis group (5.63±0.79ng/mL) were lower than the lower limit of the normal range (30-100ng/mL), but without any significant ($p>0.05$) differences between conservative and hemodialysis group. The level of the phosphorus in conservative group (1.77±0.10mmol/L) was higher than the upper limit of the normal range (0.8-1.4mmol/L), while the level of the phosphorus was within the normal range in hemodialysis group (1.47±0.07mmol/L) and was decreased significantly ($p< 0.05$) in hemodialysis group in comparison with conservative group. The levels of calcium, and magnesium were within normal range (2.1-2.6mmol/L; 0.66-1.07mmol/L) in conservative group (2.14±0.04mmol/L; 0.88±0.02mmol/L), and in hemodialysis group (2.17±0.02mmol/L; 0.83±0.02) respectively and showed non-significant ($p>0.05$) differences between two groups.

Table (1) Bone Disease Biomarkers in Conservative and Hemodialysis Groups.

Biomarker	Normal range	Conservative (n=40) Mean ± SE	Hemodialysis (n=66) Mean ± SE	t-test P value
PTH	1.6-6.9pmol/L	19.91 ± 2.65	22.4 ± 3.32	P 0.599
Vitamin D	30-100ng/mL	6.61 ± 0.90	5.63 ± 0.79	P 0.451
Phosphorus	0.8-1.4mmol/L	1.77 ± 0.10	1.47 ± 0.07	P 0.021
Calcium	2.1-2.6mmol/L	2.14 ± 0.04	2.17 ± 0.02	P 0.534
Magnesium	0.66-1.07mmol/L	0.88 ± 0.02	0.83 ± 0.02	P 0.181

Table (2) Differences of Bone Disease Biomarkers in Study Subgroups.

Biomarker	Normal range	Stage3 (N=12) M±SE	Stage4 (N=13) M±SE	Stage5 (N=15) M±SE	HD<6 months (N=21) M ±SE	HD>6 months (N=45) M±SE
PTH	1.6-6.9 pmol/L	4.08± 0.10 d	14.58± 0.52 c	37.19± 1.14 a	20.23± 2.28 b	23.43± 4.31 b
Vitamin D	30-100 ng/mL	4.29± 0.36 a	7.78± 1.95 a	7.77± 1.70 a	5.47± 1.30 a	5.79± 1.01 a
Phosphorus	0.8-1.4 mmol/L	1.28± 0.01 c	1.48± 0.01 b	2.41± 0.05 a	1.45± 0.05 b	1.48± 0.09 b
Calcium	2.1-2.6 mmol/L	2.26± 0.00 a	2.24± 0.01 a	1.97± 0.02 c	2.14± 0.01 b	2.18± 0.03 b
Magnesium	0.66-1.07 mmol/L	0.91± 0.00 a	0.90± 0.00 a	0.84± 0.01 b	0.81± 0.02 b	0.84± 1.03 b

Table (2) shows bone disease. PTH levels were within the limit of the normal range (1.6-6.9pmol/L) in stage3 (4.08±0.10poml/L) and increased than the upper limit of the normal range in stage4 (14.58±0.52pmol/L), stage5 (37.19±1.14pmol/L), HD<6months (20.23±2.28pmol/L) and HD>6months (23.43±4.31pmol/L). The PTH level were different significantly ($p<0.05$) among all subgroups stage3, stage4, stage5, HD<6months and HD>6months, but without any different significantly ($p>0.05$) between HD<6months were compared with HD>6months. The levels of PTH were showed in Figure (1).

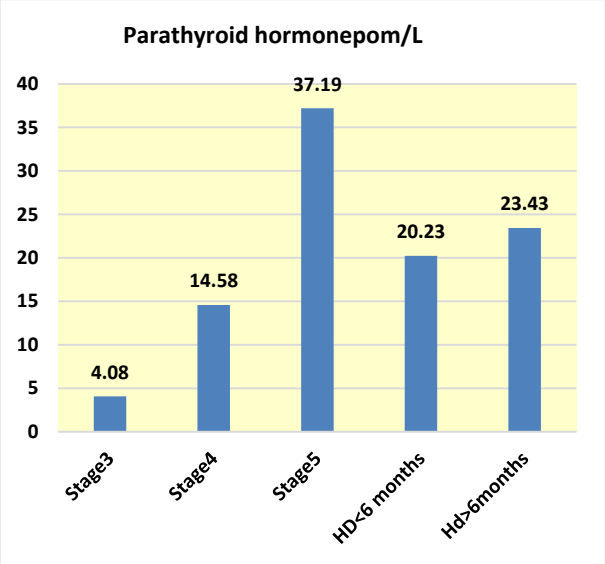

Figure (1) Parathyroid hormone levels in all subgroups.

Vitamin D levels were decreased than the lower limit of the normal range (30-100ng/mL) in all subgroups stage3 (4.29±0.36ng/mL), satge4 (7.78±1.95ng/mL), stage5 (7.77±1.70ng/mL), HD<6months (5.47±1.30ng/mL) and HD>6months (5.70±1.01ng/mL). The results showed no any significant ($p>0.05$) differences among all subgroups stage3, stage4, stage5, HD<6months and HD>6months. The levels of vitamin D were showed in Figure (2).

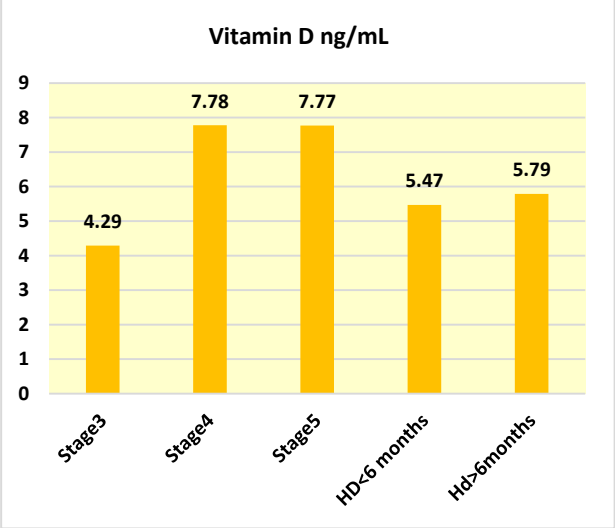

Figure (2) Vitamin D levels in all subgroups.

Phosphorus levels were within the limit of the normal range (0.1-1.4mmol/L) in stage3 (1.28±0.01mmol/L), stage4 (1.48±0.01mmol/L), HD<6months (1.45±0.05mmol/L), HD>6months (1.48±0.09mmol/L) while increased than the upper limit of the normal range in stage5 (2.41±0.05mmol/L). The phosphorus levels showed significant ($p<0.05$) difference in all subgroups among stage3, stage4, stage5, HD<6months and HD>6months except among stage4, HD<6months and HD>6months they showed any significant ($p>0.05$) differences. Calcium levels were within the limit of the normal range (2.1-2.6mmol/L) in stage3 (2.26±0.00mmol/L), stage4 (2.24±0.01mmol/L), HD<6months (2.14±0.01mmol/L), HD>6months (2.18±0.03mmol/L) while decreased than the lower limit of the normal range in stage5 (1.97±0.02mmol/L). The results showed significant ($p<0.05$) difference among stage3, stage5, HD<months, HD>6months while without any different significant ($p>0.05$) between stage3 and stage4 and also between HD<6months and HD>months. Magnesium levels were within the limit of the normal range (2.1-2.6mmol/L) in stage3 (0.81±0.02mmol/L), stage4 (0.90±0.00mmol/L), stage5 (0.84±0.01mmol/L), HD<6months (0.81±0.02mmol/L),

HD>6months (0.84±1.03mmol/L). These results showed significant ($p<0.05$) difference among subgroups stage3, stagr5, HD<6months and HD>6months, but without any significant ($p>0.05$) difference among stage5, HD<6months and HD>6months and between stage3 when compared stage4.

DISCUSSION

The inccrease in the levels of PTH that observed in consevative and hemodialysis groups in our study, maybe related to the occurrence of secondary hyperparathyroidism that is a frequently encountered problem in the management of patients with CKD. Its pathophysiology is mainly due to hyperphosphatemia and vitamin D deficiency as had been recorded in our results [8]. and resistance to the calcemic action of PTH in renal failure requires the presence of circulating levels of PTH [9]. Studies in uremic rats by Somerville and Kaye 1979 have shown that an increase in serum phosphorus produced skeletal resistance to the calcemic action of PTH [10]. Massry *et al*., observed that calcitriol administration partially corrected the resistance to the calcemic action of PTH in rats with either acute or chronic renal failure [11]. We recorded reduced of vitamin D levels in all CRF patients that the kidney plays a central role in vitamin D metabolism and regulation of its circulating levels.Therefore, impaired renal function may lead to vitamin D deficiency, as has been observed in patients with CKD. There seem to be several mechanisms involved in decreased production of 1,25(OH)2D that occur over the course of CKD progression. A decrease in renal mass limits the amount of 1α-hydroxylase available for the production of the active vitamin D metabolite [12]. That most circulating calcitriol is produced by 1-a-hydroxylation in the proximal tubule. It is now known that hydroxylation can also occur in many extra-renal tissues, where calcitriol is presumed to have a paracrine effect [13]. Fibroblast growth factor-23 appears to be produced by osteocytes in response to hyperphosphataemia that observed in CRF [14].

Phosphaturic (An excess of phosphates in the urine) and inhibits the formation of calcitriol which may exacerbate chronic kidney disease mineral and bone disorder [15]. Hyperphosphataemia, hypocalcaemia and calcitriol deficiency induce parathyroid hormone release. This is called secondary hyperparathyroidism and is treated by correction of the imbalance of calcium, phosphate and vitamin D. However, prolonged stimulation of PTH secretion leads to hyperplasia of the parathyroid glands and insensitivity to changes in calcium, phosphate and vitamin D [16]. In a study was carried out on 50 hemodialysis renal failure patients (cases) and 50 apparently healthy individual (control) by Abdelgader and Abdrabo to determine the effect of chronic renal failure on calcium, phosphorus and PTH level [17]. The age of the patients (M±SD =47.5±13.3 years) was comparable with control group (M±SD =43.1±13.4 years, the results obtained that there is no statistically significant difference in levels of calcium, in the hemodialysis renal failure patients (cases) compared with apparently healthy individuals (control), as we found non-significant difference between conservative and HD groups with the cases also the results showed significant increase in the levels of phosphorus and PTH, this indicates that chronic renal failure have effect on the levels of calcium, phosphorus and PTH. There is a certain risk that secondary hyperparathyroidism with long-term low calcium therapy will develop, even if normocalcemia is maintained. Hyperphosphatemia is one of the main factors in the pathogenesis of secondary hyperparathyroidism. These results agree with study conducted by Gallieni *et al.*, who showed significant increase in phosphorus and PTH level [18]. Silver *et al.*, reported small decreases in serum Calcium and more prolonged increases in serum phosphate stimulate the parathyroid gland to secrete PTH [19]. Excess PTH synthesis and secretion leads deficient inhibition of PTH transcription, so hyperplasia and parathyroid gland enlargement contribute to elevated serum PTH [20]. As the GFR declines to < 60 ml/min/ 1.73 m^2, phosphorus excretion becomes altered in the nephron. Although half of the nephrons are not working to excrete phosphorus, the remaining nephrons compensate by hyper-excreting the daily phosphorus load to maintain normal serum phosphorus concentrfations. Compensation can generally continue until the GFR declines to < 25–40 ml/min/1.73 m^2. With progressive CKD, when the remaining nephrons can no longer sufficiently excrete the phosphorus load, hyperphosphatemia is detected [12].

The levels of calcium, and magnesium in were within limit of the normal range and they didn't reveal any significant differences in both study groups. That Magnesium concentration in dialysis fluid influences serum Mg concentration in patients undergoing continuous ambulatory peritoneal dialysis (CAPD) [21]. Retrospectively studied 34 CAPD patients who were divided into two groups: those dialyzed with a dialysis solution with Mg concentration 0.75mmol/L (19 patients) and those dialyzed with a solution with Mg concentration 0.5mmol/L (15 patients). They found that serum Mg level was significantly higher in patients dialyzed with 0.75mmol/L versus those dialyzed with 0.5mmol/L ($p<0.01$) [21]. Ejaz *et al.*, and Hutchison *et al.*, reported similar findings [22,23]. Serum Mg in PD patients depends on the concentration gradient between serum and dialysis fluid and the use of Mg-free dialysate leads to hypomagnesemia [23,24,25]. Over the years, there has been debate on the relationship between serum Mg and PTH in HD patients. Some studies [26, 27], indicated that serum Mg level did not influence PTH in patients on regular HD. Other studies suggested a highly significant inverse correlation between serum Mg and PTH in HD patients [28.29]. The normal values for Mg in our results may be related to dialysis fluid concentration usually contained 0.75mmol/L magnesium, with mild hypermagnesaemia observed quite frequently [26,30,31]. Both mild hypermagnesaemia and normomagnesaemia were found when patients were dialyzed against a dialysis fluid magnesium concentration of 0.5mmol/L [32.33].

CONCLUSION:

In this study Parathyroid hormone was increased in chronic renal failure disease and more elevation was seen at the end stage of renal disease and decreased when patients maintain hemodialysis session while vitamin D was decreased in both of chronic renal failure (conservative and hemodialysis) groups, while electrolytes less effected in this study.

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