

Effect of haemodialysis on metabolism of calcium

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Abstract: *Background:* Secondary hyperparathyroidism is a frequent complication in chronic kidney disease patients, especially those on haemodialysis. *The objective of this study* is to find the effect of chronic haemodialysis on Calcium, phosphorus, Calcium × phosphorus product, Alkaline phosphatase (ALP) and Parathyroid hormone (PTH) in peripheral blood of a sample of Iraqi patient who were on chronic haemodialysis. *Method:* One hundred and three patients on haemodialysis were studied from February 2014 to May 2014. To evaluate the effect of duration of dialysis treatment on Parathyroid hormone and other laboratory tests, patients were divided into two groups according to the haemodialysis duration: group 1 (48 patients <1 year on haemodialysis) and group 2 (55 patients ≥ 1-10 year on haemodialysis). *Results:* Showed no significant differences ($p > 0.05$) in the level of serum calcium, phosphorus, Calcium × phosphorus product, Alkaline phosphatase and Parathyroid hormone between group 1 (<1 year on haemodialysis) and group 2 (≥ 1 year on haemodialysis). No significant association ($p > 0.05$) was found between haemodialysis duration and each of serum phosphorus, Calcium × phosphorus product, Alkaline phosphatase and Parathyroid hormone. Only significant association ($p < 0.05$) was observed between haemodialysis duration and serum calcium level. *Conclusion:* No significant increase was observed in the Parathyroid hormone level in group haemodialysis ≥ 1 year compared with haemodialysis <1 year. While haemodialysis duration less than a year were significantly more associated with decreased serum calcium compared with longer period of haemodialysis duration were significantly more to be associated with normal serum calcium.

Keywords: Haemodialysis, Parathyroid hormone, serum calcium, serum phosphorus.

Introduction

Secondary hyperparathyroidism (SHPT) is a frequent complication in chronic kidney disease patients (CKD), especially those on haemodialysis (HD) [1]. Phosphorus (P) levels increase and active vitamin D (calcitriol) synthesis decreases in direct response to declining kidney function, triggering a cascade of sequels including decreased calcium absorption and increased production of parathyroid hormone (PTH) [2]. Elevations in serum PTH concentration are observed early in the development of CKD [3]. As CKD progresses, serum PTH continues to rise [3] and patients typically develop SHPT [4]. Patients receiving dialysis have persistently elevated serum PTH [5]. Prolonged hypocalcaemia, hyperphosphataemia and low vitamin D concentrations all contribute to the increased PTH synthesis and secretion and parathyroid gland hyperplasia that are the hallmarks of SHPT [6-7].

Aim of the study: This study was to examine the effect of chronic HD on PTH, phosphorus, calcium (Ca), and Ca×P product in peripheral blood of a sample of Iraqi patient who were on chronic HD.

Material and Methods

One hundred and three patients, on maintenance HD were included in the study. Which was carried out from February 2014 to May 2014 at Alkindy teaching hospital in Iraq. All the patients were treated by conventional HD 4-5 hours, three times a week. Polysulphone membranes were used as dialyser, a dialysate was produced from 140 mmol/L sodium, 2 mmol/L potassium, 1.5 mmol/L calcium, 0.5 mmol/L magnesium, 111 mmol/L chloride, 3 mmol/L acetate and 32 mmol/L bicarbonate. Information, including age, gender, duration on dialysis were collected from questionnaires and medical records. At the moment of the

evaluation none of the patients, particular the postmenopausal women, were receiving or had received previous to the study, oestrogen or raloxifene, calcitonin, bisphosphonates, PTH or corticosteroids. vitamin D derivative (one alpha) orally, phosphate binder (calcium carbonate) and erythropoietin. None of the patients received vitamin K or aluminum hydroxide. To evaluate the effect of duration of dialysis treatment on PTH and other laboratory tests. Patients were divided into two groups according to the hemodialysis duration: group 1 (48 patients <1 year on HD), group 2 included 55 patients with HD duration ≥ 1 year (1-10 years).

Venous blood sampling was collected in the morning immediately before dialysis sessions. Intact parathyroid hormone (iPTH) was measured by using PTH intact ELISA kit. Serum calcium, serum phosphorus, total alkaline phosphatase (ALP) were measured by standard laboratory techniques using diagnostic kits.

Statistical Analysis: Statistical package for social sciences version 20 (SPSS 20) was used for data analysis.

Results

One hundred and three patients, 53 (51.4%) men and 50 (48.5%) women, were enrolled in the study. The age of the patients ranged from 19-84 years. The results showed that there was no significant differences ($p > 0.05$) in mean age between group one (patients <1 year on HD) and group two (patients with HD duration ≥ 1 years). The mean age of group one was (50.1 \pm 15.2) years and (49.6 \pm 16.0) years for group two (table1)

Variables	Classi- fication	Duration of HD	
		<1 year	≥ 1 year
		N=48 (100%)	N=55 (100%)
Age group	up to 45	17 (35.4%)	23 (41.8%)
	46 – 65	24 (50.0%)	22 (40.0%)
	>65	7 (14.6%)	10 (18.2%)
Mean \pm SD		50.1 \pm 15.2	49.6 \pm 16.0
Statistical analysis		P value = 0.869 no significant difference	

Results of biochemical tests which were included in table-2 indicated that here was no significant increase ($p \geq 0.05$) in the level of serum calcium (8.9 \pm 1.5) mg/dl and phosphorus (6.9 \pm 2.3) mg/dl in group two (≥ 1 year on HD) compared with group one (<1 year on HD) in which the level of serum calcium was (8.7 \pm 1.8) mg/dl and phosphorus was (6.6 \pm 1.9) mg/dl. Ca \times P product also showed no significant increase ($p > 0.05$) in group two (60.0 \pm 19.1) mg²/dl² compared with group one in which it was (58.0 \pm 23.3) mg²/dl².

Results also showed that there was no significant increase ($p > 0.05$) in the level of PTH (367.3 \pm 408.4) pg/ml and ALP (174.0 \pm 160.6) U/L in group two (≥ 1 year on HD) compared with group one (<1 year on HD) in which the level of PTH (275.4 \pm 270.8) pg/ml and ALP was (172.5 \pm 178.1) U/L.

Variables	Duration of HD		P value
	<1 year	≥ 1 year	
	Mean \pm SD	Mean \pm SD	
Serum calcium (mg/dl)	8.7 \pm 1.8	8.9 \pm 1.5	0.679
Serum phosphorus (mg/dl)	6.6 \pm 1.9	6.9 \pm 2.3	0.493
(Ca \times P) product (mg ² /dl ²)	58.0 \pm 23.3	60.0 \pm 19.1	0.639
PTH (pg/ml)	275.4 \pm 270.8	367.3 \pm 408.4	0.639
ALP (U/L)	172.5 \pm 178.1	174.0 \pm 160.6	0.563

Results table-3 no significant association ($p > 0.05$) was observed between HD duration and each of serum phosphorus, and Ca \times p product. A significant association ($p < 0.05$) was observed between HD duration and serum calcium levels. It was found that those with HD duration less than one year were significantly more associated 24 (50%) with decreased serum calcium while those with longer period of HD duration were significantly more to be associated 30 (54.5%)

with normal serum calcium ($p < 0.05$). Serum calcium was above the normal in 11 (22.9%) of patients in group 1 and in 9 (16.4%) of patients in group 2.

Serum phosphorus was elevated in 37 (77.1 %) of cases in group one and 46 (83.6%) in group two, while it was normal in 11 (22.9%) of patients in group 1 and 9 (16.4%) of patients in group 2. Regarding to Ca \times P product, it was found that Ca \times P product was >55 in 24 (50.0%) of patients in group one and 32 (58.2%) of patients in group two, in contrast it was <55 in 24 (50.0%) of patients in group 1 and 23 (41.8%) of patients in group 2. No significant association ($p > 0.05$) was found between duration of HD and each PTH

level and ALP level. 40 (83.3%) of patients in group one and 43 (78.2%) of patients in group two had PTH level higher than normal, in contrast PTH level was below the normal in 4 (8.3%) of patients in group one and 5 (9.1%) of patients in group two. 4 (8.3%) of patients in group one and 7 (12.7%) of patients in group two had normal PTH level. ALP was found in normal level in 16 (33.3%) of patients in group one and 20 (36.4%) of patients in group two while it was below the normal in 1 (2.1%) of patients in group one and non of patients in group two had low level. 31 (64.6%) of patients in group one and 35 (63.6%) of patients in group two had ALP level higher than normal.

Table-3: Status of studied biochemical variables for the study sample

Variables	Classification	Duration of HD		X ²	P value
		<1 year	≥ 1 year		
		N=48 (100%)	N=55 (100%)		
Serum Ca level	Below normal	24 (50.0%)	16 (29.1%)	8.083	0.018*
	Above normal	11 (22.9%)	9 (16.4%)		
	Normal	13 (27.1%)	30 (54.5%)		
Serum P level	Below normal	0 (0.0%)	0 (0.0%)	0.703	0.402
	Above normal	37 (77.1%)	46 (83.6%)		
	Normal	11 (22.9%)	9 (16.4%)		
(Ca \times P) product	>55	24 (50.0%)	32 (58.2%)	0.692	0.406
	<55	24 (50.0%)	23 (41.8%)		
PTH level	Below normal	4 (8.3%)	5 (9.1%)	0.565	0.754
	Above normal	40 (83.3%)	43 (78.2%)		
	Normal	4 (8.3%)	7 (12.7%)		
ALP level	Below normal	1 (2.1%)	0 (0.0%)	1.217	0.544 ¹
	Above normal	31 (64.6%)	35 (63.6%)		
	Normal	16 (33.3%)	20 (36.4%)		

¹Expected cell count is less than one, P value could be invalid. * P value < 0.05 , significant association

Discussion

Secondary hyperparathyroidism (SHPT) is a frequent complication in CKD [1], affecting most of those who are receiving HD [4]. Statistical analysis showed that there was no significant differences ($p > 0.05$) in mean age between group one (patients < 1 year on HD) and group two (patients with HD duration ≥ 1 year). Mortality

and survival may be similar among patients in both groups and this may be related to the fact that number of older dialysis patients was the least at this study sample. Or may be related to other factors which indicated by Lehmann et al. [8] who demonstrated that survival in patients on renal replacement therapy (RRT) seems to be affected not only by medical and technical advances in dialysis

therapy, but may reflect progressively lower mortality of individuals with cardiovascular and metabolic complications.

Jonjic et al. [9] found that the number of patients increased with increasing age in their study patients groups regarding the HD duration and the greatest number of the patients ranged between 30 and 60 years of age. In present study the largest proportion of patients was in the age group 46-65 years and then followed by the age group up to 45 years. This implies that in this study sample, the age group in which ESRD is most prevalent appears to be between 46 years and 65. Data from the United States Renal Data System indicated that incidence of ESRD is increasing among persons aged >65 years and especially among those aged >80 years [10-11].

In England and Scotland the incidence rate is highest in the 75-79 years age group, while in Wales and Northern Ireland the peak is between 80 and 84 years [12]. In our study it was observed that the smallest proportion of patients was in the age group >65 years which was limited on 7 (14.6%) of patients in group one and 10 (18.2%) of patients in group two. The difference between these populations may be attributed to the different conditions of the population studied, differences in onset, duration, and severity of some risk factors, including diabetes, hypertension and obesity.

In previous study a positive correlation was found between duration of dialysis and calcium [13]. But in present study no statistically significant differences were found in the levels of Ca between the group on HD for <1 year and the group on HD for ≥ 1 year. The explanation of these results may be attributed to implementing different modalities in regulation of phosphorus and PTH. The dialysate calcium concentration for HD patients can be adjusted to manage more optimally the body's Ca and phosphate balance, and thus improve bone metabolism as well as reduce accelerated arteriosclerosis and cardiovascular mortality [14].

Current management of mineral metabolism in ESRD involves the control of hyperphosphatemia and the use of active vitamin D compounds to suppress PTH, with an aim to obtain normalization of serum Ca and phosphate [14].

Previous study found that Pre-dialysis phosphate concentrations were similar in long and short dialysis groups [15]. We also found that there were no statistically significant differences between the level of phosphorus in the group on HD for < 1 year and the group on HD for ≥ 1 year. Fajardo et al. [16] found that mean $\text{Ca} \times \text{P}$ product decreased from $64 \pm 12.7 \text{ mg}^2/\text{dL}^2$ during CHD to $50.9 \pm 10.3 \text{ mg}^2/\text{dL}^2$ at the end of the second year of long HD. But in present study no statistically significant differences was found in the levels of $\text{Ca} \times \text{P}$ product between the group on HD for < 1 year and the group on HD for ≥ 1 year. Increased level of serum phosphorus in our study sample may explain this result. Hyperphosphatemia is the main determinant of the increased $\text{Ca} \times \text{P}$ product [17] and as demonstrated by Dhingra et al. [18] the $\text{Ca} \times \text{P}$ product was highly correlated with serum phosphorus.

It was noticed that there was no significant increase ($p > 0.05$) in the level of PTH in group two compared with group one. This result disagree with another study that found a significant positive correlation of serum PTH with HD duration [13, 19-20]. The explanation of this result may be due to the usage of the therapeutic options for management of SHPT which is limited to the use of phosphate binders (reducing serum phosphorus reduces PTH secretion), calcium and vitamin D or its analogues. Phosphate binders may help normalize serum phosphorus and, consequently, also help normalize PTH [21]. Many patients on maintenance HD receive supplemental vitamin D, which directly inhibits PTH production by suppressing messenger RNA at the transcription level within the gland [22].

Saravani et al. [23] demonstrated that vitamin D therapy caused a fall in the level of serum PTH. Dimitrakov et al. [19] also concluded that long-term low-dose conventional calcitriol therapy in combination with calcium supplementation could slow the progression of SHPT in some HD patients. It was noticed that there was no significant increase ($p > 0.05$) in the level of ALP in group two compared with group one. This was in contrast to the findings by Chadha et al. [13] where they

have found a positive correlation between ALP and duration of Dialysis. Our result may be attributed to the usage of active vitamin D product. The measurement of ALP is an important guide for monitoring therapy of PTH and calcitriol [23]. It was found that the level of circulating ALP can be effectively decreased by active vitamin D products [24-26]. Moreover ALP correlated directly with iPTH [27] and in HD patients, There was positive correlation between ALP and iPTH [13].

A significant association ($P < 0.05$) was observed between HD duration and serum calcium. It was found that those with HD duration less than a year were significantly more associated 24 (50%) with decreased serum calcium while those with longer period of HD duration were significantly more to be associated 30 (54.5%) with normal serum calcium ($p < 0.05$). Hypocalcemia is common in dialysis patients [28]. HD patients are commonly affected by SHPT [29] in which the serum PTH level is elevated, and the serum calcium level may be normal or low [30].

Additionally Hypocalcemia is often seen in CKD (pre dialysis and dialysis) due to hyperphosphatemia, deficiency of vitamin D which result in decreased intestinal absorption of calcium and skeletal resistance to the action of PTH, resulting in a decrease release of calcium from the bone, foods high in calcium are also generally restricted because of their high phosphorus contents, leading to a decreased dietary intake of calcium [31].

Regarding to the patients group who are on HD for ≥ 1 year, the normal calcium concentration may be attributed to many factors. The dialysate calcium (Ca) concentration for HD patients can be adjusted to manage more optimally the body's Ca and phosphate balance, and thus improve bone metabolism as well as reduce accelerated arteriosclerosis and cardiovascular mortality [14]. 1.5 mmol/L Ca bath has subsequently become more accepted for the majority of HD patients [32]. Current management of mineral metabolism in ESRD involves the control of hyperphosphatemia and the use of active vitamin D compounds to suppress PTH, with an aim to obtain normalization of serum Ca and phosphate [14].

Calcium supplementation may also be needed to maintain serum calcium with the normal range [33]. Serum calcium was above the normal in 11 (22.9%) of patients in group one and in 9 (16.4%) of patients in group two. Symptomatic or asymptomatic hypercalcemia is a very common problem encountered in HD patients [34]. This HD-induced hypercalcemia is mainly due to the positive intradialytic calcium balance achieved with the use of a standard dialysate calcium concentration and the administration of calcium-containing phosphate binders in conjunction with active vitamin D metabolites for the treatment of SHPT [34].

In Malaysia Chan et al. [35] found that patients who had longer lengths of time on dialysis were more likely to have hyperphosphatemia in contrast Zitt et al. [36] found that Longer dialysis vintage was associated with significant reductions in serum phosphorus. In another study no significant associations was found between phosphate control and years on dialysis or dialysis adequacy [37]. Our results showed that no significant association ($p > 0.05$) was observed between HD duration and phosphorus level. The differences can be explained by the difference in time on dialysis (dialysis vintage), the duration of weekly dialysis session and the achieved dose of dialysis. Phosphate control in dialysis patients is difficult and management relies on dietary restriction, the use of phosphate binders, many of which are Ca-based, and dialysis [14].

Among other factors contributing to phosphorus clearance during HD, it seems that frequency and duration of the dialysis sessions are the most important ones as well as the surface area of the dialyzer membrane [38].

In our study serum phosphorus was elevated in 37 (77.1 %) of cases in group one and 46 (83.6%) in group two. Hyperphosphatemia is common in patients with CKD disease [2] and it is one of the major factors responsible for alterations in mineral and bone metabolism in dialysis patients [39]. As the number of functioning nephrons decreases, the failing kidneys are unable to excrete phosphorus and there is a progressive increase in serum

phosphorus levels [40]. Increased serum phosphate is also involved in the pathogenesis of SHPT [41]. Treatment of SHPT involves suppression of the PTH production by restoration of 1,25 (OH)₂vitamin D levels by replacement therapy. However, 1,25 (OH)₂vitamin D stimulates intestinal phosphate and calcium absorption as well as phosphate and calcium mobilisation from bone, leading to an increased risk of hyperphosphatemia and hypercalcemia [42]. Additionally conventional HD does not remove sufficient phosphate to maintain phosphorus balance in the vast majority of HD patients mainly because of the pooling of phosphate in the intracellular compartment, which causes much of the phosphorus not to be readily accessible during a treatment [43].

Our result showed that phosphate level was normal in 11 (22.9%) of patients in group one and 9 (16.4%) of patients in group two. This is may be related to the medical management of SHPT which involves dietary phosphorus restriction [22], Removal of phosphate by HD [32] and reducing intestinal phosphate absorption by using phosphate binders [44]. Regarding to calcium phosphorus product, no significant association ($p > 0.05$) was observed between HD duration and $\text{Ca} \times \text{P}$ product. $\text{Ca} \times \text{P}$ product affected by the level of calcium and phosphorus in each group of our study sample. $\text{Ca} \times \text{P}$ product was >55 in 24 (50.0%) of patients in group one and 32 (58.2%) of patients in group two. hyperphosphatemia is the main determinant of the increased $\text{Ca} \times \text{P}$ product [17]. The $\text{Ca} \times \text{P}$ product was highly correlated with serum phosphorus [18].

In contrast $\text{Ca} \times \text{P}$ product was <55 in 24 (50.0%) of patients in group one and 23 (41.8%) of patients in group two. This is may be due to the fact that we have few patients in both groups with higher than normal level of calcium. Hypercalcemia, together with hyperphosphatemia, or each individually can be responsible for increased blood $\text{Ca} \times \text{P}$ product [45]. In previous study PTH levels were associated directly with duration of dialysis [46]. Another study found that high iPTH levels were associated longer duration of dialysis [47]. In present study no significant association ($p > 0.05$) was found between duration of HD and PTH level. The explanation of this result may be due to the usage of the therapeutic options for

management of SHPT which may slow the progression of SHPT in some HD patients who were on HD ≥ 1 year. Our result showed that 40 (83.3%) of patients in group one and 43 (78.2%) of patients in group two had PTH level higher than normal. HD patients are commonly affected by SHPT [29]. SHPT is a major complication of CKD, resulting from disturbances in the regulation of PTH, calcium, phosphorus, and vitamin D [40].

The serum PTH level is elevated, and the serum calcium level may be normal or low [30]. PTH level in our study sample was below the normal in 4 (8.3%) of patients in group one and 5 (9.1%) of patients in group two. 4 (8.3%) of patients in group one and 7 (12.7%) of patients in group two had normal PTH level. This result may be the consequence of PTH over-suppression from the aggressive use of high-calcium dialysate, calcium-containing phosphate binders and vitamin D analogues [48-49].

No significant association ($p > 0.05$) was found between duration of HD and ALP level. This result disagrees with the study of Yamashita et al. [50] which indicated that longer HD vintage was associated with higher serum ALP levels. This is may be due to the usage of active vitamin D products. Moe et al. [26], Coyne et al. [24] and Kalantar-Zadeh and Kovesdy [25], found that the level of circulating ALP can be effectively decreased by active vitamin D products.

Saravani et al. [23] also found that Vitamin D therapy caused a fall in the level of serum ALP and PTH. Lomonte et al. [51] also concluded that the treatment with oral calcitriol was associated with a decrease in the serum levels of ALP. It was observed that 31 (64.6%) of patients in group one and 35 (63.6%) of patients in group two had ALP level higher than normal. Serum ALP is a biochemical marker of bone turnover and is used to monitor the metabolic bone disease associated with renal insufficiency [52].

Serum ALP stems from the bone itself and reflects internal bone activities [53]. Incrementally higher levels of serum ALP can be seen with worsening magnitude

of bone turnover [52]. In HD patients, elevated levels of serum ALP are associated with SHPT [54], ROD [22, 55], cardiac failure, diastolic dysfunction [56], and cardiovascular disease (CVD) [57]. ALP was found in normal level in 16 (33.3%) of patients in group one and 20 (36.4%) of patients in group two while it was below the normal in 1 (2.1%) of patients in group one and none of patients in group two had low level. This is may be from the aggressive use of vitamin D analogues. The level of circulating ALP can be effectively decreased by active vitamin D products [24-26].

Conclusion

Based on the findings of this study, no significant increase in the level of serum PTH in group of patients who are on HD \geq 1 year compared with those with HD duration <1 year. It was found that those with HD duration less than a year were significantly more associated with decreased serum calcium while those with longer period of HD duration were significantly more to be associated with normal serum calcium.

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