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Parathyroid Hormone, Calcium and Phosphorus Levels in Hemodialysis Patients at Al-Shifa Hospital, Gaza-Palestine

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Abstract: Secondary hyperparathyroidism is one of the common complications among patients suffering from chronic kidney disease (CKD). This condition is accompanied by hypocalcaemia, hyperphosphatemia, and many other consequences.The aim of this study is to assess the levels of parathyroid hormone (PTH), phosphorus (P), albumin-corrected serum calcium, and calcium-phosphate (CaxP) product in patients who are on hemodialysis (HD) for one year or more in HD unit at Al-Shifa hospital in Gaza, Palestine. In addition, the values of these biochemical markers will be examined for their compliance with the approved guidelines set for HD patients.

The present study is a case-control one and included 80 patients in addition to 80 apparently healthy individuals who were regarded as a control group. Both groups were almost comparable for age and sex. Ethical issues were considered; approval to conduct this study was obtained from the local Helsinki committee. Albumin, total serum calcium, and serum phosphorus were assayed spectrophotometrically. Serum ionized Ca was assayed using ion selective electrode electrolyte analyzer. Parathyroid hormone (PTH) was assayed using ELISA technique, an enzymatically modified two-step sandwich-type immunoassay.

Results showed that the levels of serum PTH, CaxP product, serum phosphorus and ionized Ca differ significantly between cases and control groups; (PTH: 1715.3±1706.3 VS. 35.7±14.7 pg/ml; CaxP product: 62.7±14.6 VS 40.2±6.0mg^2/dl^2; albumin: 4.6±0.39 VS. 4.7±0.3g/dl; serum phosphorus 6.6±1.4VS 4.3±0.6mg/dl; ionized Ca: 3.78±0.47 VS. 4.7±0.1 mg/dl, respectively. On the other hand, there was no statistically significant (*P=0.394*) difference in the mean levels of albumin-corrected serum Ca between cases and control group (9.5±0.9 VS 9.4±0.3mg/dl, respectively).

Conclusions: The majority of HD patients showed elevated levels of serum PTH and phosphate ions which suggest that many patients have severe hyperparathyroidism. The observed increase in serum PTH levels and bone disease correlates with the frequency of HD, which could indicate inadequacy in the implementation of the standard protocol for managing HD patients.It is recommended to conduct clinical trials to select the most appropriate method for controlling parathyroid gland activity as well as Ca and P metabolism in this group of patients.

Key words: Parathyroid hormone, End Stage Renal Disease, Hemodialysis Patients, Gaza, Palestine.

مستويات هرمون الغدد جارات الغدة الدرقية، الكالسيوم والفسفور لدى مرضى غسيل الدم في مستشفى الشفاء – غزة – فلسطين

ملخص: إن النشاط المفرط للغدد الجارات للغدة الدرقية تعتبر من المضاعفات الشائعة للمرضى الذين يعانون من أمراض الكلى المزمنة. وهذه الحالة عادة ما يصاحبها انخفاض في مستوى عنصر الكالسيوم بالدم وارتفاع حاد في أيونات الفوسفات، هذا بالإضافة إلى مضاعفات أخرى.

إن الهدف من هذه الدراسة هو تقييم مستويات هرمون الغدد جارات الغدة الدرقية، الفوسفور، الكالسيوم المرتبط بالزلال، وكذلك نتيجة معامل ضرب الكالسيوم والفوسفور لدى المرضى الذين يخضعون لغسيل الدم باستمرار لمدة سنة أو أكثر في مستشفى الشفاء بغزة. وبالإضافة لذلك فإن هذه الدلالات البيوكيماوية سيتم مقارنة مستوياتها للتأكد من مطابقتها للمعايير المتعارف عليها لهؤلاء المرضى.

هذه الدراسة عبارة عن "Case control" وقد شملت (80) مريضاً بالإضافة إلى نفس العدد من الأصحاء الذين اعتبروا كعينة ضابطة وكانت المجموعتان متوافقتان من حيث الجنس والعمر. وتم الأخذ بعين الاعتبار للمعايير الأخلاقية حيث حصل الباحثون على موافقة لجنة هلسنكي.

تم تحليل الزلال، الكالسيوم الكلى والفوسفور باستخدام طرق مقياس الطيف الضوئي، أما الكالسيوم المتأين فقد تم قياسه بواسطة جهاز " Ion selective electrode electrolyte analyzer" أما مستوى هرمون الغدد جارات الغدة الدرقية فقد تم قياسه بواسطة تقنية (ELISA) .

أظهرت النتائج أن مستويات هرمون الغدد جارات الغدة الدرقية، معامل ضرب الكالسيوم والفوسفور، الفوسفور، والكالسيوم المتأين لدى المرضى تختلف عن نتائج العينة الضابطة وكان هذا الاختلاف ذا دلالة إحصائية. وفي المقابل لم يكن الاختلاف في نتائج الكالسيوم المرتبط بالزلال بين المرضى والعينة الضابطة ذا دلالة احصائية. وقد استنتجنا من هذه الدراسة أن غالبية مرض غسيل الدم لديهم مستويات مرتفعة من هرمون الغدد جارات الغدة الدرقية، وكذلك في أيونات الفوسفات. وهذا يعطي دلالة واضحة أن هؤلاء المرضى يعانون من نشاط متزايد في الغدد جارات الغدة الدرقية. وأظهرت الدراسة كذلك وجود علاقة بين هؤلاء المرضى والمعاناة من أمراض العظام وكذلك مع عدد مرات غسيل الدم. وأظهرت الدراسة بما لا يدع مجالاً للشك عدم تطبيق المعايير المتعارف عليها عالمياً للتعامل مع هؤلاء المرضى لذلك فإن من توصيات هذه الدراسة أن تُجرى تجارب اكلينيكية لاختيار أفضل السبل للتحكم في نشاط الغدد الجارات للغدة الدرقية، وكذلك مستويات عنصري الكالسيوم والفوسفور لدى هذه المجموعة من المرضى.

الكلمات المفتاحية: هرمون الغدد جارات الغدة الدرقية، المرحلة الأخيرة لمرضى الكلية، مرضى غسيل الدم – غزة – فلسطين.

Parathyroid Hormone, Calcium and Phosphorus Levels

Introduction

Among the common complications seen in patients with chronic kidney disease (CKD), particularly in those on long term hemodialysis (HD), is secondary hyperparathyroidism, this affects one in four patients receiving HD (1). Hypocalcaemia is a common condition in CKD because of declining levels of calcitriol. Rising serum phosphorus levels due to its impaired excretion by the kidneys further contributes to hypocalcaemia by lowering serum ionized calcium levels and by inhibiting the action of calcitriol (2). Generally, renal osteodystrophy includes all the disorders of bone and mineral metabolism caused by chronic renal failure (3). Chronic kidney disease is associated with substantially increased risk for cardiovascular disease morbidity and mortality, independent of traditional cardiovascular risk factors such as diabetes, hypertension, lipoprotein levels and tobacco use (4).

Hyperphosphatemia, elevated levels of the CaxP product and hyperparathyroidism, plays a crucial role in the development of cardiovascular disease in end stage renal disease (ESRD). Artery calcification among young adults receiving dialysis for more than 10 years has been demonstrated elsewhere (5). Hyperphophatemia stimulates the evolution of parathyroid gland hyperplasia (6), persistent hyperphosphatemia may also lessen the efficiency of treatment with calcitriol in secondary hyperparathyroidism patients (7). Hyperphosphatemia has been considered as an independent risk factor for death in HD patients even after adjusting for other comorbid conditions (8).

The active form of vitamin D, 1,25 (OH)2D3 has no direct effect on PTH secretion as it suppresses PTH gene transcription. Calcium regulates the biosynthesis of PTH; studies in rats showed that acute hypocalcemia led within one hour, to an increase in PTH mRNA. In contrast, hypercalcemia leads to little or no change in PTH mRNA (9). Chronic renal insufficiency is associated with hyperphosphatemia; the elevated serum phosphate directly depresses serum calcium levels and thereby stimulates parathyroid activity. Vitamin D analogues control PTH secretion without affecting bone turnover (10).

Kidney Disease Outcomes Quality Initiative (KDOQI) guidelines for bone metabolism and disease in chronic kidney disease (CKD) recommend that, in stage 5 CKD, the target levels for calcium (Ca) (corrected for serum albumin), phosphate (P), calcium x phosphate (Ca x P) product and parathyroid hormone (PTH) levels should be maintained at 8.4-9.5 mg/dl, 3.5-5.5 mg/dl, $< 55 mg^2/dl^2$ and 150-300 pg/ml, respectively (11).

A group of researchers have shown that Cinacalcet lowers fibroblast growth factor-23 (FGF-23) in hemodialyzed patients with secondary hyperparathyroidism. Cinacalcet mimics the action of calcium ions in tissues by allosteric activation of the calcium-sensing receptor, thus, Cinacalcet decreases serum calcium and phosphorus and effectively reduce serum PTH in dialysis patients (12,13). Other researchers used paricalcitol which is an agonist of vitamin D receptor, thus lowers the blood parathyroid hormone levels (14).

Very low protein diet was attempted by a group of researchers, despite the limited success in controlling uremia; they recommended that initiation of dialysis should not be excessively delayed (15).

The aim of the present study is to assess the levels of PTH, P, albumin-corrected serum Ca, and CaxP product in patients who are on HD for one year or more in the HD unit at Al-Shifa hospital as well as investigating the relation between PTH, P, albumin-corrected serum calcium, and CaxP product with the frequency of HD or with vitamin D analogue alfacalcidol (1α-hydroxyvitamin D3) consumption.

Materials and Methods

The present study is a case control one, the target population is HD patients diagnosed as ESRD and undergoing hemodialysis for ≥ 12 months. The records of the nephrology and dialysis department at AL Shifa hospital showed that about 150 patients fit within the inclusion criteria of the study, therefore, for a precision level of 10% at least 61 patients should be included (16). Thankfully, 80 cases represented all HD patients diagnosed as ESRD and undergoing hemodialysis for ≥ 12 months were recruited, randomly selected and freely accepted to be included to the study, with participation percentage of 53.3% (80/150). The sample size was 160 subjects divided as 80 cases and 80 apparently healthy individuals as a control group. Subjects of the control group were randomly selected from those accompanying the patients at the hospital facilities, and they were interviewed and answered health related questionnaire necessary for the inclusion criteria of the control group. Both groups were almost comparable for age and sex.

All patients (80) were on phosphate binder (calcium carbonate), 55 patients were receiving vitamin D analogue (0.5µg alfacalcidol daily), and the other 25 patients did not receive this analogue. The study was conducted at Al-Shifa hospital in Gaza city.

Ethical issues were considered; an approval to conduct this study was obtained from Helsinki committee in the Gaza Strip. Personal and medical

information were collected through a questionnaire. Body mass index (kg/m^2) was determined by dividing weight in kilograms by height in squared meters. Blood samples were collected by certified laboratory technician from cases (before HD session) and from the control group while fasting. Five ml of blood were delivered into vacutainer plain tubes and left to clot, then serum was separated by centrifugation at 3000 rpm for 15 minutes. All serum samples were kept at -70C until analysis.

Albumin, total calcium and phosphorus were analyzed using Biosystem BTS-310 spectrophotometer, ionized calcium was analyzed using ion selective electrode electrolyte analyzer (AVL 9180 Electrolyte analyzer, Roche, Germany). PTH was analyzed using ELISA method (ELISA reader, Diamed, Italy).

Statistical analysis, descriptive and independent t-test were performed using statistical package for social sciences (SPSS) program. The results were statistically significant when p-value was ≤ 0.05.

Results

The sample size was 160 subjects; cases and controls were almost comparable for age and sex. The percentage of males was 51% while that of females was 49%. The mean age was 47.2 years for cases and 47.3 years for control group.

The values of PTH, CaxP product, albumin-corrected serum calcium and phosphorus between male and female in cases and controls were not significantly different (inside each group).

Table 1 shows that 83.7% of cases had high levels of PTH (more than 300pg/ml), CaxP product was high in 67.5% of cases (more than 55 mg^2/dl^2) and albumin-corrected serum calcium (>9.5mg/dl) was elevated in 46.3% of cases while serum phosphorus was high in 77.5% of cases (more than 5.5mg/dl). Statistical analysis showed highly significant difference between cases and controls in relation to PTH, CaxP product, serum albumin, serum-free ionized calcium and serum phosphorus while the albumin-corrected serum calcium difference was not significant (table 2).

The values of PTH were highly significant as compared between the patients who underwent hemodialysis for more than 48 months and those of less than 48 months (table-3). The same table shows that differences in CaxP product, albumin-corrected serum calcium as well as phosphorus were not significant.

Regarding the frequency of hemodialysis and the administration of vitamin D analogue (alfacalcidol), the values of PTH, CaxP product, albumin-corrected serum calcium and phosphorus of both groups were not significant (tables 4 and 5).

Table1. Distribution of cases by levels of parathyroid hormone, (Ca×P) product, albumin-corrected serum calcium and phosphorus

Variable	Groups	No	%
PTH level (pg/ml)	Less than 150	2	2.5
	150-300	11	13.8
	More than300	67	83.7
(Ca×P) product (mg^2/dl^2)	Less than 55	26	32.5
	55 or more	54	67.5
Albumin-corrected serum Ca (mg/dl)	Less than 8.4	10	12.4
	8.4- 9.5	33	42.3
	More than 9.5	37	46.3
Serum phosphorus (mg/dl)	Less than 3.5	0	0
	3.5-5.5	18	22.5
	More than 5.5	62	77.5

PTH; parathyroid hormone

Table 2. Averages of parathyroid hormone, Ca×P product, serum albumin, albumin-corrected serum calcium, serum free-ionized calcium and serum phosphorus among cases and controls

Variable	Cases (n=80)	Controls (n=80)	P-value
	Mean±SD	Mean±SD	
PTH (pg/ml)	1715.3±1706.3	35.7±14.7	0.000*
Ca×P (mg^2/dl^2)	62.7±14.6	40.2±6.0	0.000*
Serum albumin (g/dl)	4.60±0.39	4.7±0.3	0.024*
Albumin-corrected serum Ca (mg/dl)	9.50±0.90	9.4±0.3	0.394
Serum free-ionized Ca (mg/dl)	3.78±0.47	4.7±0.1	0.000*
P (mg/dl)	6.6±1.4	4.3±0.6	0.000*

*Statistically significant, PTH; parathyroid hormone

Parathyroid Hormone, Calcium and Phosphorus Levels

Table 3. Averages of parathyroid hormone, (Ca×P) product, albumin-corrected serum calcium and serum phosphorus among cases by duration of hemodialysis

Variable	Hemodialysis duration		P-value
	Less than 48 months (n=49)	48 months or more (n=31)	
	Mean±SD	Mean±SD	
PTH (pg/ml)	1401.4±1485.2	2211.3±1929.3	0.038*
Ca×P (mg^2/dl^2)	62.1±15.4	63.7±13.4	0.630
Albumin-corrected serum Ca (mg/dl)	9.5±0.9	9.4±0.9	0.311
P (mg/dl)	6.5±1.5	6.8±1.3	0.337

*Statisticallysignificant, PTH; parathyroid hormone

Table 4. Averages of parathyroid hormone, Ca×P product, albumin-corrected serum calcium, and serum phosphorus among cases by frequency of hemodialysis

Variable	Hemodialysis frequency		P-value
	Two sessions (n=31)	Three sessions (n=49)	
	Mean±SD	Mean±SD	
PTH (pg/ml)	1790.7±2062.7	1667.5±1458.2	0.755
Ca×P (mg^2/dl^2)	61.6±15.7	63.4±14.0	0.592
Albumin-corrected serum Ca (mg/dl)	9.5±0.8	9.5±1.0	0.963
P (mg/dl)	6.5±1.7	6.7±1.3	0.611

PTH; parathyroid hormone

Table5. Averages of parathyroid hormone, Ca×P product, albumin-corrected serum calcium and serum phosphorus among cases by vitamin D analogue supplying

Variable	Supplied with Vitamin D analogue (0.5µg) daily. (n=55)	Not Supplied with Vitamin D analogue (n=25)	P-value
	Mean±SD	Mean±SD	
PTH (pg/ml)	1749.0±1907.6	1641.0±1177.7	0.795
Ca×P (mg^2/dl^2)	61.9±13.8	64.4±16.3	0.480
Albumin-corrected serum Ca (mg/dl)	9.4±0.8	9.6±1.0	0.381
P (mg/dl)	6.6±1.4	6.7±1.4	0.829

PTH; parathyroid hormone

Discussion

Minerals are very important for the human body. They have various roles in metabolism and body functions and are essential for the proper function of cells, tissues and organs. Many people who have severe CKD will eventually develop kidney failure and will require dialysis. Because of the importance of maintaining the levels of serum calcium, phosphorus and PTH to be in the recommended range described by KDOQI guidelines (11) in HD patients, we conducted this study to assess their levels.

Eighty HD patients in the HD unit at Al-Shifa hospital as well as 80 apparently healthy controls were included in the study. It was shown that there were no statistically significant differences between males and females with regard to PTH, CaxP product, albumin- corrected serum calcium and phosphorus levels within each group, which means that gender has no effect on the concentrations of these parameters. These results are congruent with others who did not find any statistically significant differences in these biochemical markers between males and females (17). This may be explained by the fact that PTH secretion is not controlled by any other endocrine gland (18). The major regulator of PTH secretion is the concentration of ionized calcium in blood, where PTH levels increase in response to decreased serum calcium and decrease in response to increased serum calcium.

Parathyroid Hormone, Calcium and Phosphorus Levels

The present study showed highly statistically significant differences between cases and control groups with regard to PTH, CaxP product and phosphorus, where their mean values were higher in cases, and serum albumin and ionized calcium, where their mean values were lower in cases. It was shown that there was no statistically significant difference between the two groups with regard to the mean of albumin-corrected serum calcium, where the values were in the recommended reference range, where it was found that with initiation of regular HD, the levels of serum total calcium usually normalize (11). In advanced stages of CKD, the fraction of total calcium bound to complexes was increased (19), thus, free (ionized) calcium levels were decreased despite normal total serum calcium levels.

Also, it was reported that impaired phosphate excretion, with the resulting hyperphosphatemia, is one of the earliest consequences of chronic renal failure. Hyperphosphatemia in turn plays an important role in the development of secondary hyperparathyroidism (20). Moreover, phosphate retention leads to a decrease in serum free calcium levels, which in turn stimulates PTH secretion (21)

Although, the value of serum albumin of the patients is in the accepted reference range, which indicate that the patients are maintained in a good nutrition state, as serum albumin levels have been used extensively to assess the nutritional status of individuals with and without chronic renal failure (22), the value of serum albumin in the case group was less than that of the control group. It is known that about 6–10 g of amino acids are lost into the dialysate during one session of HD with a low-flux membrane, and a loss of 1–2 g of albumin can be added if a high-flux membrane is used (23). However, very low protein diet has limited success in controlling uremia (15).

Concerning KDOQI guidelines for mineral metabolism values in HD patients, the study revealed that 13.8%, 32.5%, 41.3% and 22.5% of the HD were in the range recommended by KDOQI guidelines for PTH, Ca × P product, albumin-corrected serum calcium and serum phosphorus, respectively. Only, 2.5% of the HD patients were within range for all the previously mentioned parameters. These results indicate that most of the HD patients are away from the recommended range. The percentage of patients, who were in the recommended range, is less than that obtained in other studies (24); only, calcium levels were in the accepted range (25). The explanation of these differences may be attributed to implementing different modalities in regulation of phosphorus and PTH in different institutions, such as using other phosphate binders as, sevelamer hydrochloride, which is widely available in the USA and Europe for the treatment of

hyperphosphatemia in patients with CKD (26), another phosphate binder in use is lanthanum carbonate (27). In addition, other vitamin D analogues as, 22- oxacalcitriol (28), paricalcitol (29), or doxercalciferol(30), may be used for controlling PTH secretion with minimal hypercalcemia and hyperphosphatemia compared to calcitriol. Paricalcitol and doxercalciferol are currently available for clinical use in the USA (31). Also, using of cinacalcet HCl, which is a new calcimimetic agent that acts at the level of the calcium-sensing receptor. Activation of this receptor by calcimimetics increases intracellular calcium concentration, which causes rapid reduction in PTH secretion, serum phosphorus levels and the Ca × P product, which remain suppressed for up to three years (12,13, 32).

The inability of the HD unit at Al-Shifa hospital in achieving a high percentage of patients in the approved range may be explained by many factors; firstly, using calcium carbonate as a phosphate binder only. Moreover, the dose of calcium carbonate used may be less than that required for optimal effect. Secondly, using daily oral doses (0.5 µg) of the vitamin D analogue, alfacalcidol only for controlling PTH secretion, while most HD patients in the USA are now managed with thrice- weekly intravenous doses of calcitriol or other vitamin D analogues (31).

According to KDOQI guidelines, alfacalcidol, should be discontinued when PTH levels decrease below target levels, or if calcium or phosphate levels increase above target levels. Moreover, parathyroidectomy, (subtotal or total), was not performed to the HD patients whose PTH values were more than 800 pg/ml as indicated by KDOQI guidelines; parathyroidectomy should be recommended in patients with severe hyperparathyroidism (persistent serum levels of PTH >800 pg/mL, associated with hypercalcemia and/or hyperphosphatemia that are refractory to medical therapy (11). It was found that parathyroidectomy rates in U.S. HD patients increased between 1998 and 2002. The annual incidence of parathyroidectomy was 6.8 per 1000 patients/ year in 1998 but, the rates increased progressively after 1998, reaching 11.8 per 1000 patients/year in 2002 (33).

In studying the effect of duration of HD on the levels of PTH, Ca × P product, albumin- corrected serum calcium and phosphorus, it was found that there were no statistically significant differences in the levels of Ca × P product, albumin-corrected serum calcium and phosphorus in the group on HD for < 48 months and the group on HD for ≥ 48 months. Conversely, the difference in PTH levels was statistically significant, where it was higher in the group on HD for ≥ 48 months, which indicates that the parathyroid glands activity was in a positive correlation with the duration of HD. This result is supported by another study that found a significant positive

correlation of serum PTH with HD duration (17). Also, an increase in PTH was found with time on dialysis, an increase that is significant even after adjusting for calcium and phosphorus concentration (34). The explanation of this result may be due to the fact that the parathyroid glands were more activated due to the continuous state of stimulation as hyperphosphatemia is persistent and consequently, low concentration of ionized calcium. High phosphate enhances parathyroid cell proliferation and PTH synthesis and secretion directly and indirectly through both a reduction in serum calcitriol and ionized calcium levels (35).

It seems that 2 or 3 sessions of HD a week were inadequate for maintaining the levels of PTH, Ca × P product and serum phosphorus to be in the recommended ranges. Results from clinical trials using daily HD strongly suggest that thrice-weekly HD regimens are only marginally adequate for achieving weekly phosphorus balance in many patients with ESRD (31). Because of the kinetics of phosphate, increasing the frequency of dialysis sessions more effectively removes phosphate than increasing time of individual dialysis sessions (36). Alternative dialysis regimens, such as daily nocturnal HD and short-duration HD done 6 days per week, provide much better control of serum phosphorus concentrations than conventional thrice-weekly HD (37).

The present study revealed that the correlation between the PTH with albumin-corrected serum calcium among cases was weak, inverse and statistically not significant. This result is similar to that obtained by others who demonstrated that serum PTH was not related to total serum calcium(38).

The present study showed no statistically significant correlation between PTH with either serum urea or creatinine which indicates that the secretion of the PTH is independent of the effect of serum urea or creatinine.

Recent evidence has shown a high prevalence of coronary artery calcifications in the ESRD population, and they probably play a major role in the high cardiac morbidity and mortality rates. Coronary artery calcifications are much more common and more severe in patients on HD than in subjects without renal failure (39). Most studies have found correlations of calcifications with uncontrolled hyperphosphatemia, an increased CaxP product and duration of dialysis (40). The present study showed that 22.5% of HD patients suffered cardiovascular diseases; however, exact diagnosis was not investigated.

In conclusion, the unsatisfactory results of the present study are most probably due to not complying with KDOQI guidelines for HD patients at Al-Shifa hospital. In addition, it seems that treatment protocol is not

effective. Authors recommend that the Ministry of Health should provide resources to implement KDOQI guidelines. Conducting clinical trials is of utmost importance to find the most appropriate methods of controlling parathyroid gland activity for HD patients attending this hospital.

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