Original Article

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Biochemistry Section

Influence of Renal Impairment on Serum Parathyroid Hormone and Vitamin D Status and their Association with Serum Creatinine in Patients Undergoing Haemodialysis: A Case-control Study

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ABSTRACT

Introduction: A transition in the lifestyle of Saudi population over the past few decades has increased the burden of various metabolic disorders including, diabetes mellitus type 2, Chronic Kidney Disease (CKD), cardiovascular diseases, and vitamin D deficiency. Deficiency of vitamin D has been linked to the progression of kidney disease and many cardiovascular complications.

Aim: The study focuses on the vitamin D status and associated changes in serum Parathyroid Hormone (PTH) in End Stage Renal Disease (ESRD) patients undergoing haemodialysis in the Northern Border Region (Arar city) of Saudi Arabia. The present study also investigated the relationship between serum creatinine, PTH and vitamin D levels in these patients.

Materials and Methods: This case-control study was carried out for a period of five months (September 2019 to January 2020). It included 60 patients, suffering from ESRD on haemodialysis (cases) attending the Nephrology Centre of Prince Mohammed bin Saud Al Kabeer renal dialysis unit in Arar Central Hospital, Arar, Saudi Arabia. A control population (n=60) with normal kidney function, who visited the hospital for other reasons, was also identified. Their blood samples were collected for estimation of renal function parameters {Blood Urea Nitrogen (BUN) and creatinine}, serum calcium, phosphate, vitamin D and PTH. Statistical analysis was performed using the Statistical Package for the Social Sciences version 22.0.

Results: The study included 60 patients (50% males and 50% females) undergoing haemodialysis and 60 healthy controls (50% males and 50% females) with a mean age of 46.83±14.19 (range 18-73 years) and 39.25±5.11 (range 30-54 years) years, respectively. The mean BMI of the patients was 27.3±3.4 kg/m^2 and that of controls was 23.7±2.2 kg/m^2. A significant elevation (p-value <0.001) of serum PTH showing hyperparathyroidism accompanied by significant (p-value <0.001) hypovitaminosis D and hypocalcaemia was observed in the patients as compared to controls. The results also demonstrated significantly elevated (p-value <0.001) levels of BUN and serum creatinine in ESRD patients. Results of correlation analysis exhibited a significant (p-value <0.05) positive correlation between serum creatinine and PTH whereas, there was a significant (p-value <0.05) negative correlation between serum creatinine and vitamin D; and serum PTH and vitamin D among the patients.

Conclusion: This study highlights the importance of monitoring changes in PTH levels in patients with impaired renal function for the early detection and treatment of CKD. The study also showed a significant (p<0.05) positive association between serum creatinine and PTH followed by a significant (p<0.05) negative correlation between serum creatinine and vitamin D; and serum PTH and vitamin D.

Keywords: Blood urea nitrogen, Chronic kidney disease, Hyperparathyroidism, Serum calcium

INTRODUCTION

Vitamin D, a prehormone is converted to its active form 1,25 vitamin D or calcitriol in the kidneys. The role of calcitriol in sustaining serum calcium and phosphate homeostasis is imperative and well established [1-3]. Furthermore, 25-hydroxycholecalciferol D {25-(OH) D} and calcitriol have also been recognised to stimulate the secretion and action of insulin [4], hinder the rennin-angiotensin system [5] and alter the inflammatory reaction linked to atherosclerosis [6]. Thus, deficiency of vitamin D may lead to hypertension, insulin resistance, inflammation, and progression of CKD [7-9].

Inspite of the regular dietary supplementation, vitamin D insufficiency remains a common problem in people suffering from fat malabsorption, older age groups and those having inadequate exposure to sunlight [10]. Studies have revealed deficiency of vitamin D in 70-80% of the people suffering from stage 3 and 4 CKD with severe deficiency in 26% of these patients [11]. A reduction in serum calcium triggers the release of Parathyroid Hormone (PTH), which regulates plasma calcium and phosphate levels. Advanced renal disease is linked to decreased production of vitamin D, thus causing depleted serum calcium followed by increased serum phosphate levels owing to their reduced clearance. This may lead to the development of Secondary Hyperparathyroidism (SHPT).

A dramatic and unhealthy change in the lifestyle of Saudi population over the past few decades has increased the burden of various metabolic disorders including, diabetes mellitus type 2, CKD, cardiovascular diseases and vitamin D deficiency. To the best of our knowledge this is the first study carried out to investigate the vitamin D status and PTH levels in haemodialysis patients in the Northern region (Arar city) of Saudi Arabia. The results of this study may be helpful for providing information that may aid in the management of CKD patients. Thus, the present study was undertaken to investigate the influence of renal impairment on vitamin D status and serum PTH in End Stage Renal Disease (ESRD) patients from Arar region undergoing haemodialysis. Authors also investigated the relationship between serum creatinine, PTH and vitamin D levels in these patients.

MATERIALS AND METHODS

This was a case-control study carried out in the region of Arar, Saudi Arabia from September 2019 to January 2020. The study included 60 ESRD patients receiving phosphate binders (Sevelamer) on haemodialysis in the Nephrology Centre of Prince Mohammed bin Saud Al Kabeer renal dialysis unit in Arar Central Hospital, Saudi Arabia. A control population (n=60) with normal kidney function, who visited the hospital for other reasons, was also identified. The study was approved (decision no. 38/40/H) by the ethical committee of the Northern Border University (Local Committee of Bioethics- HAP-09-A-043). Informed consent was obtained from all the participants prior to their inclusion in the study and data collection.

Inclusion and Exclusion criteria: Patients ≥18 years suffering from ESRD, either gender, on haemodialysis for more than 6 months were included in the study. Patients undergoing haemodialysis less than three times per week and who were on haemodialysis for less than six months were excluded. A control population (n=60) with normal kidney function, who visited the hospital for other reasons, was also identified.

Sample size calculation: For calculating the sample size, an online sample size calculator (Open Epi, version 3) was used assuming percentage of cases with exposure to be 25%, at 95% confidence level, with 80% statistical power and margin of error 5%. The minimum required sample size was calculated to be 59 in each group. Therefore, 60 participants were included in each group (60 cases and 60 controls).

Data Collection and Biochemical Analysis

Demographic and clinical information of all the participants was collected using a study-specific form. It consisted of information about age, sex, nationality, Body Mass Index (BMI), haemodialysis duration and co-morbidity type. Blood samples of the patients satisfying the study criteria were obtained after an overnight fast. Serum creatinine, BUN, calcium, and phosphate were measured using the Dimension (RxL XPAD-Germany). Vitamin D (25(OH)D3) levels were measured by radioimmunoassay (Diasorin, Stilwater, Minnesota, United States). Serum intact PTH was measured by autoanalyser (ELecsys 2010, Cobas E 411-Mannheim Germany). Privacy and confidentiality of the obtained data had been insured.

STATISTICAL ANALYSIS

Results are expressed as means±SD. Statistical analysis was performed using the Statistical Package for the Social Sciences (SPSS) version 22.0. Descriptive analyses were performed to describe demographic, clinical and laboratory characteristics of the participants. Unpaired t-test was used for comparison of means between different groups (patients and controls). The correlation between various parameters was determined by Pearson's correlation coefficient. The p-value <0.05 was considered significant.

RESULTS

The study included 60 patients (50% males and 50% females) undergoing haemodialysis and 60 healthy controls (50% males and 50% females) with a mean age of 46.83±14.19 (range 18-73 years) and 39.25±5.11 (range 30-54 years) years, respectively. The mean BMI of the patients was 27.3±3.4, kg/m^2 and that of controls was 23.7±2.2 kg/m^2. [Table/Fig-1] displays the demographic and clinical characteristics of patients and controls. It was observed that diabetes mellitus (46.7%) was the major comorbidity in ESRD patients followed by hypertension (40%) and cardiovascular diseases (13.3%). The changes in important biochemical parameters observed in patients and controls during the study period are shown in [Table/Fig-2]. A significant elevation in the levels of BUN, serum creatinine and PTH (p-value <0.001) was observed in the patients as compared to controls. Serum calcium and vitamin D levels of the patients were significantly lower (p-value <0.001) as compared to the controls.

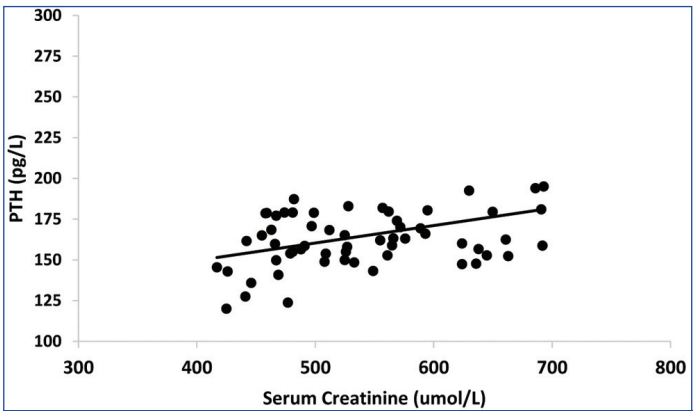
Variables	Patients (n=60)	Controls (n=60)	p-value
Age (Mean±SD) (years)	46.83±14.19	39.25±5.11	<0.001
Gender (%)			
Male	50	50	
Female	50	50	
Nationality (%)			
Saudi	32 (53.3%)	34 (56.6%)	
Expatriates	28 (46.7%)	26 (43.3%)	
Haemodialysis duration (%)			
≤1 year	17 (28.3%)	-	
>1 year	43 (71.6%)	-	
Body Mass Index, kg/m^2 (Mean±SD)	27.3±3.4	23.7±2.2	<0.001
Co-morbidities (%)			
Diabetes mellitus	28 (46.7%)	-	
Hypertension	24 (40%)	-	
Cardiovascular diseases	8 (13.3%)	-	

[Table/Fig-1]: Demographic and clinical characteristics of patients and controls.
Unpaired t-test was used to compare the means between patients and controls

Parameters	ESRD patients (n=60) Mean±SD	Controls (n=60) Mean±SD	Reference range	p-value
BUN (mmol/L)	18.78±2.87	3.15±0.38	2.5-6.4	<0.001
Serum creatinine (µmol/L)	540.03±77.75	73.61±8.23	53-115	<0.001
Serum calcium (mmol/L)	1.62±0.13	2.37±0.19	2.12-2.52	<0.001
Serum phosphorus (mmol/L)	1.25±0.17	1.15±0.16	0.81-1.58	0.002
PTH (pg/L)	164.63±25.55	41.75±7.27	15-65	<0.001
Vitamin D (ng/mL)	15.66±2.1.86	44.75±7.83	30-80	<0.001

[Table/Fig-2]: Laboratory findings in ESRD patients and controls.
BUN: Blood urea nitrogen; PTH: Parathyroid hormone
Unpaired t-test was used to compare the means between patients and controls

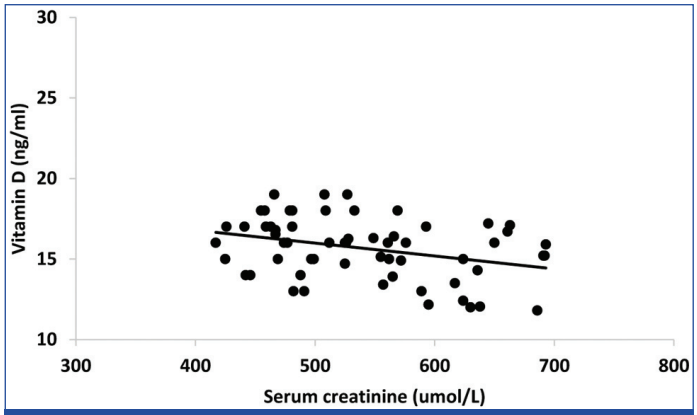
[Table/Fig-3-5] depict the correlation between creatinine, PTH and Vitamin D among ESRD patients. The correlation analysis revealed a positive correlation between serum creatinine and PTH (r=0.326, p-value=0.010) and an inverse correlation between serum creatinine and vitamin D (r=-0.333, p-value=0.009); and serum PTH and vitamin D (r=-0.250, p-value=0.053).



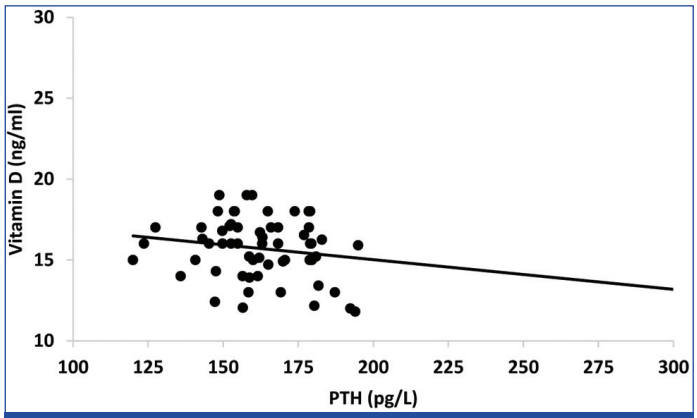
[Table/Fig-3]: Correlation between serum creatinine and PTH in ESRD patients (r=0.326, p-value=0.010).

DISCUSSION

The role of vitamin D and PTH in maintaining bone health is well established, but research indicates that deficiency of vitamin D may also be a risk factor for other diseases like autoimmune disorders, cardiovascular disease, and cancer [12,13]. The present study



[Table/Fig-4]: Correlation between serum creatinine and vitamin D in ESRD patients (r=-0.333, p-value=0.009).



[Table/Fig-5]: Correlation between serum PTH and vitamin D in ESRD patients (r=-0.250, p-value=0.053).

investigated the influence of renal impairment on vitamin D status and serum PTH in patients undergoing haemodialysis and their association with serum creatinine. The results showed increased levels of BUN and creatinine in the ESRD patients. This elevation is directly proportional to the progression of the disease and may be attributed to a reduction in the number of functioning nephrons, which decreases the GFR and hence a major reduction in excretion of water and solutes [14,15].

It is well known that CKD patients are predisposed to develop deficiency of vitamin D because of impaired renal function. Furthermore, control of dietary phosphorus is recommended for the patients on dialysis [16]. This dietary restriction of phosphorus could have an adverse effect on the vitamin D status of patients as phosphorus levels have been shown to play an important role in the renal production of 1, 25-(OH) D [17]. In this study, all the patients were deficient in vitamin D. This is in line with the study conducted by Gonzalez EA et al., who reported that that 97% of their patients on haemodialysis had vitamin D3 levels in the suboptimal ranges [18]. The major reason for vitamin D deficiency in kidney disease patients is the suppression of 1-α hydroxylase activity by uremia and acidosis and reduced availability of its substrate 25(OH)D [19]. Studies also reveal that these patients exhibit enhanced production of Fibroblast Growth Factor (FGF)-23 which causes a down-regulation of renal 1-α hydroxylase [20,21].

Significant SHPT was observed among the patients followed by a significant positive correlation between PTH and serum creatinine. The development of SHPT may be attributed to many factors including deficiency of calcitriol, a decrease in the activation of the Calcium-Sensing Receptor (CaR) in the parathyroid gland, and skeletal resistance to the calcaemic effect of PTH. The reduced calcitriol level contributes to a reduction in intestinal calcium absorption ultimately causing hypocalcaemia, which is the impetus for an increased production of PTH [18]. A slight depletion of the serum calcium was also observed in the study participants which was in concordance with other studies demonstrating constant decline in the serum calcium concentration [22]. Moreover, FGF-23 which increases in the early stages of CKD possibly as a consequence of phosphorus retention has been found to inhibit calcitriol synthesis, thus leading to increased PTH [23].

The SHPT developed during the course of CKD can cause disorders of mineral metabolism and bone disease. The results of the study showed significant negative correlation between serum PTH with vitamin D, indicating deficiency of vitamin D in patients with hyperparathyroidism. Calcitriol is a strong inhibitor of PTH production and down-regulates the expression of PTH gene by binding to receptor complex present on parathyroid cells [24]. Consequently, the reduced calcitriol synthesis during the course of CKD relieves the inhibition of PTH gene expression resulting in hyperparathyroidism [19].

To maintain the PTH levels in a normal range and hence prevent renal bone disease, clinicians may prescribe analogs of vitamin D to patients with deficiency of vitamin D. Reports suggest that early treatment with ergocalciferol [25] or high-dose supplementation of cholecalciferol (600 000 IU) [26] were effective in normalising the PTH levels and preventing renal bone disease. However, care must be taken while using high-doses of cholecalciferol as it causes significant absorption of calcium and phosphorus, causing hypercalcaemia and has been implicated in cardiovascular mortality risk [27].

Limitation(s)

The main limitation of this study was that it was confined to a single centre with smaller sample size and shorter duration.

CONCLUSION(S)

The findings of the study demonstrated deficiency of vitamin D followed by severe SHPT in ESRD patients from Arar region in Saudi Arabia. The study also showed a significant positive association between serum creatinine and PTH followed by a significant negative correlation between serum creatinine and vitamin D; and serum PTH and vitamin D. Hyperparathyroidism is one of the earliest manifestations of impaired renal function. It is important to monitor the changes in PTH levels in patients with impaired renal function for the early detection and treatment of CKD. Patients demonstrating marked changes in PTH levels should be given relatively simple treatments that have the potential to prevent adverse outcomes.

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