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Serum vitamin D and parathyroid hormone profiles in patients with various stages of renal disease

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RESEARCH

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ABSTRACT

Background

The prevalence of vitamin D deficiency among Saudi population has increased recently. The social and pathological factors, including kidney disease that may have influenced the vitamin status have not been investigated in the Hail population.

Aims

The present study aims to: (1) investigate changes in the serum vitamin D, parathyroid hormone, serum calcium, and phosphate levels in Saudi patients with kidney disease; and (2) elucidate the other possible physiological factors that may have influence on the vitamin status.

Methods

A cross-sectional study was carried out in King Khalid Hospital in Hail, Saudi Arabia. The database of kidney disease patients that attended the Kidney Unit between September 2012 and June 2013 was searched and data classified according to the estimated glomerular filtration rate into stages 1–4. Beside the kidney function parameters, serum calcium, phosphorus, vitamin D, and parathyroid hormone were measured.

Results

Out of the 167 patients who visited the kidney unit, the data of 96 patients was included in the study. The results exhibited significant reductions in serum vitamin D level in stage 4 patients by 52.05 per cent with significant increase in the serum PTH level amounting to 3.5-fold. Kidney impairment at stage 4 caused significant increase in the serum phosphate level by 15.74 per cent and the serum calcium by 8.17 per cent. Significant correlations were observed between serum creatinine and Log PTH ($r=0.704$, $p<0.0001$) and a negative correlation between creatinine and log vitamin D ($r=–0.373$, $p=0.001$).

Conclusion

The results exhibited depletion of serum vitamin D concentration accompanied with the development of severe secondary hyperparathyroidism with the progression in kidney disease. The vitamin D deficiency was more prominent in females, older ages, and advanced kidney disease.

Key Words

Vitamin D, parathyroid hormone, kidney disease

What this study adds:

1. What is known about this subject?

The prevalence of chronic kidney disease in the Saudi Arabia population is progressively increasing. Recently, vitamin D deficiency has been reported in some regions of the country.

2. What new information is offered in this study?

The present results have shown that stage 4 kidney disease patients from Hail, Saudi Arabia, have an increased rate of vitamin D deficiency with secondary hyperparathyroidism. Women and elderly individuals are at higher risk.

3. What are the implications for research, policy, or practice?

A countrywide population study to evaluate the prevalence of vitamin D deficiency in females and older adults is

required. Physicians may need to consider requesting that serum vitamin D be tested routinely in females, the elderly, and kidney disease Saudi patients.

Background

Vitamin D is either obtained from diet or synthesised in the skin from 7-dehydrocholesterol. In the liver the vitamin undergoes hydroxylation into 25(OH)D, the major circulating form of the vitamin. Another hydroxylation at 1-α-carbon takes place in the renal tubules to form 1, 25-dihydroxy-D (calcitriol), the biologically active form. Calcitriol maintains the plasma calcium and phosphorus levels by increasing the expression of the epithelial calcium channel–TRPV6 and the intracellular calcium transporter-Calbindin 9 K.[1,2] In the presence of calcitriol, the efficiency of intestinal calcium and phosphorus absorption increases to 40 per cent and 80 per cent, respectively.[3] Moreover, the 25(OH)D and calcitriol are known to stimulate the secretion and action of insulin,[4] inhibit renin angiotensin aldosterone system,[5] and alter the inflammatory response associated with atherosclerosis.[6] Thus low serum levels of vitamin D are known to be associated with hypertension, insulin resistance,[3] inflammation, and progression of chronic kidney disease (CKD).[7–9]

Despite the routine dietary supplementation, vitamin D deficiency is common in elderly individuals, people with limited sun exposure, and those with fat malabsorption.[10] It was reported that 70–80 per cent of patients with CKD stages 3 and 4 were vitamin D deficient and 26 per cent of these patients were severely deficient.[11]

The parathyroid hormone (PTH), an 84-amino acid polypeptide hormone, is also involved in the regulation of plasma calcium and phosphate levels. The drop in serum ionised calcium levels is known to trigger the synthesis and release of PTH. In patients with advanced renal disease, the synthesis of calcitriol is depressed leading to reduction in the serum-ionised calcium levels with elevated serum phosphate concentration due to reduced clearance. Both phenomena may lead to the development of secondary hyperparathyroidism. The resultant increased PTH production is believed to be the predominant cause of renal osteodystrophy and the common treatment to control the secondary hyperparathyroidism is vitamin D therapy, which ameliorates renal osteodystrophy[12,13] and improves patient survival.[14,15]

The lifestyle of the Saudi population has changed dramatically in the past few decades causing a more sedentary type of life. This has caused an increase in the prevalence of several metabolic disorders such as obesity, type 2 diabetes mellitus, cardiovascular diseases, and more recently vitamin D deficiency.

Hail district lies in the mid-north of Saudi Arabia at a higher altitude and with sunshine throughout the year. No study has been carried out in this region to investigate the vitamin D status and PTH levels in kidney disease patients. Therefore, in the present study we aimed to investigate the influence of renal impairment on vitamin D status and the associated changes in serum PTH in a group of patients from Hail region. We also examined the possible co-existence of other factors that may affect the serum vitamin D and PTH levels in these patients.

Method

Sample frame

This was a cross-sectional study carried out in King Khalid hospital, Hail, Saudi Arabia, between September 2012 and June 2013. The project was in compliance with the Helsinki Declaration and was approved by the Research Ethical Committee, Faculty of Applied Medical Sciences, University of Hail. The patient electronic database was searched for patients with various stages of kidney disease who were registered at the Kidney Unit. Files of patients with abnormal liver function, overt diabetes mellitus, or with history of thyroidectomy, and those who were taking calcium or vitamin D supplement were excluded. During their visit to the clinic, the patients' blood samples were received in the laboratory for their renal function tests. Following the release of results, a copy of the data was entered in our records and the residual serum samples were stored at -20°C for the assay of vitamin D and PTH using commercial kits.

The estimated glomerular filtration rate (eGFR) for each patient was then calculated according to the CKD Epidemiology Collaboration Equation.[16] The patients were then classified into stage 1 (with eGFR≥90), stage 2 with eGFR 89–60, stage 3 with eGFR 59–30, and stage 4 with eGFR≤29. Unfortunately, only two patients had eGFR<15 ml/min/1.73m^2 (stage 5), therefore, they were excluded and the study was confined to the stages 1 to 4.

Biochemical analysis

The measurements of serum creatinine, blood urea nitrogen (BUN), uric acid, calcium, and phosphate were carried out using The Dimension (RxL XPAD-Germany). Serum intact PTH (1–84) and vitamin D (25-(OH)D) were estimated by Autoanalyser (ELecsys 2010, Cobas E 411-Mannheim Germany).

Statistical analysis

Results are expressed as means ± SD. The differences between the means were computed by one-way ANOVA using Statistical Package for Social Sciences version 16.0 (SPSS Inc, Chicago, IL, USA). The significance of differences between the means was carried out by Unpaired Student`s T-test. *P* values <0.05 were considered significant. The regression analysis between the various parameters was carried out by Spearman`s Regression analysis. *P* values <0.05 were considered significant.

Results

From the total number of patients who visited the Kidney Unit during the study period (n=167), 71 patients (M=27 and F=44) were excluded, and 96 patients files (M=42, F=54) were selected. The patients had an average age (39.09 ± 14 yrs), range (14–85 yrs). As shown in Table 1, on the basis of the eGFR, the patients were classified into CKD stages 1–4. The mean age increased progressively from stage 1 (32.19 ± 9.74 yrs) to stage 4 (45.60 ± 19.46 yrs). In the stage 4 patients, the ratio of female to male was 5:1 compared to stage 1 (ratio 1:1). As expected, the concentrations of serum creatinine, BUN, and uric acid concentrations increased progressively from stage 1 to stage 4. On the other hand, there was a slight but significant (p<0.05) increase in the serum total calcium concentration by 8.17 per cent in the stage 4 patients, whereas the serum phosphate increased by 15.74 per cent in stage 4 patients compared to the stage 1 group.

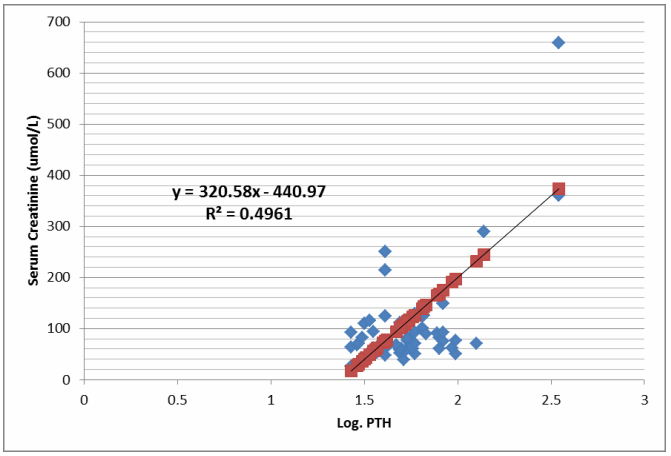
Table 1: Distribution of sex, age, serum kidney function parameters, serum calcium and serum phosphate levels in patients with various stages of kidney disease

	Stages of kidney disease			
	Stage 1	**Stage 2**	**Stage 3**	**Stage 4**
eGFR (ml/min/1 .73m^2)	118.50 ± 17.08 (≥ 90)	74.40 ± 6.85 (89–60)	52.13 ± 7.71 (59–30)	19.83 ± 6.06 (≤29)
Age (Yrs)	32.19 ±9.74 (14–56)	44.66 ±22.13 (14–85)	48.16± 13.49 (21–65)	45.60 ±19.43 (33–65)
Gender	M=10, F=14	M=12, F=12	M=16, F=12	M=4, F=16
Creatinine (umol/L)	63.194 ±14.17	92.75± 18.27 a‡	123.50 ± 14.45 a‡ b‡	354.40 ± 56.49 a‡ b‡ c‡
BUN (mmol/L)	03.58 ± 0.87	04.69 ± 01.48 a‡	05.75 ± 01.76 a‡ b†	11.44 ±03.41 a‡ b‡ c‡
Uric acid (umol/L)	288.83 ± 74.67	297.50 ± 41.30 a‡	310.16 ± 51.45 a‡ b‡	341.81 ± 58.15 a‡ b‡
Calcium (mmol/L)	2.08 ± 0.60	2.31 ± 0.31	2.48 ± 0.96 a*	2.52 ± 0.44 a*
Phosphate (mmol/L)	1.08 ± 0.41	1.05 ± 0.53	1.22 ± 0.42 a*	1.25 ± 0.32 a*

Presented data are means ± SD. † p<0.01; ‡ p<0.001. (a) significantly different from stage 1, (b) significantly different from Stage 2; and (c) significantly different from stage 3.

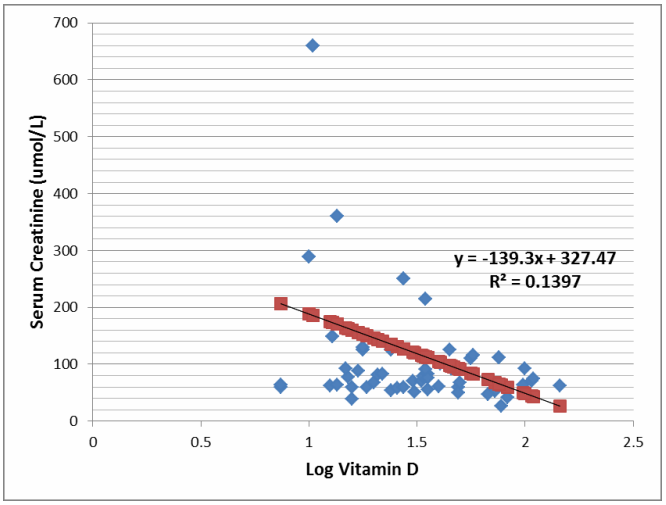
There was a highly significant correlation between serum creatinine and Log PTH (r=0.704, p<0.0001) (Figure 1), between eGFR and Log PTH (r=0.375, p=0.001), between Log PTH and uric acid (r=0.33, p=0.006), whereas there was a reverse correlation between Log PTH and Log vitamin D (r=–0.407, p=0.0006).

Figure 1: Plot of regression analysis between log PTH concentration and serum creatinine (r=0.704, p<0.0001)



Moreover, there was a significant negative correlation between log vitamin D and creatinine (r=–0.373, p=0.001) (Figure 2), and between log vitamin D and age (r=–0.237, p=0.05). However, no significant correlations were observed between vitamin D or PTH and calcium or phosphate.

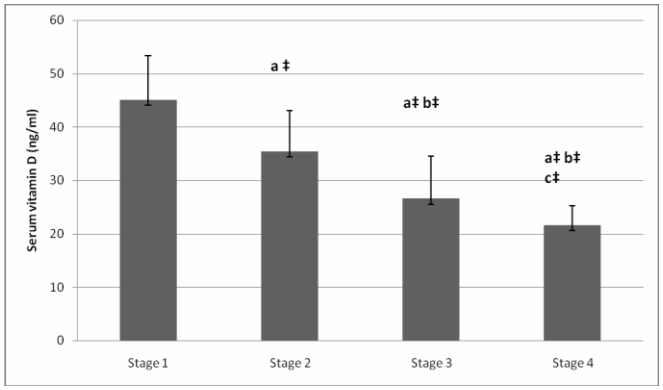
Figure 2: Plot of regression analysis between log vitamin D concentration and serum creatinine (r=–0.373, p=0.001)



As depicted in Figure 3, the concentration of vitamin D was sufficient in the stage 1 subjects, whereas in stage 2, the vitamin concentration dropped by 21.60 per cent, and severely decreased in stage 4 by 52.01 per cent compared to stage 1 subjects. In contrast, the concentration of serum PTH increased in stage 2 subjects by 13.16 per cent and

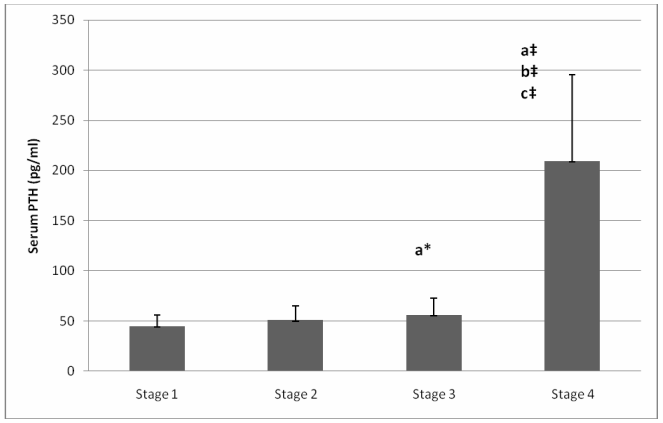
severely elevated in the stage 4 patients by 3.5-fold (Figure 4). Table 2 summarises the important possible factors that may influence the vitamin D status in the body. Analysis of gender showed that the percentage of male individuals with severe vitamin D deficiency and those with sufficient vitamin were not different (33.33 per cent vs. 25.00 per cent). However, 38.23 per cent of the female subjects had severe deficiency compared to only 8.82 per cent with sufficient vitamin.

Figure 3: Serum vitamin D concentrations measured as 25(OH)D, in kidney disease patients at various stages of kidney impairment



Column and vertical bar represent mean ± SD. ‡ p<0.001. (a) significantly different from stage 1; (b) significantly different from stage 2; and (c) significantly different from stage 3.

Figure 4: Serum PTH concentrations in kidney disease patients at various stages of kidney impairment



*Column and vertical bar represent mean ± SD. * p<0.05; ‡ p<0.001. (a) significantly different from stage 1; (b) significantly different from stage 2; and (c) significantly different from stage 3.*

In contrast, 35.71 per cent of subjects with high PTH level had severe vitamin deficiency compared to only 7.14 per cent of those with high PTH having sufficient vitamin level. In relation to the effect of age, 18.18 per cent of younger subjects aged >20 years had vitamin deficiency compared to 27.27 per cent with sufficient vitamin. In contrast, 50 per cent of subjects aged ≥34 years had severe vitamin deficiency compared to only 18.75 per cent with sufficient vitamin level.

Table 2: The effects of gender, age, serum PTH, and creatinine levels on the vitamin D status

		% of subjects with various levels of vitamin D (ng/mL)			
Factor influencing Vitamin D status		SD (≤10)	D (10–20)	MD (20–30)	S (≥30)
Gender	Male (n=42)	33.33	37.50	04.16	25.00
	Female (n=54)	38.23	29.41	23.52	8.82
Age	(≤ 20 yrs)	18.18	36.36	18.18	27.27
	(21–33 yrs)	43.75	31.25	18.75	6.25
	(≥34 yrs)	50.00	31.25	0.00	18.75
Serum PTH (pg/ml)	Low (≤40)	41.66	8.33	8.33	41.66
	Medium (4–60)	41.17	41.17	11.76	5.88
	High (≥61)	35.71	42.85	14.28	7.14
Serum Creatinine (µmol/L)	Normal (≤60)	31.57	31.57	26.31	10.52
	Medium (61–93)	41.66	33.33	4.16	20.80
	High (≥94)	33.33	33.33	20.00	13.33

The vitamin D status was classified according to Lavie et al.[17] as: (SD: severely deficient, D: deficient, MD: mildly deficient and S: sufficient).

On the other hand, the kidney function exhibited that 33.33 per cent of patients with abnormally elevated serum creatinine level had severe vitamin deficiency, whereas, only 13.33 per cent of them had vitamin sufficiency.

Discussion

The well-established functions of vitamin D and PTH are associated with the bone health, but several epidemiological studies have shown that vitamin D deficiency is also associated with increased risk of many non-skeletal diseases such as cancer, autoimmune, and cardiovascular diseases.[18,19] In the present study we investigated the possible important factors which may predispose subjects to vitamin D deficiency. Female subjects were more vulnerable to vitamin D deficiency than male

subjects, which is understandable considering sunlight is the most important source of vitamin D, but for religious reasons Saudi females have their bodies entirely covered in black whenever they leave home. This is likely a main factor contributing to widespread vitamin deficiency among the Saudi female population. Similar findings were also reported where Saudi females in other regions of the country had low serum vitamin D levels compared to their counterparts in other countries.[20] Furthermore, obesity is also more prevalent among the Saudi female population than the male population[21] and it is known that more body fat hinders the absorption of UV light by the skin, which may in turn impair the vitamin synthesis by the body.[22] Also, more vitamin D is known to be sequestered in the excess adipose tissue.[23]

The second important factor observed in this study is age, where older subjects were more likely to be vitamin D deficient. This factor corresponded with some studies where the elderly population had reduced serum vitamin D levels compared to younger people. It has been suggested that the elderly have lower capacity for UVB-induced vitamin D synthesis in the skin, thus making them more susceptible to vitamin deficiency.[24,25] Moreover, younger subjects are healthier and are more likely to be exposed to sunlight.

Kidney function was the third factor that demonstrated a strong influence on the vitamin homeostasis. Our data shows 66 per cent of the patients with impaired kidney function had mild to severe vitamin D deficiency. The association of kidney disease with vitamin D deficiency emerges from the fact that healthy kidneys play an important role in metabolising vitamin D. It was reported that on average, only about one-quarter of stages 3 and 4 CKD patients seem to have sufficient vitamin D levels of more than 30 ng/ml.[26] The mechanism underlying this phenomenon is believed to be multifactorial:

1. Patients with CKD have limited exposure to sunlight due to their inability to participate in outdoor physical activity.
2. Patients with CKD are known to be unable to produce vitamin D3 in the skin even though the concentration of 7-dehydrocholesterol in their epidermis is similar to their age-matched controls.[27]
3. The proteinuria in these patients leads to urinary waste of vitamin D-binding protein and the vitamin D metabolites.[28]

Since the activation of 25-OH-D into calcitriol takes place mainly in the kidney, the calcitriol deficiency occurs with progression in kidney disease. The mechanism underlying the calcitriol deficiency in the CKD patients is that the activity of 1-α hydroxylase, the renal enzyme responsible for calcitriol synthesis, is suppressed by uraemia and acidosis, and also due to the reduced availability of its substrate-25 (OH)D.[29] Moreover, in these patients there is increased production of the fibroblast growth factor (FGF)-23 that down regulates the expression of renal 1-α hydroxylase enzyme.[30–32]

Our data indicated significant secondary hyper-parathyroidism in patients with stage 4 of the disease, with a significant correlation between the log PTH and serum creatinine (r=0.704, p<0.0001). In normal subjects, the secretion of PTH is maintained by the presence of FGF-23,[33] whereas in hypocalcaemia caused by the calcitriol deficiency, the expression of Klotho is increased in parathyroid gland and kidneys.[34] The expressed Klotho plays a role in extracellular calcium regulation and release of PTH-causing hyperparathyroidism. Klotho raises the serum calcium by stimulating tubular calcium reabsorption through glycosylation and anchoring of the calcium-transporting channel.[35] This explains the severe hyperparathyroidism in stage 4 patients. Although the exposure of parathyroid glands to FGF23 is believed to inhibit PTH secretion, patients with CKD were shown to develop secondary hyperparathyroidism despite the high levels of serum FGF23, indicating development of a parathyroid-FGF23 resistance.[36]

The secondary hyperparathyroidism that ensues in CKD can lead to disturbance in mineral metabolism and high-turnover bone disease. Our results indicated a strong correlation between PTH and the vitamin status. It showed that 42.8 per cent and 35.7 per cent of the subjects with high serum PTH levels had vitamin D deficiency and severe deficiency, respectively. This association between PTH and vitamin D level was supported by the significant negative correlation (r=–0.407, p=0.0006). Several investigators have also reported the correlation between the induced secondary hyperparathyroidism and vitamin D deficiency in CKD. The calcitriol is known as a potent negative regulator of PTH production. It binds the vitamin D-receptor complex on the parathyroid cells and down regulates PTH gene expression.[37] Thus, with progression of kidney disease the diminished calcitriol production reverses the suppressed PTH gene expression leading to the hyperparathyroidism.[29]

Our results showed significant increases in serum phosphate levels in stage 3 and stage 4 patients. This was in congruence with several reports that showed overt

hyperphosphataemia in patients with CKD when the GFR falls below 40 mL/min/1.73m^2 caused by inability of the kidneys to excrete phosphate.[38,39] However, the serum phosphate homeostasis in CKD is a balance between the phosphate retention by the kidney and the stimulatory effect of PTH for phosphate excretion. Moreover, the elevated FGF-23 level is known to decrease the expression of a sodium-phosphate co-transporter in the proximal tubule, a protein responsible for phosphate reabsorption, and thus enhances the excretion of phosphate in urine.[40]

Interestingly, our data also showed a slight but significant increase in the serum calcium concentrations of the stage 3 and stage 4 patients. This was in contrast to the findings of other authors who reported consistent depression in the serum calcium levels.[36] The mechanism underlying the serum calcium homeostasis in CKD is rather complex. Although, vitamin D deficiency is believed to reduce the intestinal calcium absorption by about 50 per cent, the reduction in serum calcium triggers the release of PTH, which is believed to correct the serum calcium by promoting mobilisation of calcium from bone and increasing its reabsorption from the renal tubules.[41,42]

High dietary calcium content is believed to influence the plasma calcium concentration. This is also true in patients treated by calcium based-phosphate binders that showed positive calcium balance.[36,43,44] In a study involving Saudi haemodialysis patients receiving sevelamer carbonate, it was shown that 52 per cent of the patients developed serum calcium levels greater than 2.75mmol/L.[45] Spiegel and Brady[46] reported that subjects with advanced stage 3 or stage 4 CKD were in slightly negative calcium balance on 800mg calcium intake, but became in marked positive balance when they ingested 2000mg of elemental calcium. The calcium load in these patients was even higher than the normal controls.

Hail's population is mostly Bedouins raising camels and consuming significant amounts of camel milk. Studies have shown camel milk to be very rich in calcium, containing about 0.84g/L.[47] In a study comparing camel milk with the human milk, it was shown that camel milk contains about three-fold the calcium content of human milk (109mg/100ml of camel milk compared to 34mg/100ml of human milk).[48] This indicates that an individual consuming 2.0 to 2.5 litres of camel milk per day will be close to the target of 2000mg calcium. Thus, the amount of dietary calcium consumed by the Hail CKD patients from the camel milk may in part underlay this elevated serum calcium levels.

The present study has investigated, for the first time, the vitamin D status and the secondary hyperparathyroidism in kidney disease patients of Hail region. It has also highlighted the social factors that may influence the vitamin status. The author suggests a wide-scale population study to determine the prevalence of vitamin deficiency among the elderly and females. A limitation of the study is the relatively small sample size and not involving the stage 5 (with eGFR <15 ml/min/1.57m^2) patients. A wider study involving the end-stage kidney disease patients on haemodialysis is now underway, and it may consider more of the unanswered questions.

Conclusion

The present results demonstrate vitamin D deficiency and secondary hyperparathyroidism in stage 4 CKD patients from Hail region in Saudi Arabia. In these patients, the vitamin D deficiency was prominent in females and older ages. There was a slight increase in serum calcium and significant increase in the serum phosphate concentrations. These findings are useful for providing data that may assist with management of CKD patients.

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CONFLICTS OF INTEREST

The author declares that he has no competing interests.

ETHICS COMMITTEE APPROVAL

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