

Frequency of Vitamin D deficiency and its association with serum PTH levels in end stage renal disease patients

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Abstract

Objective: To assess the frequency of Vitamin D Deficiency and its association with serum Parathormone (PTH) levels in End stage renal disease patients in a tertiary setup.

Methods: This cross sectional study was conducted in the Department of Nephrology, Liaquat National Hospital from January to December 2016 and comprised patients with End stage renal disease on maintenance haemodialysis. Sample size of 113 at 8% prevalence was calculated inflated to 150. Participants were selected through purposive sampling technique. Numerical variables were expressed as mean \pm SD (standard deviation) while categorical variables were expressed as frequency and percentages. To determine association between Vitamin D and serum Parathormone (PTH) levels chi-square test was applied. Association of serum alkaline phosphatase levels with both Vitamin D levels and PTH levels was analyzed using chi-square test. SPSS 20 was used for data analysis. P-value <0.05 was taken as significant.

Results: Of the 150 participants, 33 were drop outs, 63(53.8%) were males and 54(46.2%) were females. The overall mean age was 52.47 ± 15.21 years. Of all, hypertension as a comorbidity was present in 64(54.7%), Diabetes mellitus was present in 8(6.8%) and cardiovascular disease in 7(6%). Among the biochemical markers, mean serum vitamin D levels were 18.6 ± 13.6 ng/ml, mean Serum PTH levels were 253.8 ± 227.2 pg/ml, mean serum alkaline phosphatase levels were 143.7 ± 125.4 μ g/L, mean serum phosphorus levels were 4.81 ± 3.46 mg/dl and mean serum calcium levels were 21.41 ± 114.4 mg/dl. Among the study participants, 67(57.3%) were found to be Vitamin D deficient.

Both low and normal vitamin D was associated with High PTH (P <0.001)

Other significant associations noted were that of High Alkaline Phosphatase with High PTH levels and a normal Vitamin D level (P <0.001)

Conclusion: Our study revealed more than half of our participants were Vitamin D deficient and an association was found between Normal Vitamin D levels and high serum PTH levels with associated high alkaline phosphatase levels.

Keywords: Vitamin D homeostasis, Serum PTH levels, End-stage Renal Disease, maintenance hemodialysis.

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Introduction

Adynamic bone disease is the new evolving concept when discussing the pathogenesis of "Disordered Mineral Metabolism". This in regards to the symptomatology of bone disease prevailing in End Stage Renal Disease (ESRD), explains the low levels of renal $1-\alpha$ -hydroxylase due to its corresponding low levels of plasma $1, 25$ -dihydroxy vitamin D, in patients with chronic uraemia. This concept plays a very important in atherosclerotic cardiovascular disease among patients on maintenance haemodialysis.¹

It is a common practice when treating ESRD patients, to treat serum vitamin D critically keeping a strict check so as to prevent bone related and other

cardiovascular symptoms. However, this sometimes outrages the balance towards overtreatment and can lead to extra skeletal vascular calcifications but has shown some benefit in cardiovascular related morbidities.²

Vitamin D homeostasis plays a pivotal role in major implications of human health. On a larger scale, there is a huge number seen with Vitamin D deficiency or insufficiency, which is required for not only in bone physiology but for optimal functioning of other vital organ systems such as cardiovascular, endocrine, immune system, this deficiency can lead to detrimental diseases like, hypertension, diabetes and heart failure. Nonetheless, management is slightly different for ESRD patients.^{3,4} According to Kidney Disease Outcomes Quality Initiative (K/DOQI) guidelines,² it is recommended to hold vitamin D therapy if serum PTH is <150 pg/ml. Since when intact PTH levels are below 65 pg/ml (7.15 mmol/L), the occurrence of Adynamic bone disease becomes inevitable.^{5,6}

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This study aimed to assess frequency of vitamin D deficiency among patients with End Stage Renal Disease and its association with serum PTH levels. Treating patients with vitamin D is difficult in order to avoid over treatment but its beneficial effect on cardiovascular morbidities has also been shown. Today's need is to optimize treatment for mineral bone disease to an extent that cardiovascular morbidity is simultaneously addressed.

Methods

This cross-sectional study was conducted from January to December 2016 at a tertiary care setup (Liaquat National Hospital) in Karachi and comprised of End stage renal disease patients on maintenance haemodialysis. Study was approved by the ethical review board of Liaquat National Hospital. Participants were selected through purposive sampling technique.

Sample size of 113 at 8% prevalence was calculated utilizing WHO sample size calculator for the standard formula of prevalence as:⁷

$$n = z^2 p (1-p) / d^2$$

The sample size was inflated to 150 to accommodate non response and incomplete questionnaires. The sample was selected through Non probability consecutive sampling technique. Participants consisted of all patients with end stage kidney disease receiving dialysis based on weekly sessions. Diagnosis and duration and co-morbid status were confirmed through their medical records and personal interviews.

Inclusion criteria consisted of End stage renal disease patients on dialysis for at least one year with ejection fraction >55%. These patients were routinely checked, via blood samples, for serum levels of Vitamin D3 (25 hydroxycholecalciferol), calcium, Phosphate, PTH and alkaline phosphatase that were sent from Dialysis unit. Hence patients in whom these labs were done at time of data collection were consecutively enrolled with no extra burden on patient for any of the lab parameters reviewed in the study.

While those in whom relevant blood samples were not sent and data was missing were excluded from the study.

SPSS 20 was used for data analysis. P-value <0.05 was taken as significant.

Numerical variables were expressed as mean \pm SD (standard deviation), while categorical variables were expressed as frequency and percentages. Serum Vitamin D levels were categorized into three categories that is

Low (<20 ng/ml), Normal (>20ng/ml)⁸ and were computed against serum PTH levels which were categorized as Normal (13.2 - 64.1 pg/ml) and High (> 64.1 pg/ml). To determine association between Vitamin D and serum PTH levels chi-square was applied. Serum alkaline phosphatase levels were further categorized into two categories, that is, Normal (35-50 IU/L) and High (> 50 IU/L). Association of serum alkaline phosphatase levels with both Vitamin D levels and PTH levels was analyzed using three-way cross tab and chi-square test with alkaline phosphatase levels as a control variable.

Results

Of the 150 participants, 33 were dropouts, among remaining 117 participants 63(53.8%) were males and 54(46.2%) were females. The overall mean age was 52.47 \pm 15.21. Of all, hypertension as a comorbidity was present in 67(57.2%), Diabetes mellitus was present in 38(32.4%) and cardiovascular disease in 12(10.2%). All the 117 participants were dialysis dependent, of these 65(55.5%) had thrice weekly frequency of dialysis and 52(44.4%) had twice weekly frequency of dialysis. From these, 47(40.1%) had each dialysis session of 4hours whereas 70(59.8%) had each dialysis session for 3hours.

Among the biochemical markers, mean serum vitamin D levels were 18.6 \pm 13.6ng/ml, mean Serum PTH levels were 253.8 \pm 227.2pg/ml, mean serum alkaline phosphatase levels were 143.7 \pm 125.4 IU/L, mean serum phosphorus

Table-1: Association between Vitamin D and PTH levels.

Vitamin D levels* (ng/ml)	PTH levels* (pg/ml)			
	Normal (n=23)		High (n=94)	
	n**	%	n	%
Low (n=67)	14	12.0	53	45.3
Normal (n=50)	9	7.7	41	35.0

* Parathyroid levels

** no. of study participants.

Table-2: Association between Vitamin D, Parathormone and Alkaline Phosphatase Levels.

Alkaline Phosphatase (IU/L)	Parathormone (pg/ml)	Vitamin D levels (ng/ml)			
		Low (n=67)		Normal (n=50)	
		n*	%	n	%
Normal (n=45)	Normal	11	24.4	3	6.7
	High	19	42.2	12	26.7
	Total	30	66.6	15	33.4
High (n=72)	Normal	3	4.2	6	8.3
	High	34	47.2	29	40.3
	Total	37	51.4	35	48.3

*no. of study participants.

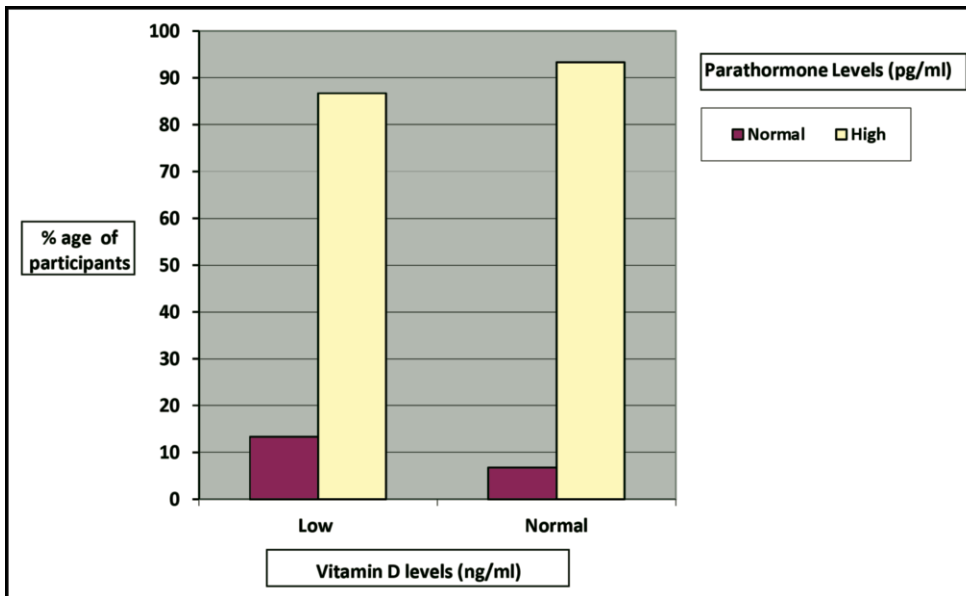


Figure: Association between vitamin D and parathormone levels.

levels were 4.81 ± 3.46 mg/dl and mean serum calcium levels were 21.41 ± 114.4 mg/dl.

Frequency of vitamin D deficiency among patients with End Stage Renal Disease was found to be 57.3 % (n=67). Normal vitamin D levels were associated with High PTH levels (P <0.001) (Table-1) (Figure). Another significant association noted was that of Normal Vitamin D levels with high Alkaline Phosphatase and high parathormone levels (P <0.001) (Table-2)

Discussion

In this study, occurrence of vitamin D deficiency or insufficiency was significantly higher in comparison to current literature, other studies of CKD patients have not considered age as an effect.⁹ We also observed that males were more in our study when considering gender population.

CKD- mineral and bone disorders has been defined as a shift in bone modeling that occurs in patients with chronic kidney disease (CKD) due to a constant change in serum levels of calcium, vitamin D, PTH levels and an inability to maintain that homeostasis as a consequence of disease process as seen in ESRD patients.¹ "Based on histomorphometric analysis of biopsy specimens obtained from ESRD patients, these patients with a compromised renal function were classified based on the bone turnover into the following types; namely, high-turnover states that included high bone turnover and high PTH levels (including osteitis fibrosa, the hallmark lesion of secondary hyperparathyroidism or predominant

hyperparathyroid bone disease (PHBD) and mixed lesion such as mixed uraemic osteodystrophy (MUO), another category was of low-turnover states comprised of low bone turnover and low or normal PTH levels such as osteomalacia and adynamic bone disease (ABD)".^{3,10} This was how we divided our patients in groups while performing analysis to see the association between vitamin D and PTH levels.

Bone biopsy provides the definitive diagnosis of CKD-mineral and bone disorders^{3,10} but this seems impossible in clinical practice, because of the invasive nature and cost associated,

hence serum markers of bone makeover appeared to be more convenient in clinical approach to evaluate bone makeover in CKD patients, in this regard "intact parathyroid hormone (iPTH) is regarded as an integral biochemical marker for diagnosis and in monitoring therapy".⁴ Sherrard et al,¹¹ have similarly shown that "iPTH could be a good predictor of bone metabolism disease in patients undergoing maintenance haemodialysis". Relevant studies have demonstrated "the direct relationship between iPTH and bone histomorphometric parameters, mainly bone formation rate".^{12,13}

Recently, the "National Kidney Foundation Kidney Disease Outcomes Quality Initiative (NKF K/DOQI) Clinical Practice Guidelines for Bone Metabolism and Disease in Chronic Kidney Disease have provided guidance on the use of iPTH to evaluate CKD- mineral and bone disorders. A target range of plasma iPTH for stage 5 CKD patients has been suggested to be between 150 and 300 pg/ml."¹⁴

Our study included patients with S.PTH levels 253.8 ± 227.2 pg/ml with a wide range hence by theory should have a normal turnover state. Literature review suggested that "Low turnover bone disease is characterized by a decrease in bone turnover or remodeling with a reduced number of osteoclasts and osteoblasts and an overall decreased osteoblastic activity. In osteomalacia, there is an accumulation of unmineralized bone matrix, or increased osteoid volume, which might be caused by vitamin D deficiency or excess aluminum. Whereas, Adynamic bone disease is characterized by reduced bone volume and

mineralization and might be due to excess aluminum or over suppression of PTH production with calcitriol".¹¹ In our study, both low and normal Vitamin D was significantly associated with serum PTH levels and not much literature showed such an association, a few population based studies observed these parameters.¹²

"The definition of vitamin D deficiency is not clear and a serum 25(OH)D concentration lesser than 20 ng/mL is considered indicative of vitamin D deficiency, while between 20-30 is insufficiency. According to DOQI guidelines, it is recommended to hold vitamin D therapy if serum PTH is <150 pg/ml, since when intact PTH levels are below 65 pg/ml (7.15 pmol/L), the occurrence of Adynamic bone is inevitable.^{2,15}

Adynamic bone disease is considered to be the progressive stage of category low bone makeover. In these patients, bone formation and bone desorption are both reduced and bone as one of the integral player of calcium regulation fails to do its role. For this reason of disequilibrium in calcium homeostasis administration of vitamin D serves to be a disaster rather than being beneficial culminating in hypercalcaemia.^{10,16} Our study showed that normal alkaline phosphatase was associated with high PTH and both low and normal vitamin D, whereas high alkaline phosphatase was associated with both low and normal vitamin D ($P<0.001$). This was statistically significant, not much evidence has been found on such correlation and literature suggested a grave area of research studies needed to establish such an effect.¹⁷

Furthermore, extravascular calcification is most likely to occur and is imminently related to complications seen in dialysis patients such as atherosclerosis and is a very important risk factor determining the survival of these patients.¹⁸⁻²⁰ Iwasaki et al,²¹ "in a control trial on Sham operated rats with secondary hyperparathyroidism induced by partial nephrectomy, concluded that if renal function deterioration was accompanied by reduced bone turnover, in bone both the inflow and outflow of calcium, results in hypercalcaemia and hence leads to the viscous circle of ectopic calcification. Another bone marker alkaline phosphatase (an indicator of osteoblast function) was also noted."²²

As reflected in literature review, our results matched the other studies in which it was observed that there is significant deficiency of Vitamin D in dialysis patients, also patients with normal vitamin D levels, there is higher levels of serum PTH with a raised level of alkaline phosphatase leading to CKD- mineral and bone disorders.²³

Other identified risk factors of vitamin D deficiency in dialysis dependent patients include age (>22 years), female gender, obesity, proteinuria, low physical activity, impaired tubular reabsorption of 25(OH) D, From these age, female gender and diabetes were factors present in our study.²⁴ There is a well known association between Vitamin D deficiency and increased risk of Cardiac morbidity with risk of developing Adynamic bone disease.^{11,25}

The limitations of this study were smaller sample size with dropout participants, this was a single center study and other confounding factors attributing to vitamin D deficiency in ESRD patents which were not thoroughly studied.

Conclusion

We concluded that there was a significant deficiency of Vitamin D levels in patients who are on maintenance haemodialysis. The normal Vitamin D levels associated with high normal or higher serum PTH levels with an associated higher alkaline phosphatase levels necessitates the need to ponder on other mechanisms leading to hyperparathyroidism and associated renal osteodystrophy than just vitamin D deficiency in end stage renal disease patients.

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