25-Hydroxy Vitamin D Deficiency May Be the Secret Actor in the Pathogenesis of Uremic Pruritus in Hemodialysis Patients

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Abstract

Background: Uremic pruritus (UP) is a chronic, unpleasant, and distressing symptom in hemodialysis (HD) patients and up to 90% of chronic kidney disease (CKD) patients undergoing maintenance HD suffer from UP. Although the improvements in HD and development of biocompatible dialysis membranes have decreased the prevalence of UP, the underlying mechanisms of pathogenesis of UP are still unknown. Vitamin D, a multifunctional vitamin, has an important immunomodulatory role. In CKF patients, 25-hydroxy vitamin D [25(OH)D] deficiency and 1,25 dihydroxyvitamin D [1,25(OH)2D] are well-known phenomena.

In this study, we aimed to investigate the association between 25(OH)D levels and UP in HD patients.

Methods: A total of 47 HD patients complaining of pruritus and 47 controls receiving HD without any symptom of pruritus according to the Yosipovitch Pruritus Wuestionnaire (YPQ) and McGill Pain Questionnaire were analyzed between February 2013 and February 2014. Demographic features of the study group, etiology of CKD, duration of dialysis, monthly biochemical parameters, and serological markers of viral hepatitis were recorded retrospectively. Blood samples for 25(OH)D were collected before the initiation of HD, and sera were immediately separated, and serum samples were transferred to Baskent University, Biochemistry Laboratory. Plasma 25(OH)D levels were measured by high performance liquid chromatography (HPLC) method.

Results: There was no statistically significant difference in age, HD duration, creatinine, hemoglobin, serum iron, serum iron binding capacity, albumin, C-reactive protein (CRP), calcium, magnesium, alanine aminotransferase (ALT), alkaline phosphatase (ALP), parathyroid hormone (PTH), total bilirubin, serological tests for hepatitis, and active vitamin D use between the groups. Although ferritin level was higher in the patient group, it did not reach statistical significance. The level of phosphorus (p=0.08), calcium and phosphorus (p=0.08) were found to be higher in the study group, whereas the 25(OH)D level was found to be lower (p=0.045), indicating a statistically significant difference. Pruritus was reported to be more common in common in women (p=0.047). Dry skin was also found to be more common in the patient group (p=0.003). Pruritus was more concentrated in the extremities (44.7%) and the back (29.8%), and mostly seen in the evening and night hours (34% and 34%, respectively), and 48.9% of the patients reported that pruritus interrupted their sleep. About 53.2% patients with pruritus reported that HD had no effect on pruritus. On the other hand, 36.2% patients who received antihistamine treatment and 14.9% of patients who received topical treatment responded well to treatment.

Conclusion: Our study results show a relationship between UP and 25(OH)D deficiency. In addition, 25(OH)D may be a responsible factor in the UP pathogenesis. Therefore, we recommend analyzing 25(OH)D levels in patients with pruritis.

ABBREVIATIONS

CKD: Chronic Kidney Disease; PTH: Parathyroid Hormone; HD: Hemodialysis; 25(OH)D: 25-hydroxyvitamin D; UP: Uremic pruritus

INTRODUCTION

Chronic kidney disease (CKD) is a global, endemic health concern [1]. Uremic pruritus (UP) is a chronic, unpleasant, and distressing symptom in hemodialysis (HD) population, and up to 90% of CKD patients undergoing maintenance HD suffer from UP [2]. Uremic pruritus remains to be the most common skin problem in HD population, leading to impaired quality of life, mood disorders, sleep disorders, and higher morbidity rates [3-6].

Although the improvements in HD and development of biocompatible dialysis membranes have decreased the prevalence of UP, the underlying mechanisms of pathogenesis of UP are still unknown. Although several factors have been implicated, it is mostly multi-factorial. Uremia, dry skin, calcium, iron, phosphorus, and magnesium, secondary hyperparathyroidism, histamine, and elevated serum vitamin A level have been suggested to play a key role in the pathogenesis of the disease [7]. However, there is insufficient data to confirm the association between these factors and UP [7-9].
In addition, 25(OH)D is a multi-functional variant of vitamin D, which has an important immunomodulatory role, and it is one of the main components of the mineral metabolism.

The level of 25(OH)D is known to be lower than in normal population in CKD patients undergoing dialysis, however, previous studies have shown that low vitamin D level may present with secondary hyperparathyroidism [10]. This is due to a decreased glomerular filtration rate (GFR), increased loss of 25(OH)D and vitamin D binding protein in the urinary tract, low intake of vitamin D from foods due to diet, reduced contact with the sun due to increased melanin in the skin associated with endogenous synthesis of vitamin D in individuals aged above 60 years, and HD [10,11]. Furthermore, 25(OH)D deficiency has a major effect in biological systems. Previous studies have demonstrated that vitamin D plays a central mediating role in the autoimmune mechanism which underlines diseases such as asthma, other atopic diseases, and a wide range of autoimmune diseases associated with clinic visits to allergy specialists [12-16].

In this study, we aimed to investigate the association between 25(OH)D levels and UP in HD patients.

**PATIENTS AND METHODS**

The study protocol was approved by the Ethics Committee of Baskent University. A written informed consent was obtained from each participant. The study was conducted in accordance with the principles of the Declaration of Helsinki. A total of 47 HD patients with a complaint of pruritus and 47 controls receiving HD without any symptom of pruritus according to the Yosipovitch Pruritus Questionnaire (YPQ) [15] and McGill Pain Questionnaire [16] were analyzed between February 2013 and February 2014. All patients were on HD treatment for at least six months with a Kt/V ratio higher than 1.4 in the past six months. All patients included in the study received HD treatment as 350 mL/min blood flow rate by the arteriovenous fistula route and 800 mL/min dialysate flow rate synthetic dialyzer. The calcium concentration of dialysis fluid was 1.25 mmol/L.

The severity of the pruritic symptoms were evaluated using the Visual Analog Scale (VAS) [17]. Demographic features of the study group, etiology of CKD, duration of dialysis, monthly biochemical parameters and serological markers of viral hepatitis were recorded retrospectively. Blood samples for 25(OH)D were collected before the initiation of HD, and sera were immediately separated, and plasma samples were transferred to Baskent University, Biochemistry Laboratory. Plasma 25(OH)D levels were measured by high performance liquid chromatography (HPLC) method.

Patients with any pathological skin lesions such as allergies, scabies, fungal infections, disseminated acne, a Kt/V ratio of <1.4, parathyroidectomy, chronic inflammatory disease, malignancy, chronic liver disease accompanying hyperbilirubinemia, polycythemia and active infection, acute inflammatory disease, and autoimmune diseases were excluded. Comorbidities which played a key role in the etiology of or concomitant CKD in the two groups included hypertension, type 2 diabetes, polycystic kidney disease, pyelonephritis, glomerulonephritis, and vesicoureteral reflux.

**Statistical analysis**

Statistical analysis was performed using SPSS version 16.0 software (SPSS Inc., Chicago, IL, USA). All numerical variables were expressed in mean ± standard deviation (SD). The Mann-Whitney U and Student-t tests were performed to compare variables. The cut-off points were determined using the receiver operating characteristic (ROC) curve. A p value of <0.05 was considered statistically significant.

**RESULTS**

A total of 94 HD patients (39 females, 55 males) with a mean age of 59.2 ± 13.6 (range: 24 to 88) years were included to the study. The duration of dialysis of CKD patients varied from 7 to 300 months. Diabetic nephropathy (28.7%) and hypertensive nephrosclerosis (14%) were the two most common etiologies of end-stage renal disease in the patient group. There was no statistically significant difference in age, HD duration, creatinine, hemoglobin, serum iron, serum iron binding capacity, albumin, C-reactive protein (CRP), calcium, magnesium, alanine aminotransferase (ALT), alkaline phosphatase (ALP), parathyroid hormone (PTH), total bilirubin, serological tests for hepatitis, and active vitamin D use between the groups. Although ferritin level was higher in the patient group, it did not reach statistical significance.

The level of phosphorus (p=0.08), calcium and phosphorus (p=0.08) were found to be higher in the study group, whereas the 25(OH)D level was found to be lower (p=0.045), indicating a statistically significant difference. Pruritus was reported to be more common in women (p=0.047). Dry skin was also found to be more common in the patient group (p=0.003). Pruritus was more concentrated in the extremities (44.7%) and the back (29.8%), and mostly seen in the evening and night hours (34% and 34%, respectively), and 48.9% of the patients reported that pruritus interrupted their sleep. About 53.2% patients with pruritus reported that HD had no effect on pruritus. On the other hand, 36.2% patients who received antihistamine treatment and 14.9% of patients who received topical treatment respond well to treatment. Demographic and biochemical characteristics of the study groups are summarized in Table (1).

**DISCUSSION**

The skin is one of the organs which are affected by CKD. The most common symptom is pruritus, although there are other skin findings [17-19]. In our study, we showed that female patients had a higher prevalence of UP, compared to male patients (p=0.04). There was no statistically significant difference in age, HD duration, creatinine, hemoglobin, serum iron, serum iron binding capacity, albumin, CRP, calcium, magnesium, ALT, ALP, PTH, total bilirubin, serologic tests for hepatitis, and active vitamin D use between the groups. Although ferritin level was higher in the patient group, it did not reach statistical significance.

The phosphate dispersion load per nephron increases with time during CKD. Serum FGF23 levels increase accordingly to compensate for this load. On the other hand, Klotho values, which increase calcium reabsorption in the distal tubules, inhibit phosphorus reabsorption, and play a key role in the FGF23 signal mechanism decreases with elevated PTH levels. However, an
increased FGF23 activity is reported to block vitamin D synthesis. Reduced calcitriol activity and hypocalcemia stimulates PTH secretion, leading to secondary hyperparathyroidism [20,21]. Secondary hyperparathyroidism is suggested to play a role in the pathogenesis of UP, and the fact that pruritus disappears after parathyroidec­tomy supports this notion [19]. On the other hand, absence of pruritus in all patients with severe hyperparathyroidism, lack of any difference in the level of PTH between those with and those without pruritus, absence of pruritus following intradermal PTH injection, and negative immunohistochemical PTH values on skin biopsy samples supports the fact that PTH has no direct role in the development of pruritus [7,19,22-24]. Consistent with previous studies, we found no statistically significant association between PTH and the development of pruritus.

Recent studies have demonstrated a relationship of serum phosphorus and calcium with stage 1-5 CKD [36]. In the present study, we found no association between serum phosphorus levels and increased pruritus. However, we demonstrated a close relationship of high levels of serum phosphorus and calcium and phosphorus with UP (p=0.008). Therefore, serum phosphorus and calcium and phosphorus levels are suggested to have a possible role in UP. These results highlight the importance of maintaining phosphorus control in patients undergoing HD treatment [30-33].

Due to a decreased glomerular filtration rate (GFR), increased loss of 25(OH)D and vitamin D binding protein in the urinary tract, decreased intake of vitamin D containing food due to dieting, reduced contact with the sun due to increased melanin in the skin associated with endogenous synthesis of vitamin D in individuals aged above 60 years, and loss through HD, levels of 1,25(OH)2D and 25(OH)D are shown to be lower in CKD patients undergoing dialysis with concomitant secondary hyperparathyroidism [10,11]. Active vitamin D is known to have important effects on cellular differentiation, cerebral development, and immunity. Vitamin D deficiency may lead to osteomalacia, rachitis, multiple sclerosis, type 1 diabetes, and prostate and colorectal cancers [34]. Recent studies have shown that vitamin D plays a key mediating role in the autoimmune mechanism, which underlines diseases such as asthma, other atopic diseases, and a wide range of autoimmune diseases associated with clinic visits to allergy specialists [14].

According to the Kidney Dialysis Outcomes Quality Initiative Guidelines (KDOQI), serum 25(OH)D sampling should be performed, when PTH is above the target value [35]. However, vitamin D2 (ergocalciferol) replacement therapy should be initiated, when serum 25(OH)D levels fall below 30 ng/mL [34,35]. It does not always increase PTH levels; however, it may lead to the concern of inadequate treatment in patients who frequently experience vitamin D deficiency. The KDIGO recommending sampling of serum 25(OH)D levels and the treatment of vitamin D deficiency, as in the overall population, in patients with stage 1-5 CKD [36].

Furthermore, kidney 1-α hydroxylase activity is known to decrease, leading to reduced calcitriol production and increased PTH levels, as CKD worsens [21]. Apart from the kidney, 1-α hydroxylase activity has been identified in many normal and pathological tissue cells, such as in the skin (basal keratinocytes and hair follicles), lymph nodes, colon (epithelial cells and parasympathetic ganglion), pancreas (islet cells), vascular, adrenal medulla, brain (cerebellum and cerebral cortex), and placenta (decidua) [37]. Recent studies have shown that active
vitamin D produced with 1-α hydroxylase in renal tubal cells is responsible for the autocrine effect of calcium, phosphorus, and PTH metabolism, while active vitamin D produced with 1-α hydroxylase from other cells is responsible for the paracrine effect [34]. This results suggest that management of vitamin D deficiency is of utmost importance in patients with advanced stage CKD and that 25(OH)D levels should be evaluated independently of PTH in all patients with advanced CKD [34].

In a cohort study where patients who presented with unexplained generalized pruritus, angioedema, skin eruption or urticaria were evaluated, the level of 25(OH)D was analyzed and 50.000 IU/week of vitamin D treatment was administered for 8 to 12 weeks in patients who had 25(OH)D <32 ng/mL [14]. Treatment was continued with daily supplementations and was suggested to be successful, as the symptoms resolved completely in 84% of the patients.

In another study including 50 patients with UP who underwent HD treatment, the relationship of severity of pruritus with 25(OH)D level was evaluated in 25 patients who received 50.000 IU ergocalciferol (Vitamin D2) every week for 12 weeks, and in 25 patients who received placebo [38]. The severity of pruritus was evaluated in all patients once for two weeks. Reduction in the severity of pruritus, although not significant, was observed in the group which received ergocalciferol; however, it did not reach statistical significance (p=0.34).

In our study, we found the level of 25(OH)D to be lower in the patients with pruritus (p=0.04), indicating a relationship between UP and low levels of 25(OH)D. Consistent with previous findings, we also showed that dry skin was also a key factor of UP and that it was associated with the degree of dryness (p=0.003). In our patients undergoing HD, UP was mostly seen in the back and extremities, and usually reported to commence during night hours and lasted for 10 minutes. These results also demonstrated that pruritus was accompanied with sleep irregularities [36-42].

Our study has limitations. A limitation of our study is the relatively small sample size. For this reason there is only marginal significance (p=0.045) between the levels of 25(OH)D in pruritus and non-pruritus subjects.

CONCLUSION

In conclusion, levels of 25(OH)D decrease in patients with CKD, and there is a relationship of pruritus with the level of 25(OH)D in healthy subjects. Although most patients with CKD received active vitamin D, symptoms of UP were reported to continue, which shows that 25(OH)D deficiency is induced by UP through unexplained mechanisms. Therefore, further large-scale studies are required to confirm these findings.

REFERENCES


Cite this article