Interleukin-31 levels among Dialysis Patients and its relation with chronic kidney disease-associated Pruritus: A Cross-Sectional Study

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Abstract

Background: Chronic kidney disease associated-pruritus (CKD-aP) is a common cutaneous complication and an important prognostic factor in patients with chronic kidney disease. The mechanism of Pruritus in those patients is poorly understood. This study aims to assess the burden of CKD-aP among patients receiving dialysis and the role of interleukin -31 in the development of Pruritus.

Methods: This cross-sectional study included 183 patients, 172 on hemodialysis and 11 on peritoneal dialysis. Each patient underwent a physical examination and was assessed for Pruritus. The 12-item pruritus severity scale determined the severity of Pruritus. Interleukin -31 levels were measured by ELISA using a special kit. All patients had other lab tests, including hemoglobin, platelets, WBCs, BUN, creatinine, albumin, ALP, total bilirubin, phosphate, calcium, ferritin, iron, transferrin, total iron-binding capacity, parathyroid hormone. Calculation of Kt/V and corrected calcium with albumin were also done

Results: The mean level of interleukin -31 was higher in patients with CKD-aP than in those without Pruritus (4936.6 ±33611.5 vs 3919.2 ±15914.4), but it wasn't statistically significant *(p value>0.05).* About 52.1% of diabetic patients have CKD-aP *(p value=0.01).* Phosphate level was significantly higher in patients with CKD-aP compared to those without (4.8 ±1.3 vs 4.4 ±1.3) *(p value= 0.002)*, whereas Albumin level was significantly lower in patients with CKD-aP compared to those without (3.6 ±0.4 vs 3.7±0.4) *(p value=0.008).*

Conclusion: In this study, there was no statistically significant association between interleukin -31 and CKD-aP. We recommend that further research be conducted to determine the role of inflammation in the development of Pruritus in patients with chronic renal disease.

Background

Chronic Kidney Disease-associated Pruritus (CKD-aP) is a frequent symptom associated with advanced or end-stage renal disease (ESRD). The prevalence of CKD-aP among adult dialysis patients was between 18% and 97.8%; the pooled prevalence is 55% (1). CKD-aP affects the entire body in half of these patients; in the other half, it primarily affects the back, face, and arms(2), in a bilateral symmetry(3). In addition, the skin of affected patients is often unchanged, resembling patients without Pruritus, which presents dry and scaly in most cases (2).

CKD-aP often constitutes a major, bothersome and often persistent complication of ESRD. Both presence and severity of Pruritus may negatively affect the well-being of dialysis patients and their quality of life. Severe Pruritus has been linked to depression and poor sleep quality, with the severity of depressive symptoms correlating with the severity of the pruritus, which may be associated with an increased risk of mortality (3, 4).

Several hypotheses were developed to explain the pathophysiology of CKD-aP. Some have shown that metabolic abnormalities have a role in CKD-aP, such as hyperparathyroidism and diabetes mellitus(5).

Also, hyperphosphatemia could induce Pruritus by depositing calcium-phosphate in the skin (6). Others hypothesized that Pruritus in hemodialysis (HD) patients is caused by the overexpression of opioid - receptors (7). In addition, many other factors can contribute to Pruritus like xerosis, histamine, and high levels of BUN (8–10). However, despite all of the research into the pathophysiology of Pruritus, the specific mechanism remained unclear.

There is increasing evidence that CKD-aP is a systemic rather than an isolated skin disease(11). The immune-mediated theory stands out to be the closest to explaining its pathophysiology. Patients with CKD-aP have alterations in their immune system manifested by increased pro-inflammatory factors, with no clinical signs of inflammation. HD patients with CKD-aP show an elevation in pro-inflammatory cytokines such as interleukin-6 (IL-6), tumor necrosis factor-alpha (TNF-α), and serum acute-phase proteins (12). Others have suggested that Th-1 cells differentiation in patients with HD may play a role by releasing some cytokines such as IL-2 (13).

Interleukin-31 (IL-31) is a novel T-cell-derived cytokine part of the gp130/IL-6 cytokine family, including IL-6, viral IL-6, IL-11, and IL-27(14). IL-31 mRNA is mainly expressed by CD4 + T helper 2 (Th2) cells after activation and could be produced by other cell types, such as cutaneous lymphocyte cells, dendritic cells, basophils, mast cells, and eosinophils (15–17). It has a crucial role in many biological functions, such as neuronal growth, bone metabolism, and immune system regulation processes (18). Recently, it has been found to have a role in skin itching. Dillon SR et al. investigated the role of IL-31 in inducing Pruritus in transgenic mice. They found that IL-31 can cause severe Pruritus and dermatitis by signalling through a heterodimeric receptor composed of IL-31 receptor A and oncostatin M receptor, which is expressed on epithelial cells and keratinocytes (19). In human subjects, enhanced expression of IL-31 is associated with induction and persistence of Pruritus and chronic skin inflammation, such as atopic dermatitis and allergic contact dermatitis(20). A study has shown that serum IL-31 is significantly higher in HD patients with pruritus symptoms, along with a positive exposure-response relationship between serum IL-31 and pruritus intensity(21).

Observations showed that some treatment modalities have an inhibiting effect on Th1-cells. For example, patients treated with ultraviolet B (UVB) light were accompanied by relief from CKD-aP as UVB exposure leads to an attenuated Th1-cells differentiation (22). Current management of CKD-aP depends on trials of different modalities of treatment, trials of mast cell stabilizers, phototherapy, HD prescription modification, and trials of other systemic medications such as Nalfurafine Hydrochloride, Ondansetron, Naltrexone, Primrose oil, Cholestyramine, and other topical treatments, but with only limited success(22). The purpose of this study was to determine the burden of CKD-aP and its relationship to the immune system's role in its development by examining the relationship between IL-31 levels and pruritus and its severity in dialysis patients. The study will shed some light on the pathophysiology of CKD-aP and perhaps help develop new treatment strategies to treat it.

Methodology

Study design and setting

This cross-sectional study was performed on 183 dialysis patients at the Dialysis Unit of An-Najah National University Hospital, Nablus, Palestine, in July 2019. Patients were excluded if they were less than 18 years of age or if they had any of the following conditions: hypothyroidism, hyperthyroidism, active infection, psychotic or other communication problems, primary skin disorders, cholestatic liver or acute hepatitis, active malignancy, connective tissue disease or dialysis for less than three months. All HD patients had three daily sessions a week (4 hours a session) using high-flux dialysis. The Institutional Review Board of An-Najah National University has granted ethical approval for this study, and all patients have signed informed consent to participate in the study.

Pruritus assessment

Patients were deemed to have Pruritus if they had the following: at least three episodes of Pruritus over two weeks or less, with symptoms occurring a few times a day, lasting at least a few minutes; or the daily occurrence of Pruritus for six months, but less often than stated above. The intensity of Pruritus and its features were evaluated using a 12-item pruritus severity scale(23). It provides data on the location, length, frequency, and severity of Pruritus. It also offers information on the scratch response, disability and quality of life impairment, with a total score ranging from three (minimum Pruritus) to 22 (most serious Pruritus). It was translated from English into Arabic and subsequently revised by three specialists in the field. Cronbach's alpha was calculated to evaluate the Arabic version's internal consistency, which was found to be 0.81.

Measures

Qualitative and quantitative serum levels of interleukin-31 were determined in plasma using a commercial DuoSet enzyme-linked immunosorbent assay kit (DY008 catalog number) from R&D Systems as instructed by the manufacturer. The detection limit was (100–10000) pg / ml, the amount above 10000 pg / ml had to be diluted. Blood specimens for measurement were sampled on recruitment, immediately centrifuged and stored at-20 ° C before assay.

Medical and demographic characteristics have been obtained from participants and their medical records. This included age, sex, other chronic diseases (hypertension, diabetes mellitus or other), and forms, durations, and etiology of the dialysis.

The participants' biochemical measures were collected from their medical files, where these laboratory measurements are done on a monthly basis for dialysis patients in the unit. These included white blood cells (WBCs) ($x10^3/\mu L$), hemoglobin (Hb) (g/dl), platelets (g/L), ferritin (ng/mL), transferrin (mg/dl), iron(µg/dl), total iron binding capacity (TIBC) (mg/dl), albumin (g/dl), creatinine (mg/dl), BUN (mg/dl), calcium (mg/dL), phosphate (mg/dL), PTH (pg/dL), total bilirubin (mg/dl), ALT (U/L), AST (U/L), ALP(U/L), Kt/v, and TSH (mU/l).

Statistical analysis

All statistical analysis was performed using SPSS 21.0 (SPSS Inc., Chicago, IL, USA) software. A P value < 0.05 was considered to be statistically significant. Continuous variables with normal distributions are expressed as mean ± standard deviations. The Independent t-test (two-tailed) was used to compare continuous variables. Categorical variables are described as percentage numbers. The Pearson chi-square test has been used to compare the categorical variables. In addition, multivariable logistic regression was performed to estimate the relation between pruritus status and specific factors. Variables used in the model were chosen based on previously reviewed studies about CKD-aP and associated factors. We checked the linearity of continuous variables with the result using the Box-Tidwell method, where we assumed that the relationship between continuous predictors and log odds was linear. Interactions between continuous predictors and their logs were also included in the model. The significance value of the linearity variance for the duration of the dialysis, Ktv, TSH, PTH, IL31 > 0.05, indicates a linear relationship between them and the status of the Pruritus.

Results

Patient characteristics

A total of 183 participants, including 172 HD patients and 11 PD patients, contributed to this study. The participants' demographic and clinical characteristics are summarized in Table 1. Their mean age was 57.4 years, with 36.6% females and 51.4% diabetics. The mean dialysis duration was four years. CKD was attributed to diabetes in 43.2% of patients.

Table 1
Demographic and clinical characteristics of the participants (n = 183)

Background variables	**Frequency**	**Percentage**
Age (Mean ± SD)	57.4 ± 14.3	
< 65	120	65.6%
≥ 65	63	34.4%
Gender		
Male	116	63.4%
Female	67	36.6%
Hypertension		
Yes	149	81.4%
No	34	18.6%
Diabetes		
Yes	94	51.4%
No	98	48.6%
Dialysis type		
Hemodialysis	172	94.0%
Peritoneal dialysis	11	6.0%
Dialysis duration in years (*Mean ± SD*)	*4 ± 3.5*	
Causes of dialysis		
Hypertension	38	20.8%
Diabetes	79	43.2%
Drugs	15	8.2%
Pyelonephritis	9	4.9%
Unknown	19	10.4%
Others	23	12.5%

Mean values and standard deviation of laboratory results of dialysis patients are summarized in Table 2. The mean Kt/v was 1.2 *± 0.4*, and the mean levels of IL-31 and phosphate were 4313.9 ± 2473.9pg/mL, 4.6 ± 1.3 mg/dL, respectively.

Table 2
Mean values and standard deviation of laboratory results of dialysis patients

Lab test	Value	Normal range
Kt/v	1.2 *± 0.4*	> 1.2
Albumin(g/dL)	3.6 *± 0.4*	3.5–5.2
BUN (mg/dL)	55.3 *± 14.7*	5–22
Calcium, Albumin adjusted(mg/dL)	9.3 *± 0.82*	8.5–10.2
Phosphate(mg/dL)	4.6 *± 1.3*	2.5–4.5
Ferritin(ng/dL)	602.6 *± 540.0*	20–300
WBCs(x10³/μL)	6.5 *± 2.0*	4–9
PTH(pg/dL)	482.3 *± 653.9*	15–65
IL-31(pg/mL)	4313.9 *± 2473.9*	--
Kt/V: Kt stands for dialyzer clearance multiplied by time (mL/min) and V for the volume of water a patient's body contains.		

Prevalence and characteristics of CKD-aP

Among the participants, 71 patients [38.8%, 95%CI 32.2–46.8] had CKD-aP, with a mean duration of 26.6 ± 35.3 months. For most patients, the Pruritus was located on the trunk (43.7%) or generalized (38%). About 57.7% of the patients developed Pruritus after starting the dialysis, and mostly (47.9%) occurred at night. The mean total score of the 12-Item Pruritus Severity Scale used to measure the pruritus severity was 10 ± 4.2. Table 3 summarizes the characteristics of Pruritus among dialysis patients.

Table 3
Characteristics and distribution of Pruritus among dialysis patients(n = 71)

Characteristics	Frequency	Percentage
Duration (Mean ± SD) *	26.6 *± 35.3*	
Location of pruritus#		
Trunk	31	43.7%
Generalized	27	38%
Lower limbs	9	7%
Upper limbs	3	4.2%
Both upper and lower limbs	6	8.5%
Head	3	4.2%
Symmetry		
Symmetrical	62	87.3%
Non-symmetrical	9	12.7%
Onset (Timing) of Pruritus		
Before Dialysis	30	42.3%
After Dialysis	41	57.7%
Time of Pruritus during the day		
Day	11	15.5%
Night	34	47.9%
All the time	32	36.6%
Change in severity of Pruritus		
Increase	29	40.8%
Decrease	15	21%
No Change	27	38.2%
Severity score (Mean *± SD.)*	10 *± 4.2*	

**duration of Pruritus is in months, #the frequencies does not sum up to 100% as Pruritus can be located on more than one location.*

Factors associated with CKD-aP

Table 4 summarizes the demographic and clinical characteristics differences between patients with and without CKD-aP. About 52.1% of diabetic patients have CKD-aP *(p value = 0.01)*. The mean levels of IL-31 were higher in patients with CKD-aP than those without CKD-aP (4936.6(± 33611.5) vs 3919.2(± 15914.4), but it was not statistically significant *(p value = 0.78)*. However, the mean Phosphate level was significantly higher in patients with CKD-aP (3.6 ± 0.4) than those without CKD-aP (3.7 ± 0.4) *(p value = 0.002), whereas albumin level was* significantly lower in patients with CKD-aP (4.4 ± 1.3) than those without CKD-aP (4.4 ± 1.3) *(p value = 0.002)*.

Table 4
Demographic and clinical data for patients with and without CKD-aP

	With CKD-aP (n = 71)	Without CKD-aP (n = 112)	P Value	Adjusted p value	Adjusted OR (95%CI)
Age (Mean ± SD)	57.8 ± 13.7	57.1 ± 14.7	0.75	0.58	1.0(0.98-1)
Gender					
Male	46(39.7%)	70 (60.3%)	0.75	–	–
Female	25(37.3%)	42 (62.7%)			
Type of dialysis					
Hemodialysis	65(37.8%)	107(62.2%)	0.27	–	–
Peritoneal dialysis	6(54%)	5(45%)			
Hypertension					
Yes	55(36.9%)	94(63.1%)	0.27	–	–
No	16(47.1%)	18(52.9%)			
Diabetes mellitus					
Yes	45(47.9%)	49(52.1%)	0.01	0.008	2.4 (1.2–4.6)
No	26(29.2%)	63(70.8%)			
Dialysis Duration *(years)*	4.4 ± 3.7	3.5 ± 3.3	0.093	–	–
Kt/v	1.2(*± 0.3)*	1.3(*± 0.4)*	0.142	–	–
Albumin(g/dL)	3.6(*± 0.4)*	3.7(*± 0.4)*	0.03	0.008	0.3 (0.13–0.74)
BUN (mg/dL)	56.3(*± 14.5)*	54.6(*± 14.8)*	0.454	–	–
Calcium, Albumin adjusted(mg/dL)	9.3(*± 0.92)*	9.3(*± 0.75)*	0.802	–	–
Ferritin(ng/mL)	686.2(*± 294.6)*	612.9(*± 366.8)*	0.605	–	–
Phosphate(mg/dL)	4.8(*± 1.3)*	4.4(*± 1.3)*	0.025	0.002	1.5 (1.1-2.0)
WBCs(x10³/µL)	6.6(*± 1.9)*	6.3(*± 2)*	0.301	–	–
PTH(pg/dL)	408.7(*± 340.2)*	529(*± 786.2)*	0.22	0.253	0.99 (0.99-1.0)
IL_31(pg/dL)	4936.6(± 33611.5)	3919.2(± 15914.4)	0.78	0.244	1.0 (1.0–1.0)

Kt/V: Kt stands for dialyzer clearance multiplied by time (mL/min) and V for the volume of water a patient's body contains.

CKD-aP severity and clinical

Patients with higher phosphate levels have lower pruritus severity scores (r= -0.296, p-value = 0.023). None of the other variables was significantly associated with pruritus severity (Table 5).

Table 5
Pearson correlation of CKD-aP severity with various clinical and biochemical parameters

Characteristic	Correlation coefficient (r)	P value
Kt/v	-0.114	0.364
Dialysis duration	-0.031	0.797
Albumin	-0.021	0.318
ALP	-0.141	0.248
BUN	-0.218	0.068
Calcium, Albumin adjusted	0.133	0.270
Phosphate	-0.269*	0.023
Ferritin	-0.071	0.557
Iron	-0.051	0.672
TIBC	0.078	0.520
Transferrin	0.152	0.207
Hemoglobin	0.066	0.587
Platelets	-0.057	0.640
WBCs	-0.153	0.204
PTH	0.125	0.300
IL-31	0.104	0.386

Discussion

CKD-aP is a cutaneous complication that affects many dialysis patients and is linked to poor outcomes. Patients with severe Pruritus have a worse prognosis, as severe Pruritus is associated with death independently of other co-morbidities (6). We found that about 38.8% of the patients had Pruritus, with a mean severity grade of 10 ± 4.2. Mostly being generalized or localized to the trunk, or to a lesser extent to the upper limbs, lower limbs, or the head with symmetrical distribution, 47.9% of patients implied having

the symptoms at night. These findings are consistent with the literature, where the pooled prevalence of Pruritus is 55%. About 50% of these patients have generalized Pruritus, and in the remaining patients, CKD-aP seems to affect predominantly the back, face, and shunt arm with bilateral symmetry (1–3).

Many tried to explain what could be the cause behind CKD-aP, but the pathophysiology of this condition is still elusive. One of the most robust hypotheses is the immune-mediated hypothesis. Several studies show a central role of inflammation in the pathogenesis of Pruritus in dialysis patients (24). Furthermore, patients on dialysis have an alteration in their immune system, with 30–50% of them having a pro-inflammatory state(25).

In this study, we believe patients with pruritus experience inflammation more than patients without Pruritus, which is suggested by the significantly lower levels of albumin in those with Pruritus *(p value < 0.05)*. Albumin is considered a negative inflammatory marker, and it's found that there is an association between lower levels of albumin and CKD-aP(26). In addition, patients with Pruritus had higher levels of ferritin and WBCs. However, they were not statistically significant, but it is well known that ferritin and WBCs levels are reliable inflammatory markers(26, 27). Unfortunately, CRP levels could not be obtained for those patients to provide evidence for the inflammatory state further.

In addition, we found a significant association between DM and CKD-aP *(p value < 0.05).* Therefore, it is suggested that DM causes neuropathy in peripheral nerves (c-fibres) in the skin that transmits the itching sensation and that glycemic control correlates with itch severity. However, the exact mechanism remains to be determined (5). On the other hand, inflammation is acknowledged as a key factor in the development and progression of CKD in diabetics (13), with evidence that diabetic patients experience a low-grade inflammatory state, with increased blood concentrations of inflammatory markers such as alpha-1 acid glycoprotein, serum amyloid A, CRP, cortisol, and the main cytokine mediator of the response, IL-6 (28), which supports the presence of an inflammatory state in people with Diabetes with Pruritus.

New evidence shows that IL-31, a member of the IL-6 family of cytokines, is associated with Pruritus in atopic dermatitis patients (29) and other autoimmune skin diseases, like Bullous pemphigoid (30). Ko MJ et al. show that there was indeed a significant association between IL-31 and CKD-aP in HD patients (21). In our study, we could not find one, the mean levels of IL-31 were higher in those with Pruritus than those without Pruritus (*4936.6, 3919.2)*, respectively, but it was statistically insignificant (*p value = 0.78).* This difference could be related to racial differences. According to Hoffmann SC et al., ethnicity may play a role in expressing inflammatory cytokines (31). Alternatively, it could be related to the fact that their blood samples were collected after an overnight fast of more than 8 hours, whereas our samples were not.

In addition, we found a statistically significant negative correlation between phosphate levels and Pruritus *(r= -269, p value < 0.05)*, which is opposite to what has been reported by Gatmiri. et al. (32). We believe this result was most likely because most patients took one form of phosphate-binding medications, e.g., calcium gluconate or sevelamer, which led to this unexpected negative correlation between pruritus severity and phosphate levels.

Up to our knowledge, this study was the first to address CKD-aP in the region. It offered a better understanding of the mechanism of Pruritus as it took into consideration a lot of variables and the association between them and Pruritus. Although the data gathered is comprehensive and covers a variety of laboratory testing and clinical evaluations, the study still has some possible limitations. First, as this is a cross-sectional study, we could not follow up the patients without Pruritus and with high levels of interleukin to see if they would have a possibility of developing Pruritus in the future. Secondly, C-reactive protein (CRP) and other inflammatory cytokines have not been used to support the pro-inflammatory state further. Thirdly, during the study, patients were on phosphate binders, which could affect the 12-item pruritus severity scale results.

Conclusion

In this study, there was no statistically significant association between IL-31 and CKD-aP. However, the laboratory findings of pruritus patients have shown significantly lower albumin levels and higher mean levels of ferritin and WBCs, suggesting that those patients undergo a more intense inflammatory state. On the other hand, we found a significant association between Pruritus and other variables such as diabetes mellitus, phosphate levels, and lower albumin levels. Therefore, our recommendation is to investigate further the role of inflammation in CKD-aP and its effect on the IL-31 signalling pathway.

Abbreviations

CKD: Chronic kidney disease.

CKD-aP: chronic kidney disease-associated Pruritus.

CRP: C-reactive protein.

DM: Diabetes Mellitus

ESRD: end-stage renal disease.

HD: Hemodialysis.

IL: interleukin.

TNF-α: tumor necrosis factor-alpha.

Th2: T helper 2.

UVB: ultraviolet B.

WBCs: white blood cells.

Declarations

Ethics approval and consent to participate:

All procedures performed in this study complied with the institutional and/or national research committee ethical standards and the 1964 Helsinki declaration and subsequent amendments or equivalent ethical standards. The study was approved the Institutional Review Board (IRB) of An-Najah National University, and appropriate permissions were taken from the hospital. Full verbal and written consent have been obtained from all patients. Participants' data confidentiality was ensured, and all of the data collected were used for the research purpose only.

Consent for publication:

"Not applicable."

Availability of data and materials:

The datasets used and analyzed during the current study are available from the corresponding author on reasonable request.

Competing interests:

"The authors declare that they have no competing interests" in this section.

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Conflicts of Interest:

The authors declare no conflict of interest in this study.

Authors' Contributions:

All authors contributed to the reported work; ZH, LT, EK, and ZH participated in conceiving the idea and study design, supervised data collection, data analysis, and manuscript writing. IA, Amna A, MA, WB and Adham A performed the material preparation, data collection, and analysis. All authors interpreted the results. IA, Amna A, and ZN wrote the first draft of the manuscript, and all authors commented on previous versions of the manuscript. Finally, all authors revised the final version of the manuscript and approved its submission.

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