ORIGINAL ARTICLE

The impact of underlying diseases-related drugs on the chronic kidney disease-associated pruritus in hemodialysis patients

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Background: Uremic pruritus or chronic kidney disease-associated pruritus (CKD-aP) is a frequent compromising symptom in end-stage renal disease. Despite the little attention paid to drugs used among hemodialysis (HD) patients, investigating medications used in this population of patients and examining the status of CKD-aP may lead to the identification of medications that improve or worsen the pruritus condition. We aimed to assess the role of underlying diseases-related drugs on CKD-aP in HD patients. **Materials and Methods:** We performed a case – control study on HD patients aged over 18 years old. The demographic data and clinical parameters including HD parameters, drug history, dermatologic assessments, and laboratory examination were assessed. **Results:** We compared 128 patients with CKD-aP as cases and 109 patients without CKD-aP as controls. Cases were on the longer course of dialysis (44.69 ± 43.24 months for cases vs. 38.87 ± 50.73 months for controls; $P = 0.02$). In multiple analyses of variables related to CKD-aP, backward LR logistic regression revealed that only atorvastatin ($P = 0.036$) was considered to be a predictive factor associated with CKD-aP. Thus, the use of atorvastatin reduced the index of CKD-aP (95% confidence interval: 0.256–0.954, odd's Ratio = 0.494). **Conclusion:** Atorvastatin was associated with decreased frequencies of CKD-aP among HD patients in our study. This knowledge may guide further clinical trials to evaluate atorvastatin's immunomodulatory and anti-inflammatory effects on the CKD-aP in HD populations.

Key words: Amiodarone, atorvastatin, chronic kidney disease, hemodialysis, pruritus, valsartan

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INTRODUCTION

Pruritus is a common and distressing symptom in patients with chronic kidney disease (CKD).[1] The incidence and severity of pruritus rise with the progression of renal failure.[2,3] CKD-associated pruritus (CKD-aP) is considered a predictor of mortality in hemodialysis (HD) patients.[4-6] CKD is associated with immune system dysfunction and this can induce pro-inflammatory cytokines resulting in CKD-aP and cardiovascular disease.[6,7]

The pathogenesis of CKD-aP is unclear. It may be due to a malfunction of various systems. Immune system dysfunction and elevated pro-inflammatory cytokines has been increasingly recognized as an important modulator of CKD-aP. It has been shown that numerous immunomodulatory treatments have been associated with reduction in itching.[3] Although some factors are mentioned as effective factors in pruritus in dialysis patients, but in different studies, the results are different. The absence of pruritus in all HD patients may be due to the variety of medications used in patients in addition to the difference in paraclinical parameters. Despite the little attention paid to this issue, investigating medications used in this population of patients and examining the status of uremic pruritus may lead to the identification of medications that improve or worsen the

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pruritus condition. This study aimed for assessing the role of underlying disease-related drugs on the pruritus in HD patients among two groups of CKD-aP and CKD without pruritus (CKD-wP) by considering paraclinical parameters.

MATERIALS AND METHODS

We conducted a case – control study between May and November 2019. The participants were patients on maintenance HD (local protocol based on the nephrologist's judgement 2–3 times a week). The inclusion criteria for CKD-aP were patients older than 18 years, who had been on stable chronic HD (patients who need dialysis regularly) for at least 6 months ago, had pruritus, and were cooperative with examining physician. The exclusion criteria consisted of the patients with primary pruritic skin lesions such as lichen planus, atopic dermatitis, immunobullous diseases, and cutaneous lymphoma. Furthermore, patients with pruritus due to other systemic diseases except chronic renal failure were excluded. The diagnosis was made according to a detailed history taking and physical examination of HD patients by a dermatologist. 632 CKD patients were evaluated for presence or absence of CKD-aP. Anemia and hyperparathyroidism which are the potential causes of pruritus were considered as the complications of end-stage renal disease (ESRD); so were enrolled in the study. From 147 patients with CKD-aP, 19 patients were excluded due to their dermatologic diseases. Finally, 128 patients with CKD-aP remained in this study according to the inclusion and exclusion criteria and were considered as our case group.

385 patients did not have CKD-aP. Among these CKD-wP, 138 HD patients were matched with the case group according to their age and gender. The inclusion criteria were those wP or any other dermatological disease and aged older than 18 years, had been on stable chronic HD for at least 6 months ago, and were cooperative with examining physician [Figure 1].

All participants were of skin types 3 and 4 according to the Fitzpatrick skin phototype classification which classifies skin type consistent with the amount of pigment in the skin and its reaction to sun exposure.[8] All of the participants had been on emollient at least for the last 2 months. None of them had been on phototherapy. Informed consent was obtained from all cases and controls. The study protocol was approved by the Ethics Committee of the Guilan University of Medical Sciences registered NO. IR.GUMS.REC.1396.237.

Chronic kidney disease-associated pruritus

The different features of pruritus were assessed by a single investigator. The skin examination included color, dryness, desquamation, and skin integrity. The diagnosis of CKD-aP

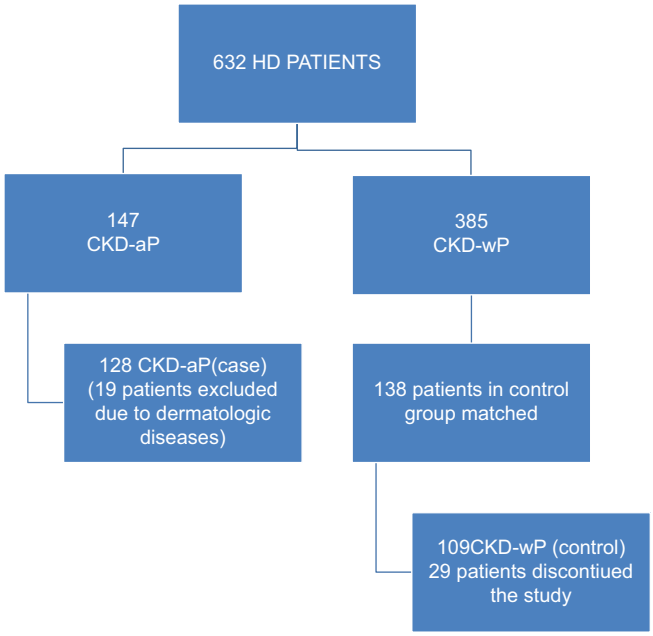

Figure 1: Flow chart of HD patients with and without CKD-aP

was based on the following criteria: (i) pruritus lasting for more than six weeks and (ii) pruritus occurred at least in 3 episodes for 2 weeks or less and itches were noted several times a day and last for more than 5 min and are annoying.[9] Furthermore, patients completed questionnaires including the Visual Analog Scale (VAS) during their dialysis sessions. Patients were asked to score the intensity of their feeling about itch with the use of a VAS. This method ranges from 0 which means no itching to 10 which denotes the worst insufferable itching.[3]

Data collection

The demographic data and clinical parameters including HD parameters, laboratory examination, as well as the drugs used by patients (cases and controls) were assessed. The demographic data were collected through structured interviews and paper questionnaires. The HD treatment was done based on the nephrologist's judgment 2–3 times a week. Polysulfone/polyamide membranes were used in the dialysis centers.

Experimental methods

For all the cases and controls, after a long dialysis-free weekend, 10 ml of blood was taken immediately before starting the HD. Routine laboratory tests, as well as albumin (Normal; 3.4–5.4 g/dL), calcium (Normal: 8.6–10.3 mg/dL), phosphate (Normal: 2.8–4.5 mg/dL), intact parathyroid hormone (iPTH) (Normal: 14–65 pg/mL), 25-hydroxyvitamin D3 (25 [OH] D3) (normal: 30 and 50 ng/mL), C-reactive protein (CRP) (normal: <10 mg/L. High: ≥10 mg/L), and erythrocyte sedimentation rate (normal: 1–13 mm/h for males and 1–20 mm/h for females) were measured. We evaluated the dialysis adequacy index (Kt/V)

based on the Daugirdas formula.[10] Indices ≥ 1.2 revealed the adequacy of dialysis[11] and tried to adjust the KT/V within 1.2–1.4.

Statistical analysis

We presented the demographic, clinical characteristics, and laboratory data of the study population by the cases and controls; presence and absence of the CKD-aP. Data analyses were performed using SPSS Statistics software, Version 22 (IBM Corp, Armonk, New York, USA).

We assessed the normal distribution of all continuous variables with Kolmogorov–Smirnov test. The continuous variables were presented with means and standard deviations. We used the parametric test of independent *t*-test for the normally distributed variables and nonparametric test of Mann–Whitney U-test for nonnormally distributed variables. The categorical variables were presented with the use of frequencies and proportions, and we compared two groups with the Chi-squared and Fisher's exact test. Statistical significance was considered as the $P < 0.05$.

We used logistic regression model to find the predictors in the multivariate analysis. All the variables with $P < 0.01$ in univariate analysis entered into the initial model of multiple analysis.

RESULTS

A total of 128 HD patients with CKD-aP (case) and 138 HD patients CKD-wP (control) were matched for this study. During the study, 29 patients in the control group refused to continue the study. Finally, 109 patients remained in the control group [Figure 1]. The clinical and laboratory characteristics of the participants are shown in Table 1.

The course of dialysis was significantly longer in cases than in control (44.69 ± 43.24 months vs. 38.87 ± 50.73 months; $P = 0.02$). No significant difference was found in the age (59.80 ± 15.47 cases vs. 58.45 ± 13.94 controls, $P = 0.63$), gender ($P = 0.86$) [Table 1], and underlying renal diseases which resulted in ESRD between cases and controls ($P = 0.19$) [Table 2]. The levels of serum urea nitrogen, creatinine, serum phosphorus, calcium, albumin, hemoglobin, and iPTH were not significantly different between two groups [Table 1].

The median itch intensity of cases was 5.47 ± 2.46. Within the patients with pruritus, 4.6% expressed their condition as severe (VAS = 10). According to physical examination cases, 116 (91%) had skin signs of dryness, 89 (69%) scratch marks, and 20 (16%) nodular lesions. Furthermore, pruritus affected trunk 57.81%, extremities 57.03%, head and neck 17%, and the whole body 11.72% patients, respectively.

Evaluating the drugs used in two groups of HD patients, we found that cases used amiodarone more than controls ($P = 0.06$). The maintenance dose was 200 mg orally once a day. Furthermore, the prevalence of valsartan and atorvastatin in controls was higher than in cases; however, they were not statistically significant ($P = 0.07$ and $P = 0.08$, respectively). The mean duration of usage was 28 ± 16.7 and 35 ± 20.3 months, respectively. The maintenance dose of valsartan was 80 mg twice daily. Most patients with atorvastatin used 20 mg nightly. We found no difference between the prevalence of anti-pruritic drugs used among cases and controls (gabapentin and hydroxyzine) [Table 3].

In multiple analyses of variables related to CKD-aP, backward LR logistic regression was used. The method was such that the variables which had a significant level of <0.1 in the univariate analysis, entered into the initial model of multiple analysis. In the final model, among the variables entered (duration of dialysis, age, white blood cells, BUN, Cr, Kt/V, and atorvastatin usage), only atorvastatin ($P = 0.036$) was considered to be the predictive factor associated with CKD-aP. Thus, the use of atorvastatin reduced the index of CKD-aP (95% confidence interval (CI): 0.256–0.954, ODD's Ratio = 0.494) [Table 4].

DISCUSSION

Pruritus is a common symptom in patients with CKD undergoing HD. The management of patients with CKD-aP is a challenge to dermatologists and nephrologists.[12,13]

The pathophysiology of CKD-aP is weakly identified. During the last two decades, various mechanisms have been proposed to explain the pathophysiology of CKD-aP including metabolic derangements that occur with hyperparathyroidism-associated bone disease, increasing pro-inflammatory mediators, immune system dysfunction, opioid imbalances, bivalent ion hypothesis, molecular hypothesis, and dehydration-related skin structural alterations. According to recent investigations, CKD-aP seems to be a systemic disorder and immune system dysfunction and pro-inflammatory cytokines including Th1 cell, interleukin (IL) 6, IL-31 play an important role in the pathogenesis of CKD-aP.[14,15]

It has been shown that pro-inflammatory cytokine levels are increased with the decline in glomerular filtration rate.[16] The inflammatory markers such as T-helper 1 cells, IL6, IL-2, and CRP levels are higher in HD patients with CKD-aP. Many therapies such as topical calcineurin inhibitors, ultraviolet B (UVB), activated charcoal, oral thalidomide, gabapentin (GBP), and pregabalin (PGB) have been mentioned as useful in the treatment of patients with CKD-aP. The studies showed that most of them likely

Table 1: Clinical and laboratory characteristics of cases and controls

	Pruritus												*P**
	Yes (*n*=128)						No (*n*=109)						
	Mean±SD	Percentile 25	Percentile 75	Median	Minimum	Maximum	Mean±SD	Percentile 25	Percentile 75	Medium	Minimum	Maximum	
Age (year)	59.80±15.47	49.50	71.00	60.50	22.00	94.00	58.45±13.94	50.00	69.00	62.00	19.00	82.00	0.63
Duration of ESRD (year)	6.58±4.74	4.00	6.00	6	1.00	25.00	6.18±4.54	3.00	7.00	6.00	1.00	25.00	0.40
Duration of dialysis (month)	44.69±43.24	12.00	61.00	36.00	6.00	276.00	38.87±50.73	7.00	48.00	22.00	6	276.00	0.02
WBC (per μL)	7354.26±2819.9	5600.00	8600.00	6900.00	3200.00	21400.00	7023.59±2017.63	5600.00	8000.00	6900.00	2900.00	13300.00	0.89
RBC (per μL)	3.87±0.68	3.43	4.25	3.80	2.27	5.93	3.91±0.70	3.50	4.30	3.85	1.87	6.52	0.38
Hb (g/dl)	10.86±1.86	9.75	12.00	10.75	5.90	15.00	11.12±2.00	9.70	12.80	11.20	5.30	14.70	0.19
HCT (%)	34.19±5.49	31.20	38.40	33.80	13.90	46.90	35.11±5.73	32.00	39.60	35.20	17.50	48.40	0.13
MCV (fL)	89.41±9.36	85.20	95.10	91.30	62.70	109.70	89.71±8.99	86.50	95.00	91.40	63.50	108.60	0.81
ESR (mm/h)	45.22±38.24	13.00	71.00	30.00	2.00	129.00	39.24±26.72	15.00	55.00	37.00	5.00	120.00	0.84
CRP (mg/L)	10.22±17.41	1.00	11.00	2.00	1.00	75.00	8.44±12.20	1.00	9.00	4.00	1.00	61.00	0.53
FBS (mg/ml)	125.74±83.01	84.00	142.50	96.00	59.00	503.00	122.42±68.66	82.00	149.00	92.00	70.00	381.00	0.94
BUN (mg/ml)	60.15±18.51	51.00	73.00	58.90	11.00	114.00	60.63±16.93	50.00	72.00	60.00	17.00	117.30	0.98
CR (mg/ml)	7.99±2.94	5.85	9.30	7.88	2.30	19.30	7.84±3.06	5.80	9.70	7.90	2.77	22.70	0.82
URR	0.67±0.12	0.62	0.74	0.67	0.11	0.92	0.69±0.09	0.64	0.72	0.69	0.44	0.93	0.21
KT/V	1.34±0.32	1.17	1.46	1.30	0.71	2.25	1.36±0.28	1.19	1.48	1.31	0.78	2.46	0.42
SGPT (18-48)	18.18±9.78	12.00	22.00	16.00	3.00	49.00	17.46±9.79	11.00	21.00	15.00	6.00	62.00	0.55
SGOT (20-50)	19.24±15.57	13.00	22.00	15.50	4.00	137.00	17.79±9.96	12.00	20.50	16.00	7.00	79.00	0.65
AlkP (40-350)	302.65±187.66	165.00	415.00	221.00	75.00	910.00	325.60±223.29	187.00	406.00	253.00	103.00	1292.00	0.38
Ca (mg/ml)	8.88±1.31	8.20	9.40	8.80	6.30	14.80	8.77±0.88	8.16	9.30	8.70	6.72	11.00	0.69
Phosphorous (mg/ml)	5.60±1.75	4.30	6.70	5.30	1.70	12.80	5.48±1.80	4.50	6.10	5.40	2.30	13.40	0.58
iPTH (pg/ml)	231.15±244.18	71.50	294.00	130.30	2.70	935.00	218.36±240.82	34.10	327.00	119.60	2.00	988.10	0.42
Vitamin D (ng/ml)	33.48±18.46	19.85	44.30	30.50	6.50	97.80	34.14±15.74	19.90	46.50	32.00	6.80	75.50	0.64
Albumin (g/dl)	3.85±0.40	3.75	4.10	3.90	2.20	4.60	3.91±0.48	3.70	4.10	4.00	2.00	5.10	0.26
Uric acid (mg/dl)	6.52±1.85	5.30	7.80	6.30	2.60	13.00	6.60±1.51	5.60	7.30	6.40	3.60	11.40	0.81

*Independent *t*-test for normally distributed variables, and Mann-Whitney *U*-test for nonnormally distributed variables were used. *P*<0.05 was significant. WBC=White blood cell; RBC=Red blood cell; HB=Hemoglobin; HCT=Hematocrit; MCV=Mean corpuscular volume; CRP=C-reactive protein; ESR=Estimated sedimentation rate; FBS=Fasting plasma glucose; BUN=Blood urea nitrogen; Cr=Creatinin; URR=Urea reduction ratio; Kt/V=Is a measure of the dose of dialysis given in a session where K presence the dialyzer urea clearance, t presence the total treatment time, and V presence the total volume within the body that urea is distributed; SGPT=Serum glutamic pyruvic transaminase; SGOT=Serum glutamic-oxaloacetic transaminase; AlkP=Alkaline phosphatase; Ca=Calcium; iPTH=Intact parathyroid hormone; SD=Standard deviation; ESRD=End-stage renal disease

Table 2: The underlying disease of end-stage renal disease in case and control

Underlying diseases (*n*)	Count (%)		*P**
	Case (*n*=128)	Control (*n*=109)	
Primary GN (19)	8 (6.2)	11 (10.1)	0.19
PCKD (14)	6 (4.7)	8 (7.3)	
DM (48)	23 (18)	25 (22.9)	
HTN (69)	35 (27.3)	34 (31.2)	
Unknown (32)	19 (14.8)	13 (11.9)	
Reflux nephropathy (9)	7 (5.4)	2 (1.8)	
OU (6)	2 (1.6)	4 (3.7)	
DM and HTN (30)	20 (15.6)	10 (9.1)	
DM and OU (5)	3 (2.3)	2 (1.8)	
Other (5)	5 (3.9)	0	

*Q square and Fisher's exact test was performed. *P*<0.05 was considered as significant. GN=Glomerulonephritis; PCKD=Polycystic kidney disease; DM=Diabetes mellitus; HTN=Hypertension; OU=Obstructive uropathy

have an anti-inflammatory effect through inhibition of production IL6, IL8, or Th1 differentiation.[15-18] It seems the therapeutic strategies focusing on Th1 may be beneficial for CKD-aP. UVB attenuates Th1 cell differentiation and IL-2 production; thalidomide decreases tumor necrosis factor-alpha levels, and tacrolimus inhibits the activity of phosphorylase enzyme calcineurin.[12]

Our study showed that HD patients in the control group used more atorvastatin than the case group. While in the final model of multivariate just one variable remains, it shows the strongness of that variable. Thus, uremic patients with atorvastatin experienced CKD-wP, 2.024 times more than uremic patients without atorvastatin (CI: 1.05–3.91) (P = 0.036). Duque *et al*. found that HD patients receiving statins were significantly less likely to report CKD-aP.[19] Statins are believed to act by inhibiting the presentations of intercellular adhesion molecule-I, monocyte chemotactic protein-I, and lymphocyte function-associated antigen-I on leukocytes and endothelial cells. The immunomodulatory effect of statins is mostly due to the inhibitory effect of statins on the expression of major histocompatibility complex (MHC) class II. Notably, atorvastatin is the strongest inhibitor of inducible MHC class II expression.[20] Atorvastatin interferes with the regulation of T-helper cell (Th) by blockade of 3-hydroxy-3-methylglutaryl–coenzyme A (HMG-CoA) reductase which inhibits biosynthesis of cholesterol and isoprenoids. Furthermore, the phosphatidylinositol-3-kinase/Akt signal transduction pathway plays a role in a variety of T-cell functions.[21,22] Furthermore, statins reduce neutrophil migration and induce a prolonged reduction in neutrophil reactive oxygen species.[23]

Conversely, HMG-CoA reductase inhibitors (statins) have been implicated in causing pruritus.[24-26] Impaired barrier function due to inhibition of cholesterol biosynthesis is supposed to disrupt the distribution of lipids in the skin. The superiority of the anti-inflammatory effect of atorvastatin over barrier dysfunction of skin might be attributed to differences in the pharmacokinetics of the drug in HD patients. Immunomodulatory properties of statins in dermatology and CKD-aP need more research.[20,27]

Our patients were a small number in valsartan and amiodaron groups, the present study showed that valsartan may decrease and amiodarone may increase itch in HD patients. However, due to the small number of patients in both groups, this issue is not statistically reliable and needs

Table 3: Oral drugs used in case and control

Drug (count)	Count (%)		*P**
	Case (*n*=128)	Control (*n*=109)	
Cardiac drugs			
Nitroglycerin (37)	23 (18)	14 (12.8)	0.28
Carvedilol (54)	30 (23.4)	24 (22)	0.79
Amiodarone (4)	4 (3.1)	0	0.06
Anti-hypertensive drugs			
Valsartan (13)	4 (3.1)	9 (8.2)	0.08
Enalapril (5)	2 (1.6)	3 (2.7)	0.52
Captopril (4)	2 (1.6)	2 (1.8)	0.87
Amlodipine (54)	27 (2.1)	27 (2.48)	0.50
Diuretics			
Furosemide (56)	30 (2.3)	26 (2.4)	0.94
Oral anticoagulant			
Warfarin (5)	3 (2.3)	2 (1.8)	0.79
Lipid-lowering agents			
Atorvastatin (63)	28 (21.9)	35 (32.1)	0.07
Gemfibrozil (6)	5 (3.9)	1 (0.9)	0.14
Phosphate-binding drugs			
Sevelamer hydrochloride (96)	53 (41.4)	43 (39.4)	0.76
Sevelamer carbonate (6)	3 (2.3)	3 (2.7)	0.84
Supplements			
Folic acid (72)	39 (3.05)	33 (3.03)	0.97
Calcium carbonate (131)	75 (5.86)	56 (5.14)	0.26
Nephrovit (109)	56 (4.37)	53 (4.86)	0.45
Hormones			
Levothyroxine (3)	3 (2.3)	0	0.11
Cinacalcet (11)	7 (5.5)	4 (3.7)	0.51
Calcitriol (62)	35 (2.73)	27 (2.48)	0.65
Vitamin-D3 (35)	20 (4.48)	15 (1.38)	0.69
Antipruritic drugs			
Gabapentin (23)	10 (8.4)	13 (1.35)	0.29
Hydroxizine (11)	8 (6.7)	3 (2.8)	0.20
Other			
Prednisolone (7)	2 (1.6)	5 (4.6)	0.17
Pentoxifylline (15)	8 (6.2)	7 (6.4)	0.95
Carnitine (17)	11 (8.6)	6 (5.5)	0.36
Megestrol (3)	3 (2.3)	0	0.11
Fluoxitine (3)	1 (0.8)	2 (1.8)	0.47
Insulin (26)	15 (11.7)	11 (10.1)	0.69
Allopurinol (25)	10 (7.8)	15 (13.8)	0.14

*Q square test and Fisher's exact test was performed. *P*<0.05 was considered as significant

Table 4: Regression coefficients and odds ratio of chronic kidney disease-associated pruritus related factors based on a logistic regression model

Variables in the equation	*B*	SE	Wald	df	Significance	Exp (B)	95% CI for EXP (B)	
							Lower	Upper
Final model								
Atorvastatin (1)	−0.706	0.336	4.411	1	0.036	0.494	0.256	0.954
Constant	0.143	0.176	0.665	1	0.415	1.154		

[a]Variable(s) entered on Step 1: Duration of dialysis, age, BUN, Cr, Calcium, WBC, Kt/V, atorvastatin. SE=Standard error; CI=Confidence interval; BUN=Blood urea nitrogen; Cr=Creatinin; WBC=White blood cell[10]

further investigation. Some studies determined the role of these drugs in suppressing the level of TNFα and IL-6.[28] Many drugs can be responsible for chronic pruritus without skin rash. Drug-induced pruritus as an adverse effect has been shown to occur in 5% of patients after drug intake.[13,29]

To date, it seems that the immunomodulatory axis and neuronal axis play an essential role in the pathogenesis pathway of CKD-aP. Kappa opioid receptors (KOR) agonist (such as nalfurafine) that likely act on the neuronal axis can improve CKD-aP. The investigations have shown that the KOR activation induces an anti-inflammatory effect on the immune system through the downregulation of cytokines.[29] GBP and PGB can suppress the production of IL-6 and IL-8. On the other hand, it is showed that the biosynthesis of cholesterol has a key role in the training of immune cells.[30] Future studies should determine whether the cytokines exert their functions in CKD-aP directly or indirectly. The answer to this question can be useful in the proper prescription of drugs in dialysis patients. As discussed above, the immunomodulatory properties of various drugs (such as atorvastatin) may have an important role in the treatment of chronic itching in patients with HD.

This study contained limitations. The most important one was that there are several biases in the assessment of CKD-aP in HD patients. For example, anemia is a common sign in patients with CKD that may cause pruritus itself.

The finding of our study needs to be studied by clinical trials which evaluate the efficacy of different dosages and intervals of statin therapy in the reduction of CKD-aP among HD patients.

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Conflicts of interest

There are no conflicts of interest.

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