

Clinical features and risk factors of pruritus in patients with chronic renal failure

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Abstract. Dermatological manifestations are common in systemic diseases, such as chronic kidney disease. The present study investigated the clinical features and possible influencing factors of pruritus in patients with chronic renal failure (CRF). A total of 382 inpatients were enrolled from the Department of Nephrology at The Second Affiliated Hospital of Chongqing Medical University. A total of 138 subjects were hemodialysis patients, 41 were peritoneal dialysis patients, and 203 were chronic renal failure patients. The patients' clinical performance was observed, and the data was recorded for analysis. The prevalence of pruritus in hemodialysis patients was greater than that in peritoneal dialysis patients. A total of 187 patients were accompanied by xeroderma and 109 patients had pruritus at the same time. With effective and regular dialysis, pruritus could be alleviated in 40% of patients. The intensity of pruritus in the enrolled patients ranged from mild itching to irritability during day and night periods. Moreover, pruritus was intermittent or persistent, and/or limited to generalized. Following treatment, 35% of patients had poor results. A significant difference was noted in the levels of serum urea nitrogen, creatinine, serum phosphorus, calcium x phosphorus, and parathyroid hormone (PTH) between patients with pruritus and non-pruritus. Xeroderma is a common skin manifestation in patients with chronic renal failure and is associated with the occurrence of pruritus. Local cold and heat stimulation can relieve pruritus to some extent, and adequate hemodialysis can also relieve itching.

Introduction

The majority of systemic diseases have different degrees of dermatological manifestations. Chronic kidney disease (CKD)

is one of the most common systemic diseases with multiple clinical signs. This disease can cause multiple complications over time, especially in patients with comorbidities who require appropriate treatment (1,2). For example, several diseases such as hyperlipidemia associated with non-alcoholic fatty liver disease (3), anemia associated with vitamin K-dependent coagulopathies and iron deficiency (4) or infections with bacteria and fungi (these activate mast cells) resistant to treatment, develop as a result of immunosuppression (5).

In severe non-alcoholic liver disease, the mechanism is not fully elucidated, but some studies have suggested that one of the possible mechanisms of pruritus in these conditions is histamine-mediated hepatocyte related involvement and associated with elevation of aspartate aminotransferase levels (6).

Skin pruritus is one of the most characteristic clinical symptoms in patients with end-stage-renal disease (ESRD) and uremia (7). The majority of the patients with uremia suffer from skin complications. Their incidence and severity increase with the progression of renal failure (8,9). After clinical dialysis treatment, uremia is significantly alleviated (10), although the incidence of other comorbidities associated with uremia (such as porphyria cutanea tarda and skin tumors) gradually increased (11,12). Skin pruritus can appear in all parts of the body, and the duration varies, leading to secondary scratches. The moss-like skin diseases such as nodular prurigo, seriously affect the patient's physical and mental health (13).

Depending on the site and pathogenesis of pruritus, it can be divided into skin-derived pruritus, neurogenic pruritus, pruritus associated with neuropathy, cardiogenic pruritus, and mixed pruritus (14,15). For patients with end-stage renal disease, the mechanism of pruritus is more complex and may be the result of dysfunction of various organ systems (16). The present study evaluated the clinical features of skin pruritus, and investigated its relationship with several biochemical parameters. The aim was to provide theoretical background for the clinical treatment of this disease.

Patients and methods

Patients. From March 2015 to September 2017, 382 patients who were hospitalized in the Department of Nephrology, at the Second Affiliated Hospital of the Chongqing Medical

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University (Chongqing, China), were selected. The study protocol was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University (Chongqing, China), and all the patients signed an informed consent that allowed them to participate in the study. There were 225 males and 157 females and the average age of the subjects was 52.35 ± 16.72 years. The specific diagnostic criteria are shown in Table I.

When creatinine levels were higher than $707 \mu\text{mol/l}$ and the patient had clinical manifestations of uremia, dialysis treatment was performed. According to different renal replacement therapies, the patients were divided into two groups: hemodialysis group and continuous ambulatory peritoneal dialysis group.

Inclusion criteria: Patients with chronic renal failure and pruritus diagnosed by nephrologists were consistent with the diagnosis of chronic renal failure.

Exclusion criteria: Patients with poor compliance; patients with communication difficulties; patients with other pruritic skin diseases or other systemic diseases.

Clinical data collection. The demographic information (age, sex and educational level), personal history and family history of the target group was collected. The clinical parameters were obtained from each patient, including general treatment, hemodialysis, peritoneal dialysis, laboratory and auxiliary examination results, as well as blood urea, creatinine, serum calcium, serum phosphorus, and PTH values. The skin examination included color, dryness, desquamation, hair and skin integrity. The performance and characteristics of skin injuries were the following: xeroderma, manifested as dryness or desquamation of the whole body or local skin.

The patients with pruritus associated with chronic renal failure were diagnosed based on the following criteria: i) pruritus occurred at least 3 days in 12 weeks and itches were noted several times a day for several minutes each time; ii) pruritus occurred in a specific pattern lasting more than 1 month. The patients who presented with pruritus associated with other diseases were excluded from the group of those with CRF-associated pruritus.

Since pruritus is a subjective feeling of the patient and, obviously, there are individual differences, the severity of pruritus in the present study was assessed by the Visual Analogue Scale (VAS) parameter. The basic method is using a swimming scale with a length of approximately 10 cm. One side is marked with 10 scales. Both ends are '0' and '10', respectively; 0 denotes no itching, and 10 denotes unbearable itching. During the evaluation, the scaled side is facing away from the patient and the patient states his/her degree of itchiness between 0 and 10 points according to his/her feeling.

Statistical analysis. The data obtained in the present study was analyzed using Excel and statistical software SPSS 19.0 (SPSS Inc., Chicago, IL, USA). The measurement data was expressed as mean \pm standard deviation (mean \pm SD) and the differences between groups were assessed using Student's t-test. Levene tests were used to analyze homogeneity of variance prior to the t-test. The Chi-square test was used for comparison of the numerical variables. When the risk factors were analyzed,

Table I. The specific diagnostic criteria.

| Diagnostic staging | Index |
|---|---|
| Renal insufficiency compensation period | GFR (80-50 ml/min), Scr (133-177 $\mu\text{mol/l}$) |
| Renal insufficiency decompensation period | GFR (50-20 ml/min), Scr (178-445 $\mu\text{mol/l}$) |
| Renal failure stage | GFR (20-10 ml/min), Scr (446-707 $\mu\text{mol/l}$) |
| Uremia stage | GFR (<10 ml/min), Scr (>707 $\mu\text{mol/l}$) |

GFR, glomerular filtration rate; Scr, serum creatinine.

Table II. Xeroderma distribution among the patients.

| Symptom | Pruritus group | Non-pruritus group |
|--------------|----------------|--------------------|
| Xeroderma | 109 | 80 ^a |
| No xeroderma | 88 | 105 |

^aP<0.01, compared to pruritus group.

statistical significant differences were considered at P<0.05. The differences were considered highly statistically significant at P<0.01.

Results

Disease distribution of patients. The distribution of specific diseases in the patient's primary disease is shown in Fig. 1. A total of 167 cases of chronic glomerulonephritis, 77 cases of diabetic nephropathy, 58 cases of hypertensive nephropathy, 9 cases of polycystic kidney disease, 4 cases of hepatitis B associated nephritis, 2 cases of purpura nephritis, 4 cases of gout nephritis, 16 cases of lupus nephritis, 2 cases of obstructive nephropathy, 17 cases of chronic interstitial nephritis, 2 cases of unilateral renal insufficiency, 7 cases of IgA nephropathy, 8 cases of nephrotic syndrome, 1 case of hepatic syndrome, and 8 cases of unexplained causes were recruited in the present study.

Skin changes in the group. Among the subjects that were enrolled in the study, 197 cases had common skin itching, accounting for 51.57% of the total number (Table II; Fig. 2). A total of 109 cases of xeroderma were noted in the pruritus population and 80 cases of xeroderma were present in the non-pruritus group. A significant difference between the two groups was noted (P<0.01).

Clinical features of pruritus. The specific data on the pruritus statistics of the enrolled patients is presented in Table III. Moreover, no significant difference was found in the age between patients with pruritus and patients without pruritus (Table III; P>0.05 in all groups), although a signifi-

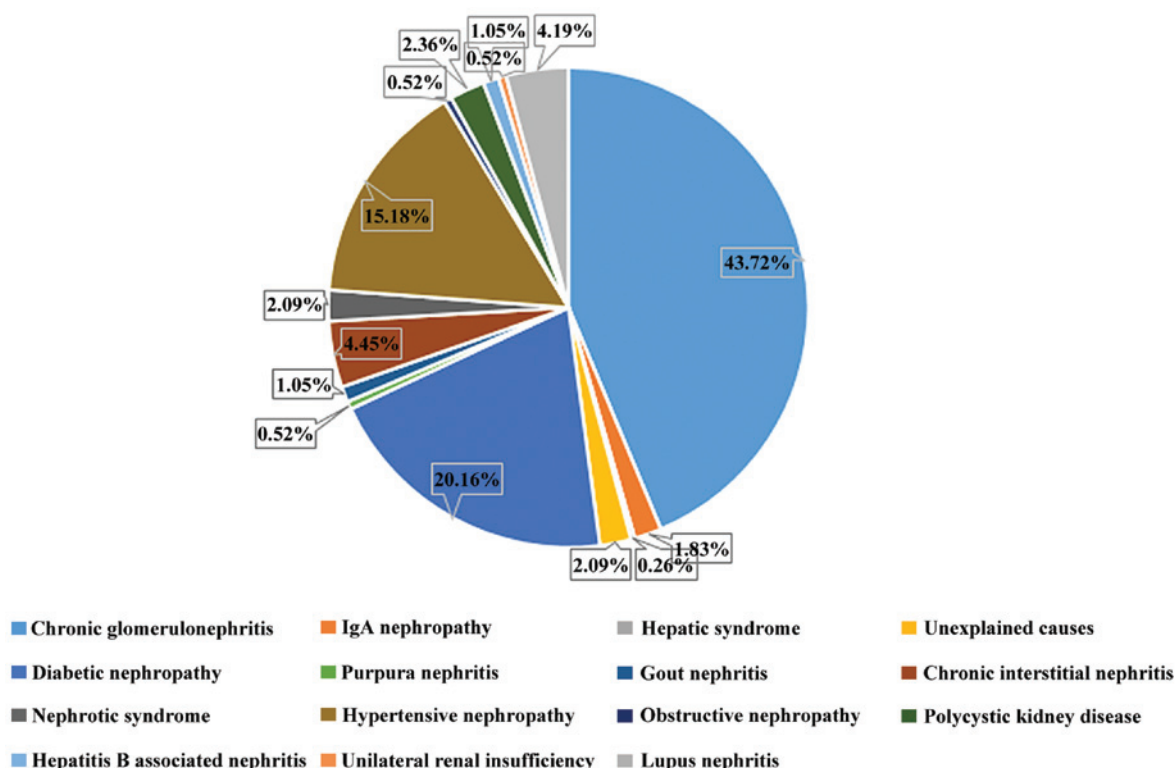


Figure 1. The distribution of specific diseases in the patient's primary disease status.

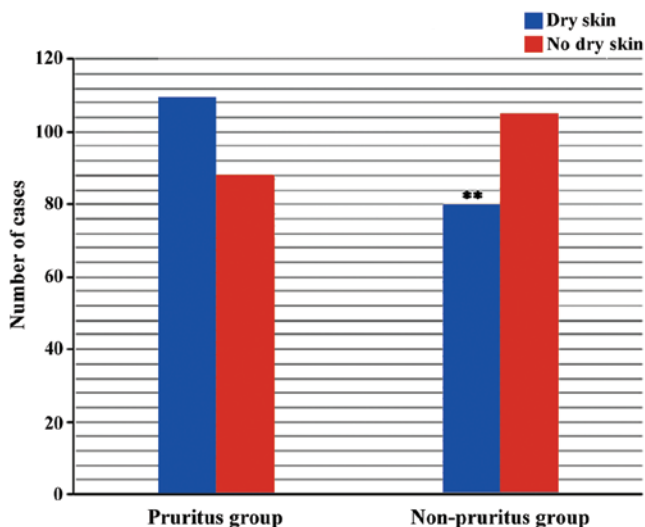


Figure 2. Distribution of skin dryness in the pruritus and non-pruritus groups. **P<0.01.

cant difference in disease status was evident in hemodialysis patients and CRF patients (P<0.05). The longer the course of disease, the more likely the itching.

According to the description of the patients pruritus affected all parts of the body, and the majority of the patients exhibited pruritus symmetry. Approximately 17% of the patients had pruritus, which could affect more than 50% of the body skin. Among them, the frequency of pruritus in patients with chronic renal failure and uremia was relatively high, which exerted an emotional impact on patients. A total of 22 patients exhibited optimal conscious therapeutic effects.

Pruritus had different degrees of influence on the quality of sleep and mood of the patient (Table IV).

Cold stimuli, thermal stimuli and changes in the weather also exerted an influence on the itchiness of the patient (Table V). For both groups of patients undergoing hemodialysis and peritoneal dialysis, the symptoms of pruritus after dialysis were reduced compared to those before dialysis. The data indicated that dialysis had a certain mitigation effect on itching.

The nature of the pruritus in the patients examined exhibited a variety of associated conditions (Table VI), and with no obvious regularity in distribution. In addition, the majority of the patients did not have skin lesions when itching, but their symptoms were often accompanied by xeroderma.

Approximately 35% of patients were treated. The common treatment options included oral antihistamines and topical medications, such as compound dexamethasone acetate cream and triamcinolone acetonide. A total of 22 patients exhibited optimal conscious treatment (Table VII). The degree of pruritus in patients was assessed using visual analogue scale (Table VIII). In the course of the study, there were 28 patients with skin lesions, including scratches, blood stasis, lichenification, and prurigo nodularis.

Risk factors analysis. The levels of serum urea nitrogen, creatinine, serum phosphorus, calcium, phosphorus, and PTH were significantly different between the pruritus group and the non-pruritus group in patients with chronic renal failure (Table IX; P<0.01). The pruritus intensity was correlated with increase level of serum urea nitrogen, creatinine, serum phosphorus, calcium, phosphorus, and PTH. However, the pruritus intensity was not correlated with serum calcium level (P>0.05).

Table III. Distribution of patient parameters in relation with skin itching.

| Parameters | CRF patients | | Hemodialysis patients | | Peritoneal patients | | All patients | |
|----------------|--------------------------|----------------------------|--------------------------|---------------------------|-----------------------|---------------------------|------------------------|----------------------------|
| | Pruritus group (n=76) | Non-pruritus group (n=127) | Pruritus group (n=96) | Non-pruritus group (n=42) | Pruritus group (n=25) | Non-pruritus group (n=16) | Pruritus group (n=197) | Non-pruritus group (n=185) |
| Age (years) | 52.43±16.24 | 51.86±17.16 | 51.56±15.33 | 54.03±15.15 | 49.46±14.61 | 46.15±13.87 | 52.26±14.86 | 50.92±16.19 |
| Disease course | 60.63±32.27 ^a | 57.13±24.47 | 44.82±18.52 ^a | 38.04±13.58 | 45.72±16.48 | 39.36±20.38 | 44.71±19.16 | 42.69±20.37 |

^aP<0.05, compared to the relevant non-pruritus group.

Table IV. Relationship between psychological factors and pruritus.

| Parameters | CRF patients (n=76) | Hemodialysis patients (n=96) | Peritoneal dialysis patients (n=25) | χ^2 value | P-value |
|---------------------|---------------------|------------------------------|-------------------------------------|----------------|---------|
| Sleep effects | | | | 4.472 | 0.593 |
| No | 19 | 18 | 4 | | |
| Mild | 31 | 46 | 12 | | |
| Moderate | 21 | 25 | 6 | | |
| Severe | 5 | 7 | 3 | | |
| Emotional influence | | | | 6.932 | 0.316 |
| No | 9 | 9 | 3 | | |
| Mild | 42 | 51 | 7 | | |
| Moderate | 22 | 33 | 13 | | |
| Severe | 3 | 3 | 2 | | |

Table V. Efficacy of physical methods in itching treatment.

| Parameters | CRF patients (n=76) | Hemodialysis patients (n=96) | Peritoneal dialysis patients (n=25) | χ^2 value | P-value |
|---------------------|---------------------|------------------------------|-------------------------------------|----------------|---------|
| Cold stimulus | | | | 3.562 | 0.568 |
| No effect | 9 | 12 | 11 | | |
| Increased itching | 25 | 25 | 2 | | |
| Reduced itching | 42 | 59 | 12 | | |
| Thermal stimulation | | | | 3.367 | 0.542 |
| No effect | 13 | 15 | 6 | | |
| Increased itching | 29 | 27 | 7 | | |
| Reduced itching | 34 | 54 | 12 | | |
| Cold weather | | | | 2.261 | 0.342 |
| No effect | 56 | 62 | 19 | | |
| Increased itching | 7 | 13 | 2 | | |
| Reduce itching | 13 | 21 | 4 | | |
| Before dialysis | | | | 1.214 | 0.537 |
| No effect | - | 61 | 18 | | |
| Increased itching | - | 26 | 5 | | |
| Reduce itching | - | 9 | 2 | | |
| After dialysis | | | | 2.124 | 0.336 |
| No effect | - | 46 | 15 | | |
| Increased itching | - | 8 | 3 | | |
| Reduce itching | - | 42 | 7 | | |

Table VI. Itching type and associated lesions.

| Parameters | CRF patients (n=76) | Hemodialysis patients (n=96) | Peritoneal dialysis patients (n=25) | χ^2 value | P-value |
|--------------------|------------------------|---------------------------------|--|----------------|---------|
| Itching nature | | | | 4.248 | 0.627 |
| No special | 28 | 40 | 13 | | |
| Ant feeling | 32 | 40 | 10 | | |
| Burning sensation | 6 | 7 | 1 | | |
| Tingling | 10 | 9 | 1 | | |
| Associated lesions | | | | 2.516 | 0.316 |
| No | 62 | 85 | 20 | | |
| Yes | 14 | 11 | 5 | | |
| Xerodermia | | | | 2.016 | 0.338 |
| No | 32 | 47 | 9 | | |
| Yes | 44 | 49 | 16 | | |

Table VII. Patient's drug treatment.

| Parameters | CRF patients (n=76) | Hemodialysis patients (n=96) | Peritoneal dialysis patients (n=25) | χ^2 value | P-value |
|------------------|------------------------|---------------------------------|--|----------------|---------|
| Treatment | | | | 5.016 | 0.082 |
| No | 44 | 61 | 20 | | |
| Yes | 32 | 35 | 5 | | |
| Treatment effect | | | | 7.529 | 0.115 |
| Cure | 5 | 11 | 1 | | |
| Effective | 20 | 7 | 2 | | |
| Invalid | 7 | 17 | 2 | | |

Table VIII. Itching intensity score.

| Itching state | State of the investigation | Worst state | Best state | Mosquito bites state |
|---------------|----------------------------|-------------|------------|----------------------|
| VAS score | 3.21±1.73 | 7.93±1.15 | 0.47±0.35 | 4.41±1.37 |

VAS, Visual Analogue Scale.

Discussion

In patients with chronic renal failure, pruritus can occur in hemodialysis and peritoneal dialysis (17). In 2007, a study in Shanghai reported that in 478 patients with chronic renal failure, 224 were subjected to hemodialysis and peritoneal dialysis. The results indicated that the incidence of pruritus was higher in hemodialysis patients than in peritoneal dialysis patients. In the present study, the incidence of pruritus in hemodialysis patients is higher than that in peritoneal dialysis patients. This is consistent with the aforementioned findings. When uremia patients undergo routine hemodialysis, the ability of dialysis membranes to remove large and medium-sized molecules is generally poor, which can easily lead to long-term accumulation of large and medium-sized molecules (18). Peritoneal

dialysis facilitates diffusion convection and ultrafiltration, and the ability to remove large and medium-sized molecules. This technique is better than hemodialysis (19).

The clinical features of pruritus are highly variable. In most patients, pruritus is symmetric, while some of them present with generalized pruritus. The data from this study suggest that uremic pruritus tends to be persistent and recurrent. The majority of the patients suffer from daily itching, while the rest of them may have itching symptoms weekly or monthly. Although pruritus tends to persist, it is not necessarily continuous, and Gilchrist also reached a similar conclusion (20). However, Stähle-Bäckdahl *et al* (21) concluded that uremic pruritus has continuity. Different results may be related to differences in the sample size and the length of follow-up. The typical characteristic is that there is no obvious primary skin

Table IX. Comparison of serum urea nitrogen, creatinine, blood calcium, phosphorus, calcium phosphorus, and PTH levels.

| Variables | Pruritus group | Non-pruritus group | t value | P-value |
|---------------------------|----------------|--------------------|---------|---------------------|
| Urea nitrogen (mmol/l) | | | | |
| Hemodialysis | 25.35±11.45 | 19.08±10.67 | 3.942 | <0.001 ^c |
| Peritoneal dialysis | 25.82±8.25 | 24.75±13.36 | 0.318 | 0.752 |
| CRF | 21.24±10.68 | 17.67±11.65 | 2.1789 | 0.015 ^b |
| Creatinine (μ mol/l) | | | | |
| Hemodialysis | 793.63±403.36 | 570.97±354.75 | 4.139 | <0.001 ^c |
| Peritoneal dialysis | 952.11±316.55 | 812.75±246.88 | 1.492 | 0.144 |
| CRF | 548.92±347.83 | 396.92±215.54 | 3.846 | <0.001 ^c |
| Blood calcium (mmol/l) | | | | |
| Hemodialysis | 1.98±0.32 | 2.09±0.21 | -2.956 | 0.003 ^c |
| Peritoneal dialysis | 1.97±0.27 | 2.01±0.29 | -0.450 | 0.656 |
| CRF | 2.01±0.31 | 2.05±0.23 | -1.050 | 0.295 |
| Phosphorus (mmol/l) | | | | |
| Hemodialysis | 1.97±0.57 | 1.65±0.67 | 3.477 | <0.001 ^c |
| Peritoneal dialysis | 1.88±0.61 | 1.86±0.62 | 0.102 | 0.919 |
| CRF | 1.68±0.59 | 1.55±0.59 | 1.519 | 0.130 |
| Calcium x phosphorus | | | | |
| Hemodialysis | 3.83±1.68 | 3.36±1.46 | 2.097 | 0.037 ^a |
| Peritoneal dialysis | 3.62±1.14 | 3.77±1.25 | -0.396 | 0.694 |
| CRF | 3.35±1.06 | 3.28±1.20 | 0.420 | 0.675 |
| PTH (pg/ml) | | | | |
| Hemodialysis | 608.15±514.44 | 243.46±206.55 | 7.099 | <0.001 ^c |
| Peritoneal dialysis | 677.34±445.74 | 373.75±226.28 | 2.517 | 0.016 ^b |
| CRF | 447.61±415.76 | 236.26±203.11 | 4.845 | <0.001 ^c |

^aP<0.05, ^bP<0.01, ^cP<0.001.

lesion, although patients with chronic renal failure secondary to diabetes usually develop hyperkeratotic nodules. Their pathology suggests that penetrating skin diseases can produce strong and persistent skin itching (22). In addition, various factors affect skin itching, although two of them are mainly responsible for aggravating this process: heat and dryness. Different temperatures exert different effects on pruritus. An appropriate increase in water temperature can increase pruritus, although it can be relieved at approximately 40°C. This is mainly due to hyperthermia, which stimulates pain-sensing nerves and blocks the symptoms of pruritus. High temperatures can further cause histamine release and increase itching. Although this process does not aggravate pruritus in high temperatures, it is possibly caused, since histamine does not play a major role in pruritus (23,24).

Xeroderma is mainly manifested as dark skin without moisture, scaling, visible small cracks and dry cracks, which occur in the extensor side of the limbs. Some studies have shown that (25) xeroderma is closely related to pruritus. The reasons are the following: changes in skin barrier function, accumulation of metabolites in patients with chronic renal failure and increased secretion of urea in sweat. The aforementioned processes interfere with the activation of ACE (Angiotensin converting enzyme) (26) and lead to impaired

skin function. The impaired function of sebaceous and sweat glands, the dysfunction of sebaceous glands and the apocrine sweat glands in patients with chronic renal failure are some of the reasons that lead to xeroderma. The increase in the pH of the stratum corneum of the skin and the increase of vitamin A concentration in the epidermis are also considered pathogenic causes of xeroderma.

Currently, the pathogenesis of uremic pruritus is not clear, but the hypotheses that are related to the pathogenesis of pruritus are the following: immune function disorder hypothesis, opioid hypothesis, parathyroid hormone hypothesis, bivalent ion hypothesis and molecular hypothesis. Thus it is very difficult to imply that itching is caused by a single factor (27).

The glomerular filtration function of patients with chronic renal failure was reduced, and the residual renal units did not excrete metabolites adequately, which caused the product to accumulate in the body and exert toxic effects. Chronic renal failure is a complex pathophysiological process that is usually responsible for a series of complications, such as calcium and phosphorus metabolism disorders. When the concentration of blood phosphorus increases, it combines with blood calcium to form calcium phosphate, which will be deposited on the skin and other tissues to reduce blood calcium. Hypocalcemia can

also promote secondary hyperparathyroidism and as a result cause higher secretion of parathyroid hormone (PTH). PTH causes renal tubular reabsorption of phosphorus and regulates blood phosphorus levels. In the present study, it was found that the levels of urea, creatinine, serum phosphorus, calcium, phosphorus, and PTH in patients with itching were significantly higher than those in people without itching ($P < 0.05$). This suggests that they play a key role in the pathogenesis of uremia.

In addition, secondary hyperparathyroidism is a common disorder in patients with chronic renal failure. It has been reported (28) that pruritus can be relieved after total parathyroidectomy. However, not all uremic patients suffering from pruritus have hyperparathyroidism. In some patients, itching determined by parathyroid hormone is still not in remission after parathyroidectomy. Injecting PTH into the human body does not cause pruritus, suggesting that PTH itself has no itching effect (29). Therefore, unless combined with hyperparathyroidism, parathyroidectomy is not effective in the treatment of uremic pruritus.

The results of the present study demonstrate that the majority of patients with chronic renal failure and uremia suffer from itching. The occurrence of pruritus is related to the course of the disease and not to age or sex. Xeroderma is the most common skin manifestation in patients with chronic renal failure. It is related to the occurrence of itching. The itching site and duration are different. Local cold or heat stimuli and reduced temperatures can, to some extent, relieve itching. In addition, adequate hemodialysis can also relieve itching. The levels of serum urea nitrogen, creatinine, serum phosphorus, calcium-phosphorus product, and PTH were associated with the occurrence of pruritus.

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Availability of data and materials

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

Authors' contributions

TH and SW contributed to the conception and design of the study. TH and BW were responsible for the collection and assembly of the data. XL completed the data analysis and interpretation. TH and SW were involved in writing of the manuscript. All authors read and approved the final manuscript.

Ethics approval and consent to participate

The study was approved by the Ethics Committee of the Second Affiliated Hospital of Chongqing Medical University (Chongqing, China). All patients included in the study provided written informed consent for their participation.

Patient consent for publication

Not applicable.

Competing interests

The authors declare that they have no competing interests.

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