



Uremic pruritus: pathophysiology, clinical presentation, and treatments

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Uremic pruritus is one of the most common and bothersome symptoms in patients with end-stage renal disease. Most patients with uremic pruritus experience a prolonged and relapsing course and significant impairments of quality of life. The pathophysiology of uremic pruritus is not completely understood. A complex interplay among cutaneous biology and the nervous and immune systems has been implicated, with the involvement of various inflammatory mediators, neurotransmitters, and opioids. Uremic pruritus treatment outcomes are often unsatisfactory. Clinical trials have mostly been small in scale and have reported inconsistent results. Recent evidence shows that gabapentinoids, nalfurafine, and difelikefalin are effective for relieving uremic pruritus in hemodialysis patients. This review provides an overview of the epidemiology and proposed mechanisms of uremic pruritus, then highlights the manifestations of and clinical approach to uremic pruritus. Current evidence regarding treatment options, including topical treatments, treatment of underlying disease, phototherapy, and systemic treatments, is also outlined. With a better understanding of uremic pruritus, more therapeutic options can be expected in the near future.

Keywords: Gabapentin, Chronic kidney failure, Pregabalin, Pruritus, Chronic renal insufficiency

Introduction

Uremic pruritus is one of the most common and distressing comorbid diseases in patients with end-stage renal disease (ESRD) and also occurs in patients with chronic kidney disease (CKD). Uremic pruritus significantly affects multi-

ple aspects of quality of life, including mood, sleep, and social relationships, and is often refractory to treatment [1,2]. Moreover, in ESRD patients, a higher intensity of pruritus is associated with worse patient survival and more technique failures of peritoneal dialysis (PD) [3-5].

In this review, we summarized the current knowledge

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regarding the epidemiology, pathophysiology, clinical presentation, clinical approach, and treatment of uremic pruritus. Due to the various definitions of uremic pruritus used in the literature, we defined uremic pruritus as symptoms of chronic itch secondary to declining renal function. Articles reporting studies on pruritus secondary to ESRD or CKD were reviewed. For the pathophysiology and treatment of other pruritic diseases, we refer readers to other review articles [6–8].

Epidemiology

The prevalence of uremic pruritus varies by country, dialysis modality, dialysis unit, and study population. Uremic pruritus affects 25% to 62% of patients receiving PD [9,10] and 38% to 84% of patients receiving hemodialysis (HD) [1,11,12]. In an international survey conducted from 1996 to 2015, the prevalence of bothersome uremic pruritus in HD patients gradually declined from 28% to 18% [11]. However, comparisons between HD patients and PD patients with regard to the prevalence and severity of uremic pruritus remain inconsistent [13,14]. In a multinational cross-sectional study of stage 3–5 CKD patients, up to 24% of participants experienced moderate to extreme pruritus [15]. Severe uremic pruritus is rare among pediatric dialysis patients, but the reason for this remains unclear. A study of

199 children on dialysis reported that only 9.1% had pruritus, and the intensity of pruritus was also mild [16].

Pathophysiology

The pathophysiology of uremic pruritus has not been fully elucidated. Along the itch-sensory pathway, the proposed origins of itch have been classified as follows: 1) pruritoceptive: itch induced by pruritogens in the skin, e.g., allergic contact dermatitis; 2) neuropathic: itch resulting from pathology in the afferent conduction pathway of the peripheral and central nervous system, e.g., itch related to multiple sclerosis; 3) neurogenic: itch originating in the nervous system without neural damage, e.g., opioid-induced pruritus; 4) psychogenic: itch owing to psychiatric and psychosomatic causes without organic problems, e.g., parasitophobia [17,18]. The mechanism of uremic pruritus may involve complex interactions of more than one proposed origin (Fig. 1).

Skin moisture is lower in dialysis patients, and dry skin is very common in patients with uremic pruritus [19,20]. Dialysis patients with uremic pruritus showed lower levels of stratum corneum hydration than nonpruritic patients [20], while some studies did not find an association between pruritus and skin hydration or transepidermal water loss [19,21]. Whether there are more skin mast cells in patients

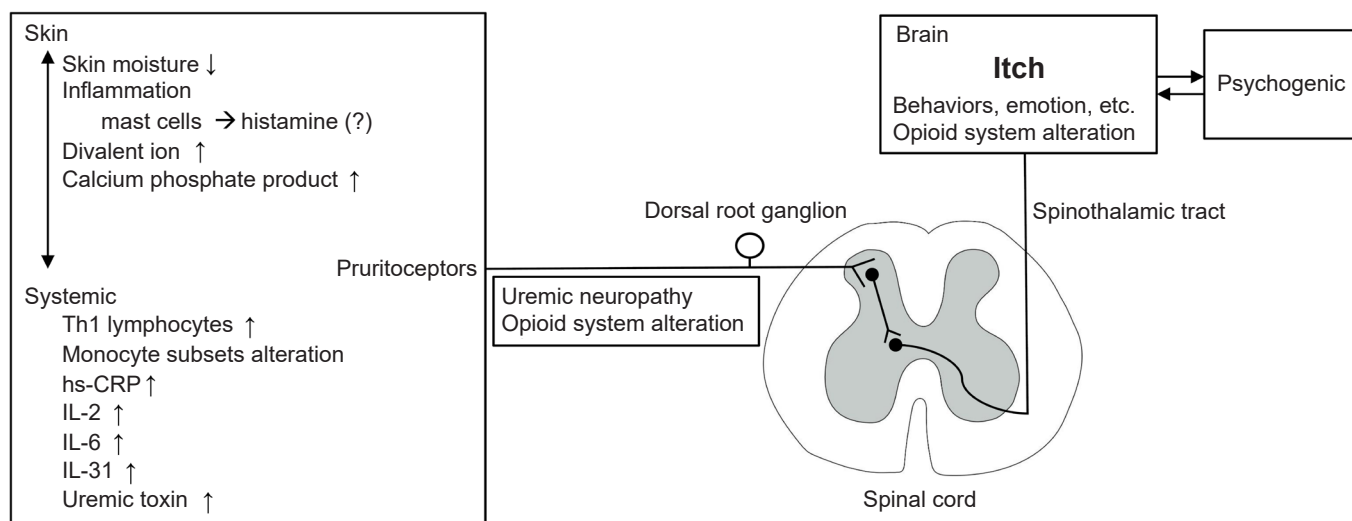


Figure 1. The pathophysiology of uremic pruritus. The mechanism of uremic pruritus implicates an interplay among cutaneous biology, the nervous system, and the immune system with the involvement of inflammatory mediators, neurotransmitters, and opioids. hs-CRP, high sensitivity C-reactive protein; IL, interleukin; Th1, T-helper 1.

with uremic pruritus remains unclear. Some studies have reported that the number of dermal mast cells in HD patients is significantly higher than that in healthy controls [22,23], while another report showed no relationship between the extent of pruritus, the number of skin mast cells, or the level of plasma histamine in dialysis patients [24]. Divalent ions, calcium-phosphate products, hyperparathyroidism, and uremic neuropathy have also been implicated in uremic pruritus [5,13,20,25,26]. The results of our previous study and those of others identified dialysis adequacy as an independent predictor of pruritus intensity in HD patients, which suggested that the clearance of pruritogenic substances could influence the severity of pruritus [27–29].

Immune dysregulation plays a critical role in the pathophysiology of uremic pruritus. Compared with nonpruritic patients, those with uremic pruritus show higher levels of C-reactive protein [4,30] and various inflammatory mediators, including histamine, interleukin (IL)-2, and IL-6 [30,31]. Animal studies reported that IL-31 induced severe pruritus and dermatitis in transgenic mice [32], and serum levels of IL-31 were positively associated with the intensity of uremic pruritus in HD patients [33]. In addition, patients with uremic pruritus were found to have an increased proportion of T-helper 1 cells [30] and altered monocyte subsets [34]. The relationship between the immune system and the itch-sensory pathway is thus an interesting field for further study.

Morphine has been reported to trigger itching, which suggests that the opioid system is involved in the mechanism of uremic pruritus [35]. There are three major types of opioid receptors: μ , κ , and δ . Itch is observed after the activation of μ -opioid receptors following systemic or neuraxial opioid administration [36], while κ -opioid receptor agonists exert antipruritic effects [37]. Although the effects of opioid receptor agonists/antagonists are mainly activated through the central nervous system [35], opioid receptors are also present on peripheral nerve fibers and various skin cells, such as keratinocytes, melanocytes, and hair follicles [38]. Expression of κ -opioid receptor was lower in the skin of patients with uremic pruritus [39], indicating a significant role of the peripheral opioid system in uremic pruritus. In addition, a peripherally restricted, selective κ -opioid receptor agonist showed a significant antipruritic effect in a recent trial on HD patients [40].

Clinical presentation

Patients suffering from uremic pruritus often experience itch daily or nearly daily [1]. Pruritus can involve all areas of the body, affecting more than 25% of the body surface area in more than half of patients with uremic pruritus [2,34]. The course is fluctuating and prolonged, usually lasting for more than one year [1,41]. Patients with uremic pruritus often have pruritus in the absence of a primary cutaneous eruption. However, the vicious cycle of itch and scratching behaviors may lead to secondary skin changes, including excoriations, prurigo nodularis, lichen simplex, or nonspecific eczema [16].

Clinical approach

The first step to managing itch in patients with reduced kidney function is accurate diagnosis. In addition to uremic pruritus, various pruritic skin diseases, such as scabies, atopic dermatitis, and drug allergies, can occur in dialysis and CKD patients. A detailed medical history and skin examination are crucial to correct diagnosis [18]. Other causes in addition to uremic pruritus should be considered if an itchy skin condition occurred before the onset of kidney disease. If pruritus is confined to localized areas or is exacerbated in a short period, exposures or aggravating factors should be evaluated. A careful review of the patient's medication history may exclude drug-related itch or drug-related hypersensitivity reactions. If skin examination reveals primary skin eruptions, such as wheals, morbilliform eruptions, or bullae, other dermatological diseases should be included in differential diagnosis. A skin biopsy is usually not necessary for diagnosis of uremic pruritus. Laboratory and imaging studies can be considered for patients with manifestations suggesting other causes of itchy skin like hyperthyroidism or cutaneous T cell lymphoma.

Treatments

Uremic pruritus is frequently refractory to multiple treatments. However, many studies on the treatment of uremic pruritus in recent years have shed light on this intractable disease (Table 1, 2 [40, 42–75]).

Table 1. Potential therapeutic options for uremic pruritus

Topical treatments
Moisturizer
Steroids
Capsaicin
Calcineurin inhibitors
Pramoxine
Gamma-linolenic acid
Cannabinoids
Treatment of underlying disease
Optimization of dialysis dosage and modality
Control of hyperparathyroidism
Kidney transplantation
Phototherapy
Systemic treatments
Gabapentinoids
Gabapentin
Pregabalin
Opioid antagonists and agonists
μ -opioid receptor antagonist
κ -opioid receptor agonist
Peripherally selective κ -opioid receptor agonist
Mixed μ -opioid antagonist and κ -opioid agonist
Antihistamines, mast cell stabilizers, and leukotriene receptor antagonists
Oral activated charcoal
Cholestyramine
Biologics
Nemolizumab
Dupilumab
Thalidomide
Sertraline

Topical treatments

Moisturizer

A high percentage of patients with uremic pruritus have dry skin [20]. Maintaining adequate skin hydration is the cornerstone of antipruritic treatment. In a noncontrolled study, 16 of 21 dialysis patients with uremic pruritus reported a reduction in the severity of pruritus after 1 week of regular emollient use [20].

Steroids

Approximately 10% of physicians prescribe topical steroids as a first-line treatment for uremic pruritus in HD patients [11], but no trials have assessed their efficacy. As microin-

flammation plays an important role in the pathogenesis of uremic pruritus, topical steroids may provide antipruritic effects against uremic pruritus, especially for skin areas with secondary scratch-induced eczema or obvious inflammation. However, as uremic pruritus usually involves a large percentage of the body surface area, the use of potent topical steroids on large skin areas may cause systemic absorption and adverse cutaneous effects, including skin atrophy and folliculitis. Topical steroids should be prescribed with caution, and patients should be educated on how to use them properly.

Capsaicin

Capsaicin, the active compound in chili peppers, depletes neuropeptide substance P from sensory nerve terminals in the skin and blocks the conduction of pain and pruritus [76]. Topical capsaicin has been used to relieve itch, especially neuropathic itch conditions, such as postherpetic itch, brachioradial pruritus, and notalgia paraesthetica [76]. Two double-blind, crossover randomized controlled trials (RCTs) of HD patients showed that capsaicin 0.025% cream was significantly more effective for alleviating uremic pruritus than placebo [42,43]. Local burning, stinging, and erythema at the site of application are common side effects.

Calcineurin inhibitors

Topical calcineurin inhibitors, including tacrolimus and pimecrolimus, selectively inhibit calcineurin and thus prevent the transcription of IL-2 and other cytokines in T lymphocytes [77]. Topical calcineurin inhibitors have been used in inflammatory skin disorders [78]. In a non-controlled study of 25 dialysis patients, Kuypers et al. [77] showed that tacrolimus ointment significantly reduced the severity of uremic pruritus after 6 weeks. However, in a 4-week double-blind RCT of 22 HD patients, Duque et al. [44] demonstrated that 0.1% tacrolimus ointment was not more effective than placebo for relieving uremic pruritus. In another 8-week double-blind RCT of 60 dialysis patients, Ghorbani et al. [45] showed no significant antipruritic benefit of topical pimecrolimus 1% compared with placebo.

Pramoxine

Pramoxine is a topical local anesthetic with a potential antipruritic effect that interferes with the transmission of impulses along sensory nerve fibers [79]. In a double-blind

Table 2. Randomized controlled trials on treatments of uremic pruritus

Study	Design	Country	Population	No. of patients	Treatment duration (wk)	Treatment	Pruritus assessment	Results
Topical treatment								
Capsaicin								
Tamg et al., 1996 [42]	Crossover	Taiwan	HD	19	4	Capsaicin 0.025% cream vs. placebo	4-Point scale	82.4% of participants experienced relief of pruritus after receiving capsaicin cream; capsaicin cream was more effective in improving itching score than placebo ($p < 0.001$).
Cho et al., 1997 [43]	Crossover	Taiwan	HD	22	4	Capsaicin 0.025% cream vs. placebo	4-Point scale	86.4% of participants experienced relief of pruritus after receiving capsaicin cream; 22.7% experienced relief of pruritus after placebo treatment ($p < 0.001$).
Calcineurin inhibitors								
Duque et al., 2005 [44]	Parallel	United States	HD	22	4	0.1% Tacrolimus ointment vs. placebo	VAS	Percentage of reduction in VAS was not different between tacrolimus (77%) and placebo groups (79%).
Ghorbani et al., 2011 [45]	Parallel	Iran	HD	60	8	Topical pimecrolimus 1% vs. placebo	VAS	Change in VAS was not different between pimecrolimus (-6) and placebo groups (-7).
Pramoxine								
Young et al., 2009 [46]	Parallel	United States	HD	28	4	1% Pramoxine lotion vs. placebo	VAS	Percentage of reduction in VAS was higher in the pramoxine group (61%) than in the placebo group (42%) ($p = 0.0072$).
Gamma-linolenic acid								
Chen et al., 2006 [47]	Crossover	Taiwan	HD, PD	17	2	2.2% Gamma-linolenic acid cream vs. placebo	VAS, QPS	More reduction of VAS in the gamma-linolenic acid group (-4.5) than the placebo group (-0.5) ($p < 0.01$).
Treatment of underlying disease								
Dialysis modality								
Chen et al., 2009 [48]	Parallel	China	HD	116	12	High-flux HD vs. low-flux HD	VAS	More reduction of VAS in the high-flux group (-3.99) than the low-flux group (-0.71).
Jiang et al., 2016 [49]	Parallel	China	HD	51	12	High-flux HD vs. hemodiafiltration	VAS, QPS	More reduction of VAS in the high-flux HD group (-7.2) than the hemodiafiltration group (-5.6) ($p < 0.05$).
Lim et al., 2020 [50]	Parallel	South Korea	HD	50	12	MCO dialyzer vs. high-flux dialyzer	VAS, QPS	MCO group had lower scores for morning pruritus distribution and frequency of scratching during sleep at week 12. Between-group differences for VAS were not significant.
Cinacalcet								
El-Shafey et al., 2011 [51]	Parallel	Kuwait, Saudi Arabia	HD	82	36	Cinacalcet vs. vitamin D + phosphate binder	QPS	Pruritus intensity decreased from 3.38 at baseline to 1.74 at week 36 in the cinacalcet group.
Phototherapy								
Gilchrist et al., 1977 [52]	Parallel	United States	HD	24	4	Broadband UVB vs. UVA	4-Point scale	90% of participants in the UVB group and 25% in UVA group showed improvement of pruritus ($p < 0.01$).
Ko et al., 2011 [53]	Parallel	Taiwan	CKD, HD, PD	21	6	Narrowband UVB vs. UVA	VAS	Change in VAS was not different between the UVB (-3.53) and UVA groups (-3.38) ($p = 0.92$).
Systemic treatment								
Gabapentinoids								
Gunal et al., 2004 [54]	Crossover	Turkey	HD	25	4	Gabapentin vs. placebo	VAS	More reduction of VAS in the gabapentin group (-6.7) than the placebo group (-0.8) ($p < 0.001$).
Naini et al., 2007 [55]	Parallel	Iran	HD	34	4	Gabapentin vs. placebo	VAS	More reduction of VAS in the gabapentin group (-6.7) than the placebo group (-1.5) ($p < 0.001$).

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Table 2. Continued

Study	Design	Country	Population	No. of patients	Treatment duration (wk)	Treatment	Pruritus assessment	Results
Solak et al., 2012 [56]	Crossover	Turkey	HD	29	6	Gabapentin vs. pregabalin	VAS	Change in VAS was not different between the gabapentin (-4.41) and the pregabalin groups (-4.43) (p = 0.844).
Yue et al., 2015 [57]	Parallel	China	HD	188	12	Pregabalin vs. ondansetron vs. placebo	VAS, QPS	More reduction of VAS in the pregabalin group (-6.6) than the ondansetron (-2.5) or placebo (-2.0) groups (p < 0.05).
Nofal et al., 2016 [58]	Parallel	Egypt	HD	54	3	Gabapentin vs. placebo	VAS, QPS	More reduction of VAS in the gabapentin group (-5.82) than the placebo group (-0.1) (p < 0.001).
Foroutan et al., 2017 [59]	Parallel	Iran	HD	90	4	Pregabalin vs. doxepin	VAS	More reduction of VAS in the pregabalin group (-5.4) than the doxepin group (-2.9) (p < 0.001).
Gobo-Oliveira et al., 2018 [60]	Parallel	Brazil	HD	60	3	Gabapentin vs. dexchlorpheniramine	VAS, QPS	Change in VAS was not different between the gabapentin (-4) and the dexchlorpheniramine groups (-4) (p > 0.7).
Rossi et al., 2019 [61]	Parallel	Italy	HD	25	2	Gabapentin 300 mg vs. gabapentin 100 mg vs. placebo	VAS, QPS	Compared with the placebo group (-11.1%), there was a higher percentage of VAS reduction in both the gabapentin 300 mg group (-81.6%, p = 0.0121) and gabapentin 100 mg group (-48.3%, p = 0.0379).
Haber et al., 2020 [62]	Crossover	Lebanon	HD	16	4	Gabapentin vs. doxepin	VAS, QPS	More reduction of VAS in the gabapentin group (-6.14) than the doxepin group (-3.78) (p < 0.001).
Opioid antagonists and agonists								
Peer et al., 1996 [63]	Crossover	Israel	HD	15	1	Naltrexone vs. placebo	VAS	More reduction of VAS in the naltrexone group (-8.3) than the placebo group (-1.1).
Pauli-Magnus et al., 2000 [64]	Crossover	Germany	HD, PD	23	4	Naltrexone vs. placebo	VAS, QPS	Percentage of reduction in VAS was not different between the naltrexone (29.2%) and placebo groups (16.9%) (p = 0.095).
Wikström et al., 2005 [65]	Parallel	Sweden, Denmark, Norway, Finland	HD	79	4	Nalfurafine vs. placebo	VAS	Change in VAS was not different between the nalfurafine (-2.5) and placebo groups (-1.27) (p = 0.0649).
Wikström et al., 2005 [65]	Crossover	Poland	HD	34	2	Nalfurafine vs. placebo	VAS	Change in VAS was not different between the nalfurafine (-2.21) and placebo groups (-1.35) (p = 0.0863).
Kumagai et al., 2010 [66]	Parallel	Japan	HD	339	2	Nalfurafine 5 µg vs. nalfurafine 2.5 µg vs. placebo	VAS	Compared with placebo group (-1.3), there was a greater reduction of VAS in the nalfurafine 5 µg group (-2.2, p = 0.0002) and nalfurafine 2.5 µg group (-2.3, p = 0.0001).
Mathur et al., 2017 [67]	Parallel	United States	HD	373	8	Nalbuphine 120 mg vs. nalbuphine 60 mg vs. placebo	11-Point NRS, QPS	A greater reduction of NRS occurred in the nalbuphine 120 mg group (-3.5) than the placebo group (-2.8) (p = 0.017).
Fishbane et al., 2020 [40]	Parallel	United States	HD	378	12	Difelikefalin vs. placebo	11-Point NRS, QPS	49.1% of the difelikefalin group and 27.9% of the placebo group exhibited improvement in pruritus intensity (p < 0.001).
Fishbane et al., 2020 [68]	Parallel	United States	HD	175	8	Difelikefalin (0.5, 1.0, or 1.5 µg/kg) vs. placebo	11-Point NRS, QPS	A greater reduction of NRS in all difelikefalin groups combined (-3.2) compared with the placebo group (-1.9) (p = 0.002).
Mast cell stabilizers & leukotriene receptor antagonists								
Vessal et al., 2010 [69]	Parallel	Iran	HD	62	8	Cromolyn sodium vs. placebo	VAS	A greater reduction of VAS in the cromolyn sodium group (-7.78) than the placebo group (-2.90) (p < 0.001).
Mahmudpour et al., 2017 [70]	Parallel	Iran	HD	80	4	Montelukast vs. placebo	VAS, QPS	A greater reduction of VAS in the montelukast group (-2.73) than the placebo group (-5.47) (p < 0.001).

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Table 2. Continued

Study	Design	Country	Population	No. of patients	Treatment duration (wk)	Treatment	Pruritus assessment	Results
Oral activated charcoal								
Pederson et al., 1980 [71]	Crossover	United States	HD	11	8	Activated charcoal vs. placebo	QPS	A greater reduction of pruritus intensity in the activated charcoal group than the placebo group ($p = 0.01$ in the first crossover period; $p = 0.05$ in the second crossover period).
Cholestyramine								
Silverberg et al., 1977 [72]	Parallel	Israel	HD	10	4	Cholestyramine vs. placebo	4-Point scale	Pruritus improved considerably in 80% of the cromolyn sodium group and 20% of the placebo group.
Biologics								
Kinugasa et al., 2021 [73]	Parallel	Japan	HD	56	4	Nemolizumab (0.125, 0.5, or 2.0 mg/kg) vs. placebo	VAS, QPS	Reduction in VAS was not different between each nemolizumab group and the placebo group.
Thalidomide								
Silva et al., 1994 [74]	Crossover	Brazil	HD	29	1	Thalidomide vs. placebo	4-Point scale	Pruritus improved in 55.6% of the thalidomide group and 13.3% of the placebo group ($p < 0.05$).
Sertraline								
Pakfetrat et al., 2018 [75]	Parallel	Iran	HD	50	8	Sertraline vs. placebo	VAS, QPS	Reduction in VAS showed a borderline difference between the sertraline group (-5.5) and the placebo group (-3.7) ($p = 0.07$).

CKD, chronic kidney disease; HD, hemodialysis; MCO, medium cut-off; NRS, numerical rating scale; PD, peritoneal dialysis; QPS, questionnaire pruritus score; UVA, ultraviolet A; UVB, ultraviolet B; VAS, visual analog scale.

RCT of 28 HD patients, Young et al. [46] reported that a lotion containing 1% pramoxine was more effective than the control lotion for reducing the intensity of uremic pruritus.

Gamma-linolenic acid

Gamma-linolenic acid is an essential fatty acid found in some plant seed oils that provides possible relief of pruritus through local anti-inflammatory or immunoregulatory effects [47]. In a double-blind, crossover RCT of 17 dialysis patients, Chen et al. [47] showed that cream containing 2.2% gamma-linolenic acid was more effective than control cream for alleviating uremic pruritus.

Cannabinoids

Cannabinoids are chemical compounds derived from cannabis and have therapeutic potential in several diseases, including chronic pruritus [80]. In a noncontrolled study of 23 HD patients, a topical cream containing endocannabinoids (*N*-acetyethanolamine and *N*-palmitoylethanolamine) completely eliminated pruritus in 38.1% of patients and significantly reduced xerosis after 3 weeks of treatment [81].

Treatment of underlying disease

Optimization of dialysis dosage and modality

Optimizing dialysis dosage and increasing the clearance of middle molecules could remove more pruritogenic substances and decrease the severity of pruritus; however, there is no standard dialysis target or dialysis modality for pruritus symptoms. In an interventional study of 22 HD patients with uremic pruritus, Hiroshige et al. [82] reported that 78% of patients had a significant reduction in the severity of pruritus after increasing Kt/V (the assessment of the dialysis dose) from 1.08 to 1.19, while only 8% of patients who remained on the same dialysis dose had reduced pruritus severity. In our 5-year cohort study of 111 HD patients, we found that a target of Kt/V ≥ 1.5 , which was slightly above the standard of ≥ 1.4 , reduced the intensity of uremic pruritus [27]. In another 2-year cohort study of 85 PD patients, we found that a weekly total Kt/V of ≥ 1.88 , which was higher than the standard of ≥ 1.7 , was associated with a lower intensity of uremic pruritus [3].

In a double-blind RCT of 116 HD patients with a similar Kt/V, patients who used a high-flux dialyzer showed more

reduction of pruritus intensity than those who used a low-flux dialyzer [48]. In another 12-week RCT of 51 ESRD patients with chronic pruritus, high-flux HD showed better efficacy in the treatment of pruritus than hemodiafiltration [49]. Additionally, a 12-week RCT of 50 HD patients, those who used a medium cut-off dialyzer showed a greater reduction in morning pruritus distribution and sleep disturbance than those who used a high-flux dialyzer, but differences in pruritus intensity assessed by visual analog scale scores were not significant between groups [50].

Control of hyperparathyroidism

In a case series of 37 dialysis patients with uremic pruritus and hyperparathyroidism, Chou et al. [83] found significantly reduced pruritus intensity 1 week after parathyroidectomy. In a 36-week open-label RCT of 82 HD patients with hyperparathyroidism, El-Shafey et al. [51] reported better alleviation of pruritus intensity in patients who received cinacalcet, a calcimimetic-targeting calcium-sensing receptor on parathyroid cells, compared with those who received conventional therapy with vitamin D and phosphate binders. Currently, parathyroidectomy or cinacalcet should only be considered based on the severity of hyperparathyroidism rather than as a standard treatment for uremic pruritus.

Kidney transplantation

Successful kidney transplantation should be able to cure uremic pruritus, as a functioning graft kidney alleviates uremic status [84]. However, a considerable number of kidney transplant recipients with good graft function still experience chronic pruritus [84]. In a cohort study of 74 kidney transplant recipients with a functional graft, the prevalence of chronic itch after transplantation (12%) was lower than that before transplantation (35%) [85]. The etiology of chronic pruritus in patients after kidney transplantation remains uncertain, and proposed mechanisms include drug-related skin manifestations, new-onset itchy dermatoses, persistent hyperparathyroidism, or decreased graft function [84,85].

Phototherapy

Ultraviolet (UV) phototherapy is effective for various skin diseases and is more tolerated than many systemic treat-

ments. In a 4-week RCT of HD patients with intractable pruritus, broadband UVB phototherapy showed better antipruritic effects than UVA phototherapy [52]. In a single-blind RCT of patients with refractory uremic pruritus, narrowband UVB phototherapy showed a marginal effect at reducing pruritus intensity [53]. UVB phototherapy may cause xerosis, erythema, changes in pigmentation, and skin aging [86]. Despite concerns about photocarcinogenesis, UVB phototherapy has not been reported to increase the risk of nonmelanoma skin cancer and cutaneous melanoma in patients with uremic pruritus [87].

Systemic treatments

Gabapentinoids

Gabapentinoids, including gabapentin and pregabalin, bind to voltage-dependent calcium channels to decrease neurotransmitter release and are used for the treatment of postherpetic neuralgia, neuropathic pain, and fibromyalgia [88]. In a meta-analysis of five RCTs with 297 HD patients, there was a significant benefit in favor of gabapentinoids compared with placebo for reducing the degree of uremic pruritus [89]. In addition, a meta-analysis of five RCTs with 220 HD patients showed a better reduction in pruritus intensity in gabapentinoid users than in antihistamine users [89]. In a single-blind RCT of 90 HD patients, pregabalin was found to be more effective for reducing the severity of uremic pruritus than doxepin [59]. In a crossover RCT of 50 HD patients, gabapentin and pregabalin showed similar antipruritic effects [56]. Somnolence and dizziness are common adverse effects of gabapentinoids, and dosage adjustment in patients with impaired renal function is necessary [89].

Opioid antagonists and agonists

Central μ -opioid receptors participate in the processing of itching sensation, and the activation of central κ -opioid receptors antagonizes the μ -opioid receptor-mediated process of itch development [35]. Thus, μ -opioid receptor antagonists and κ -opioid receptor agonists have been used in the treatment of pruritic skin diseases, such as prurigo nodularis, cholestatic pruritus, and uremic pruritus [90,91].

Double-blind RCTs on the antipruritic effect of naltrexone, a μ -opioid receptor antagonist, showed conflicting results in dialysis patients [63,64]. In a crossover RCT of 15

HD patients, Peer et al. [63] showed that using 50-mg naltrexone daily for 1 week significantly ameliorated uremic pruritus compared with placebo. In another crossover RCT of 23 dialysis patients with uremic pruritus, Pauli-Magnus et al. [64] reported that antipruritic effects did not vary between naltrexone and placebo. Nalfurafine, a κ -opioid receptor agonist, has been approved in Japan since 2009 for the treatment of pruritus in HD patients [66]. In a double-blind RCT of 337 HD patients with refractory pruritus, 14-day treatment with oral nalfurafine hydrochloride effectively reduced the intensity of pruritus compared with placebo [66]. Two double-blind RCTs of HD patients with uremic pruritus reported that nalfurafine hydrochloride administered intravenously after HD significantly reduced pruritus intensity and sleep disturbance compared with placebo [65]. In HD patients using nalfurafine hydrochloride for uremic pruritus, the most common adverse effects were insomnia, constipation, somnolence, and dizziness [92]. In a recent double-blind RCT of 378 HD patients, Fishbane et al. [40] reported that difelikefalin, a peripherally restricted and selective κ -opioid receptor agonist given intravenously, was superior to placebo in reducing the severity of uremic pruritus over 12 weeks of follow-up. Diarrhea, dizziness, and vomiting are common side effects of using difelikefalin in HD patients [40]. Compared with placebo, nalbuphine, a mixed μ -opioid antagonist and κ -opioid agonist, yielded a slightly greater reduction in itching intensity in an 8-week double-blind RCT of 373 HD patients [67].

Antihistamines, mast cell stabilizers, and leukotriene receptor antagonists

Oral antihistamines are the most commonly prescribed drugs for uremic pruritus, but few trials have assessed their efficacy on uremic pruritus. In a noncontrolled study of five HD patients with severe uremic pruritus, all patients had a significant reduction in pruritus intensity after receiving ketotifen for 8 weeks [93]. In an 8-week double-blind RCT of 62 HD patients suffering from pruritus, cromolyn sodium showed a greater reduction of pruritus intensity than placebo [69]. In a double-blind RCT of 80 HD patients with chronic pruritus, the reduction in pruritus intensity was greater in patients who received montelukast for 30 days than in those who received placebo [70].

Oral activated charcoal

Activated charcoal is used as a nonselective intestinal adsorbent for certain kinds of poisons [94]. An early double-blind crossover RCT of 11 HD patients showed that 6-g oral activated charcoal taken daily for 8 weeks was more effective for relieving pruritus and resolving scratch-induced skin lesions than placebo dextrose [71]. In a noncontrolled study of 23 HD patients with severe uremic pruritus and itchy lesions, remission of pruritus was noted in 20 patients after treatment with oral activated charcoal of 6 g daily for 6 weeks [95]. AST-120, an oral activated charcoal adsorbent used to treat uremic symptoms and postpone the initiation of dialysis, has been reported to relieve itching in HD patients with generalized pruritus [96,97]. Gastrointestinal symptoms, such as constipation, nausea, and distension, are side effects of oral activated charcoal [95,96].

Cholestyramine

Cholestyramine is a nonabsorbable resin used for the treatment of hyperlipidemia and pruritus in patients with chronic liver disease and biliary obstruction [72]. In an early double-blind RCT of 10 HD patients, Silverberg et al. [72] demonstrated that uremic pruritus improved considerably in four of five patients using 5-g cholestyramine twice daily compared with improvement in only one of five patients in the placebo group.

Biologics

Serum IL-31 is positively associated with itching and may play a critical role in uremic pruritus [33]. Nemolizumab, an anti-IL-31 receptor A antibody, has been shown to reduce pruritus intensity in patients with atopic dermatitis [73]. However, a phase II double-blind RCT comparing nemolizumab with placebo did not show a significant difference in pruritus intensity among HD patients with uremic pruritus [73]. Dupilumab, a human monoclonal antibody that blocks IL-4 and IL-13, has been approved for the treatment of moderate-to-severe atopic dermatitis [98,99]. In a case report and a case series, dupilumab significantly reduced uremic pruritus in CKD and dialysis patients [99,100].

Thalidomide

Thalidomide has been shown to have sedative, immunomodulatory, and antiangiogenic properties [101]. In a dou-

ble-blind crossover RCT of 29 HD patients with refractory uremic pruritus, Silva et al. [74] showed the antipruritic efficacy of thalidomide, as 55.6% of thalidomide users had reduced pruritus intensity compared with 13.3% of placebo users. However, the benefits and risks should be carefully assessed before initiating thalidomide therapy due to its potential side effects, including teratogenicity, peripheral neuropathy, constipation, and sedation [101].

Sertraline

Sertraline, a selective serotonin reuptake inhibitor, is used for the treatment of major depressive disorder, panic disorder, obsessive-compulsive disorder, and posttraumatic stress disorder [102]. In a retrospective cohort study of 17 patients with pruritus related to later stages of CKD, patients had reduced pruritus severity after using sertraline for a mean duration of 5.1 weeks [103]. In a noncontrolled study of 19 HD patients with uremic pruritus, the prevalence of severe pruritus decreased from 52.6% to 10.5% after treatment with 50-mg oral sertraline daily for 4 months [104]. In a double-blind RCT comparing sertraline with placebo in HD patients with uremic pruritus, both groups showed a reduction in pruritus intensity [75]. Common adverse reactions of sertraline include nausea, tremor, and somnolence [102].

Conclusions

Correct assessment and diagnosis, optimization of metabolic profiles and dialysis regimens, proper skincare and protection, selection of appropriate topical and oral medications, and monitoring of the side effects of drugs are all important in the management of uremic pruritus. Recent evidence shows that gabapentinoids, nalfurafine, and difelikefalin are effective for relieving uremic pruritus in HD patients. Topical steroids, topical capsaicin, phototherapy, antihistamines, mast cell stabilizers, leukotriene receptor antagonists, activated charcoal, and optimization of dialysis dose and modality may also be therapeutic options, although further trial results are necessary. With a better understanding of the pathophysiology of pruritus and updated clinical trials, more treatment options for uremic pruritus can be expected.

Conflicts of interest

All authors have no conflicts of interest to declare.

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Data sharing statement

The data presented in this study are available on request from the corresponding author.

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