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Uremic pruritus – a review

Prasad PVS*, Kaviarasan PK, Nethra T and Kannambal

Rajah Muthiah Medical College, Annamalai University, Tamil Nadu, India

Abstract

Uremic pruritus remains a frequent concern for hemodialysis patients with the most frustrating and disabling symptoms. The word uremic may denote that patients suffer from acute renal injury. Hence it is preferred to use the recent term "chronic kidney disease associated pruritus" (CKD- associated pruritus). The prevalence of CKD-associated pruritus in patients ranges from 15%-90% in various studies.

Interestingly, in CKD associated pruritus the skin lesions are not found. The various skin lesions which range from excoriations, impetigo, linear crusts, papules and ulcers are secondary. Other co-existing diseases like cardiovascular diseases, diabetes, hypothyroidism, chronic liver or hematological diseases may challenge the diagnosis and management.

The pathophysiology remains unexplained. There may be an imbalance between the antagonistic activities of μ- and] κ-opioid receptors. Itch sensation are correlated with the activation of certain areas in the brain, spatial and temporal aspects may be processed in the primary somatosensory cortex, planning of scratch response in the pre-motor and supplementary motor cortices, and affective and motivational aspects in the anterior cingulate cortex.

A number of different mechanisms have been proposed like xerosis, transdermal water loss, accumulation of pruritogenic substances, increase in parathyroid hormone levels, high levels of urea, calcium, phosphate, β-2 microglobulin but none are convincing.

Because of the poorly understood patho-physiological mechanisms the treatment of this condition, have been largely empirical. Reduced hydration may be alleviated by simple emollient therapy. Antihistamines have been widely prescribed in spite of lack of best evidence. UVB phototherapy helps many patients. Anti convulsant, gabapentin may have beneficial effect. Other ole remedies include fish oil, omega 3 fatty acids, IV heparin, thalidomide, lidocaine and mexitine. Recent studies demonstrated that nalfurafine as a systemic agent for two weeks would benefit most patients. All these treatment modalities are best only in addition to the dialysis related treatment like renal dialysis, erythropoietin and renal transplantation.

Introduction

Uremic pruritus with the most frustrating and disabling symptoms is a challenge to dermatologist, physician and nephrologist. The term "uremic pruritus" has been replaced by Patel etal.in the recent times as pruritus in these patients is not directly linked to acute kidney injury. Hence new term has been proposed as "Chronic Kidney Disease" (CKD) associated pruritus [1-4]. Patients with CKD not only suffer from pruritus but also from other co morbid conditions like drug induced reactions, diabetes mellitus, hypo/hyper thyroidism, lympho proliferative tumours and other neurologic, gastrointestinal and cardiovascular complications which may further complicate the treatment of pruritus [5].

CKD associated pruritus remains a frequent and sometimes a tormenting problem in patients with end stage renal disease (ESRD). Many studies were done in depth to analyze the factors behind this itch. All these were more contradictory rather than contributory. During the last two decades much importance were given for metabolic derangements and involvement of immune systems. Based on these findings, CKD- associated pruritus is now considered as systemic rather than an isolated skin disease. Hence understanding the pathophysiology will help in our concepts of management [6].

Pathophysiology

The various factors are given in Table 1.

Xerosis: Dry skin is present in the majority of patients undergoing dialysis. This could be due to atrophy of sweat or sebaceous glands or both. Some studies confirmed the findings that patients with CKD associated pruritus and level of hydration. There are contradictory reports in one study which claimed that the trans epidermal water loss is also normal in CKD associated pruritus patients [7-10].

Parathyroid hormone levels: Parathyroid hormones are not directly pruritogenic but it causes itching by a high calcium phosphorus product, precipitation of calcium and phosphorus in the skin and by causing mast cells to release histamine [11]. Disappearance of itching after parathyroidectomy is and evident for its involvement [12].

Table 1. Pathophysiology of CKD associated pruritus.

1.	Xerosis
2.	Parathyroid hormone levels
3.	Mast cells
4.	Neuropathic mechanisms
5.	Immune system and inflammation
6.	Opioid system
7.	Other mechanisms

Correspondence to: Prasad PVS, Retd Professor & Dean, Rajah Muthiah Medical College, Annamalai University, Annamalai Nagar, Tamil Nadu, India, India 608002, Tel: 919894380771; **E-mail:** prasaderm@hotmail.com

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Table 2. History and clinical examination.

History
Duration of pruritus
Type localized/generalized
Duration of pruritus
Exacerbating factors
Duration of hemodialysis/Renal failure
Sleep disturbances
Other causes of pruritus
Clinical examination for primary and secondary lesions
Other systemic examination

Table 3. Treatment of CKD associated pruritus.

Modification of Dialysis techniques
Topical treatment
A. Emollients
B. Essential fatty acids
C. Capsaicin
D. Calcinuerin inhibitors
E. others
Systemic therapy
A. Antihistamines
B. Gabapentin
C. Nalfurafine
D. Naltrexone
E. Ondansetron
F. Cholestyramine
G. Erythropoietin
H. Ketotifen
I. Thalidomide
J. I.V.lidocaine
Others
A. UVB therapy
B. Parathyroidectomy

Dialysis Outcomes and Practice patterns Study (DOPPS) showed CKD patients with pruritus have higher calcium and phosphorus levels in serum and skin [12,13]. Risk factors for CKD associated pruritus have been evaluated in one study and found that apart from male gender, high levels of blood urea nitrogen, beta2 microglobulin, calcium, phosphorus and calciumphosphorus product levels have been found to be higher whereas low levels of calcium and normal parathyroid levels are associated with reduced risk of pruritus [14]. Precipitated calciumphosphate crystals, correlated with itch intensity in hemodialysis patients, which in turn may stimulate itch receptors [15]. Calcium ion concentrations were found to be more in the deepest layer of epidermis, suggesting that disrupted calcium ion gradient in the skin may be involved in the development and maintenance of CKD associated itch [16].

Mast cells: Mast cells release histamine, a potent mediator for itching. Studies have shown that uremic patients have increased number of mast cells and also increased histamine levels [17]. Some observed contradictory findings, that even though the mast cells and histamine levels were increased there was no direct correlation between itching and histamine levels [18]. Treatment of uremic pruritus with antihistamines did not show any benefit in some supporting this view. Recent studies showed reduction of CKD associated pruritus with mast cell stabilizers, molecules that inhibit degranulation of mast cells and release of histamine and leukotriene's and leukotriene antagonists. Serotonin levels were also increased in CKD associated pruritus. Serotonin may cause itching by stimulating a $5\text{-}HT_3$ receptor ondansetron and granisetron which have shown conflicting results regarding their effectiveness in relieving itch in patients [19-21].

Neuropathic mechanism: Pruritus originates in the terminal branches of afferent nonmyelinated C fibers distinct from those involved with pain that are located in the lower epidermis and dermo-epidermal junction [22]. These C fibers enter the spinal cord through the dorsal root and travel up the spinal cord by the contralateral spino-thalamic tract reaching the superior central nervous system. From here they reach the thalamus and hypothalamus via the reticular formation to the cerebral cortex. CKD associated patients exhibit certain abnormalities. Abnormal innervations patterns and a reduced number and diminished functional activity were demonstrated [23]. Mast cells in the dermis lie adjacent to the c fibers. There is increased interaction between these two structures [24]. Proteases are pruritogenic substances and protease receptors have been described in the distal end of C fibers. Stimulation of these release substance P. Capsaicin inhibits substance P and inturn itching [25,26]. CKD associated pruritus patients also have neuropathy which is relieved with gabapentin [27].

Central imaging studies on itch using Positron Emission Tomography (PET) and functional magnetic resonance imaging (fMRI) have provided further information. In these studies, the premotor areas, prefrontal cortex, anterior cingulate cortes, and cerebellum were found to be activated. There was a large overlap in processing between the itch and pain sensory areas in the brain.

Immune system and inflammation: CKD associated pruritus remains poorly understood. There are evidences for its central role for the immune and opioidergic systems. Serum pro-inflammatory cytokine (IL-6) and C-reactive proteinlevels were raised [28,29]. Th_1 are associated with inflammatory state and Th_2 secrete anti-inflammatory cytokines. The proportion of Th_1/Th_2 cells in increased in patients with CKD associated pruritus favoring inflammation. Several treatment modalities which could lower these levels, include, UVB therapy, tacrolimus, thalidomide were helpful to a large extent. Thalidomide inhibits Th_1 activation while UVB therapy decreases Th_1 lymphocytes. White blood counts were also considered as a good predictor for pruritus as counts $>6.7 \times 10^3/\mu L$ is considered as a marker for pruritus [6,29]. Patients, with uremic pruritus also have low serum albumin levels [6]. Hemodialysis patients on statin therapy are less prone for itching as statins decrease pro-inflammatory cytokines and C-Reactive protein levels [30]. In another study it was suggested that increased levels of serine protease and Proteinase Activated Receptor-2 (PAR-2) could play important roles in the pathogenesis of uremic pruritus [31].

Opioid system: Imbalance in the endogenous opioidergic system was given much attention in the recent past in terms of pathophysiology

of CKD associated pruritus. Opioid receptor like μ-opioid can induce itch. Both μ receptor antagonist and κ receptor agonist can decrease itch. Naltrexone, a μ receptor antagonist and nalfurafine, a κ receptor agonist, significantly decreased pruritus in CKD patients [2,34].

Other factors: Other factors for pruritus include bile acids, blood urea nitrogen, and inadequate removal of middle-molecular weight uremic toxins.

Epidemiology

The prevalence of CKD associated pruritus varies substantially in various studies ranging from 22-90% [7,29,35-37]. Overall 85% of dialysis patients were affected with CKD itch in 1970s [7]. The prevalence has come down in the recent years with varying choices of treatment and also the targeted treatment approach. In the largest study the prevalence was calculated as 42% [38]. CKD associated pruritus is independent of age, sex, ethinicity, type of dialysis and underlying renal disease [35-37].

Clinical features

Clinical characteristic varies over time and between patients. Itching can vary from a few minutes to continuous throughout the day. The symptoms are more severe at night disturbs sleep patterns [7,38]. Back is the most common body site although the symptoms can be seen on the face, scalp and chest [38]. There are various exacerbating or precipitating factors like cold, warmth, ambient temperature, heat, sweat and stress. Pruritus can drastically decrease after hemodialysis. Similarly, pruritus may increase in intensity after hemo dialysis as the patient may develop hypersensitivity to certain components used in hemodialysis like dialysis catheters, cellophane adhesives and nickel containing needle tips. Hemodialysis with cuprophane dialyzer mambranes promoted complement system rapidly and hence caused itching in some patients. Patients dialyzed using polysulfone membranes more commonly experienced pruritus than those using hemophane or cuprophane dialysis membranes [39,40].

In patients with CKD, primary skin lesions are not found. Secondary skin lesions include such as excoriations, impetigo, linear crusts, papules, and ulcerations. Majority of patients have localized pruritus whereas some can have generalized itching also. Patients with ESRD also suffer from other diseases such as cardiovascular disease, diabetes mellitus, chronic liver or hematological diseases which may also provoke itching either by itself or by medication given as treatment of these patients [7,41].

Pruritus becomes problematic in a significant number of these patients, which affected the health related quality of life (HR-QOL) in terms of mood, social relations and sleep. Visual analogue scales measurements placed more than 50% at 7. Moreover all these patients also had sleep disturbances [30].

Treatment for CKD associated pruritus

Modification of dialysis techniques

Introduction of the use of biocompatible dialysis membranes has reduced the prevalence of pruritus. Lowering the dialysate magnesium concentration can restore nerve conduction velocity towards normal [42]. Similarly role of calcium has been studied. Calcium contributes to itching by degranulation of mast cells, thus modifies pruritus [43]. Polymethacrylate (PMMA) artificial kidney (AK) absorbs more cytokines than other high flux AK. PMMA AK reduced pruritus score considerably [44].

Topical treatments

Emollients: Emollients are generally lipids and oils, which play a role in filling the crevices between desqumating keratinocytes, thereby causing the appearance of a smooth skin texture, enhanced flexibility, and skin softness. They produce instant lubrication and moisturization in addition to improving barrier repair. Okada and Matsumoto reported that emollients with high water content decreased itch and xerosis in hemodialysis patients with mild pruritus and also improved their psychological wellbeing [45].

Similarly topical preparations containing stuructured natural lipids and endocannabinoids could be of benefit in controlling pruritus and xerosis in maintenance hemodialysis patients.

Essential fatty acids: Essential fatty acids and their derivatives are essential for normal cutaneous function. Evening Prim rose oil which is rich in essential fatty acid γ-linolenic acid (GLA) may be beneficial in alleviating CKD associated pruritus. GLA is metabolized to dihomogammalinolenic acid that is immediate precursor of prostaglandin $E_{2,}$ an eicosanoid with anti-inflammatory and immunoregulatory properties. Epidermal absorption of essential fatty acid exerts an anti-inflammatory and immune modulatory effect [46].

Capsaicin: Capsaicin is an alkaloid derived from the common pepper plant and marketed as a topical analgesic. Capsaicin desensitizes the nociceptive nerve endings depletes the substance P in peripheral neurons and blocks the pain of pruritus. Side effect like burning sensation sometimes may make the patient to stop using it [26,47]. Similarly pramoxine based anti-itch lotion which is also a local anesthetic agent has reduced pruritus significantly.

Calcineurin inhibitors: Tacolimus blocks the differentiation of Th_1lymphocytes, suppressing IL-2 generation [11]. Pauli Magnus etal reported a case series in which tacrolimus 0.03% ointment resulted in a dramatic decrease in pruritus in patients on peritoneal dialysis therapy [48,49]. However there are some reports which proved its inefficacy also [50].

Others: Acupuncture can be defined as the stimulation of anatomical points on the body using a variety of techniques for therapeutic purposes. The technique involves penetrating the skin with multiple thin, solid metallic needles that are manipulated by hands or by electrical stimulation. Acupuncture has been traditionally practiced in Asian countries. Kim *et al.* demonstrated the beneficial effects of acupuncture in their studies [51]. There were only very few side effects reported during or after acupuncture treatment. The mechanism of action of acupuncture is not known, but it is likely that acupuncture may modulate pruritus through the endogenous opioid system. As pain and pruritus have similar pattern of activation, acupuncture analgesia is initiated by stimulation, in the muscles of high threshold, small diameter neurons. These nerves send messages to the spinal cord and activates spinal cord, brain stem, and hypothalamic neurons, which triggers endogenous opioid mechanisms [1].

Systemic treatment

Antihistamines: Antihistamines are commonly used based on their effect on urticarial itch. However, there have been no well-conducted randomized controlled trials of anti-histamines for renal itch. They are rarely effective apart from their side effects like drowsiness.

Desloratidine: In a prospective, open label, cross-over clinical trial in 22 patients on hemodialysis with sustained pruritus for more than two months, deslaratidine 5 mg thrice weekly was compared with gabapentin 300 mg thrice weekly. This study revealed that desloratidine provided relief of UP compared with placebo therapy. Gabapentin had shown marginal efficacy. Among the two drugs desloratidine was better tolerated than gabapentin.

Doxepin, a tricyclic antidepressant with anti-H1 receptor effect can help pruritus resistant to antihistamines in end-stage renal disease patients who undergo hemodialysis. Low dose doxepin is safe and effective except for mild drowsiness. The drug is used at 10mg three times a day and relieved the symptoms in 43% of patients with CKD associated pruritus [52].

Both monteleukast and cromolyn sodium agents used in allergic disorders have shown efficacy in ESRD pruritus [53].

Gabapentin: Gabapentin, an anticonvulsant and gamma-aminobutyric acid agonist exerts a pain modulating effect in diabetic patients. In CKD associated pruritus, 300 mgms three times weekly is safe and is effective in reducing the mean pruritus score as measured by VAS [53,54]. As the drug is well tolerated, this may be considered as an important tool in the management of CKD associated pruritus. Beneficial effects of gabapentin therapy on pruritus, quality of life, depression and sleep quality are clinically important for hemodialysis patients [55]. Ofnote, the renal excretion of gabapentin is decreased in dialysis patients. Manenti *et al.,* made a similar observation, but suggested using a lower dose of 100 mg after each dialysis session, with slow upward titration to decrease the risk of gabapentin induced neuro toxicity and /or coma in patients with decreased renal function [56].

Pregabalin was given at a dose of 25 mg per day. Sedation and dizziness are some of the side effects. Side effects were noticed in 30% of patients and in 12% of patients with pregabalin. Both gabapentin and pregabalin relieved itch and pain sensation [55].

Nalfurafine: Nalfurafine shows refined opioid receptor affinity and selectively as an agent for relief of pruritus. Prospective, randomized controlled trials with oral nalfurafine 2.5 to 5μgms with a placebo in 337 patients showed a reduction in VAS. The most common ADR was insomnia observed in 22% of patients on nalfurafine. Wickstrom conducted a meta-analysis of 2 multi center, randomized, placebo-controlled, double blind trials that recruited 144 patients with CKD-associated pruritus and assigned them to post dialysis treatment with either nalfurafine, or placebo for 2-4 weeks. Nalfurafine treatment in two weeks resulted in significant, but modest decrease in itch intensity.

Naltrexone: Naltrexone is a μreceptor antagonist, eventhough was tried with all enthusiasm, was not found to be effective, not well tolerated because of its side effects.

Nalbuphine: Nalbuphine is a mixed μ-antogonist/κ-agonist opioid drug. This drug is currently available as na; buphine Hcl for injection use in CKD associated pruritus of moderate to severe nature. It also reduces substance P induced itching in animal models. By its dual action it balances opoid μ and κ neuronal activity. Later Nalbuphine HClEr tablets of 30 mg were tried twice daily with food. This drug is safe, well tolerated and effective.

Ondansetron: Histamine and serotonin have been reported as possible mediators of uremic pruritus. Ondansetron is a potent and selective inhibitor of serotonin type3 receptor and is a safe well tolerated and effective in CKD associated pruritus. The dose is 8 mg per day till pruritus subsides, then 8 mg per week thereafter. Serotonin acts on histamine containing mast cells and also has its own pruritic potency [60].

Granisetron: Instead of ondansetron, granisetron was also administered for CKD associated pruritus at a dose of 1mg twice daily for a mean duration of two weeks [61]. Granisetron acts on the receptor level and its effects are not related to blood levels of mediators. Weisshaar *et al*. demonstrated that topisetron as an inhibitor of serotonin showed a measurable effect on serotonin induced itch [62].

Other treatments: Other therapies including erythropoietin, oral activated charcoal, heparin, cholestyramine, nicergoline, lidocaine, parathyroidectomy, baleneological and sauna therapy decreased itch in a small number of patients in various clinical trials.

UVB therapy

In the late 1970s, Gilchrest *et al*. reported on the effectiveness of sunburn-spectrum (UVB) phototherapy on patients with CKD-associated pruritus [68]. The effectiveness of UV therapy (UVA, UVA1, broad-band UVB, narrow-band UVB, psoralen UV [PUVA]) are well documented for the treatment of chronic pruritus of different origin.

Mechanism of action: The effects of phototherapy are mainly caused by the inhibition of pro-inflammatory mediators, such as IL-1 and tumor necrosis factor-α or release of anti-inflammatory neuropeptides. A direct role of phototherapy on the release of other antipruritic mediators from cutaneous cells is currently unknown [69]. UV radiation exerts an immunosuppressive and anti-inflammatory effect in various pruritic inflammatory skin diseases, including atopic dermatitis or by modulating proliferation and apoptosis in neoplasms like Cutaneous T Cell Loymphoma (CTCL). A direct impact of UV light on sensory nerves during neoplastic processes is still under debate. Thus, whether UV radiation may have a direct beneficial effect on sensory nerves by controlling neuronal function is not known [70].

In addition to the decrease in pro-inflammatory cytokine levels, UVB also may mediate its beneficial effects in patients with CKD associated pruritus by inducing mast cell apoptosis [71].

Which phototherapy is better UVA or UVB? Although patients receiving long-wave UVA radiation treatment did not improve, 9 of 10 subjects treated with UVB phototherapy showed a marked reduction in pruritus [68]. Subsequently, a series of studies explored the effectiveness of phototherapy in CKD-associated pruritus, especially radiation with broadband UVB. According to a meta-analysis by Tan *et al.,* the most promising therapy for uremic itch is UVB radiation, whereas UVA does not appear to be effective [72]. Newer data suggest that less side-effects are associated with narrowband than with broadband UVB treatments [73]. The risks of skin malignancies following UVB irradiation and long-term topical immunosuppression are still matters of debate, especially in relation to immune compromised patients suffering from advanced disease or in those scheduled to receive immunosuppressive treatment after renal transplantation. Medhat *et al.,* conducted a study and concluded with the results that that hypo or hyperphosphatemia may represent a circulating pruritogenic substance that stimulates itching

pathways in uremic patients. In addition, hypocalcaemia and low skin calcium content, together with the previously reported disrupted calcium ion gradient may have a direct relation to the stimulation of itching pathways. The main role of UVB in improving pruritus may be related to its systemic normalizing effect on both calcium and phosphorus (increasing calcium and lowering phosphorus) [74]. UVB phototherapy can also cause direct photo inactivation of phosphorus ions [75]. UVB phototherapy was found to improve uremic pruritus mostly acting through a systemic mechanism in addition to its local effects, by inactivating a circulating substance or substances which are responsible for the pruritus. This mechanism is supported by the observation that exposure of one half of the body to UVB in patients suffering from uremic pruritus leads to bilateral improvement. Accordingly, it was reasonable to evaluate the effect of UVB on the expected pruritogenic substances such as Ca^{++} and phosphorus, in the study by Gilchrest *et al.,* both locally in the skin and systemically in the serum [68].

In contrast to the above hypothesis, in a study conducted by Memose *et al.,* they mentioned about the contradiction that the belief of hypercalcemia, skin calcification and microprecipitation of calcium in the skin as causes of uremic pruritus, because our patients with pruritus had low serum and skin calcium content before UVB phototherapy and the clinical improvement of itching followingUVB phototherapy was associated with an increase in the serumand skin calcium content [76].

Dosage used: Medhat *et al.* observed in his study that all patients were subjected to a total body UVB phototherapy, (UV 1000 Waldman lighting which is equipped with UVB lamps with a radiation spectrum of 285 to 350 nm with a maximum at 310 to 315 nm), treatment was given as 3 times/week. The starting dose depended on the patient's skin type, according to the schedule supplied by the manufacturer, so the starting dose was 50 mJ/cm^2. Every session the dose was increased by 0.05 J/cm^2 until disappearance of itching was reported by the patients. After disappearance of itching, the sessions were withdrawn to 2 times/ week for 1 month followed by once weekly for another month [74].

Narrowband UVB is less erythemogenic [73] and has a lower pruritogenic potential than broadband UVB [77] as well as generally being accepted as a safer option. These advantages may have important implications in terms of therapeutic options.

UVB phototherapy has got many advantages in treating uremic pruritus. However, the persistence of statistically significant high phosphorus levels after UVB phototherapy in relation to controls and in spite of significant lowering of its level by UVB may explain the recurrence of itching after stoppage of UVB phototherapy. Further studies are needed to clarify this effect on non-treated uremic pruritic patients, uremic non-pruritic patients and treated uremic pruritic patients [74].

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