

# Uremic Pruritus: Still Itching

## *Üremik Kaşıntı*

### ABSTRACT

Uremic pruritus is a common complication of chronic renal failure. It affects 50% of patients undergoing hemodialysis or peritoneal dialysis. The causes of pruritus in uremic patients are still unknown. Xerosis, intradermal microprecipitation of divalent ions, secondary hyperparathyroidism, peripheral neuropathy, allergic reactions, hypersensitivity and histamine have been considered as pathogenetic factors. The cornerstone of therapy for uremic pruritus is regular, intensive, efficient dialysis. Other therapeutic measures include topical emollients, topical capsaicin, systemic antihistaminics, gabapentine and phototherapy.

**KEY WORDS:** Uremia, Itch, Hemodialysis

### ÖZ

Üremik kaşıntı kronik böbrek yetmezliği hastalarında sık görülen komplikasyonlardan biridir. Hemodiyaliz ya da periton diyalizi programındaki hastaların yaklaşık %50'sinde görülmektedir. Üremik kaşıntının nedeni hala net olarak bilinmemektedir. Cilt kuruluğu, iki değerlikli iyonların ciltte presipitasyonu, ikincil hiperparatiroidi, periferik nöropati, allerjik reaksiyonlar, hipersensitivite ve histamin üremik kaşıntıdan sorumlu tutulan nedenlerdir. Üremik kaşıntıda en önemli tedavi basamağı düzenli, yoğun ve etkili diyaliz yapmaktır. Topikal nemiendiriciler, topikal capsaicin, sistemik antihistaminikler, gabapentin ve fototerapinin üremik kaşıntı tedavisinde yeri bulunmaktadır.

**ANAHTAR SÖZCÜKLER:** Üremi, Kaşıntı, Hemodiyaliz

### INTRODUCTION

Uremic pruritus (UP) is one of the most common skin disorders associated with chronic kidney disease (CKD) causing great distress for patients who already have a compromised lifestyle. Despite advances in care of patients with CKD, the management of UP is still a frustrating problem for the clinical nephrologists. It must be kept in mind that patients with CKD may suffer from pruritus associated with drug-induced hypersensitivity, hepatitis, diabetes mellitus, hypo/hyperthyroidism and lymphoproliferative/solid tumors as well (1).

#### Epidemiology and Clinical Characteristics

Even though the prevalence of UP has declined in the last decade as a result of improvements in dialysis techniques, biocompatible membranes and patient care,

it is still present in 42-52 % of adults with CKD (2, 3). Patients on hemodialysis and peritoneal dialysis are affected with the same frequency and severity (4). Risk factors include male gender, high levels of blood urea nitrogen, beta2-microglobulin, calcium, phosphorus and calcium phosphorus product levels whereas a low level of calcium and intact parathyroid hormone are associated with reduced risk (5). The duration, severity and characteristics of pruritus are variable, changing over time and between patients. Some patients suffer for short periods whereas some report pruritus throughout the day and night. The most affected areas are the back, arms, chest and head but generalized pruritus is not uncommon (6). External heat, sweat, stress and dry skin can exacerbate UP, while hot or cold showers, cold temperature and activity can alleviate it (2). There is controversy regarding the

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effect of hemodialysis on pruritus. Some reports show relief of itching after hemodialysis sessions while some report worsening of symptoms during or after hemodialysis (7, 8). While one study reported that patients dialyzed using polysulfone membranes experienced pruritus more commonly than those using hemophane or cuprophane membranes, another study failed to show any correlation between pruritus and the type of dialysis membranes used (8, 9). There are studies reporting reduced pruritus scores in patients dialyzed with high-flux polymethylmethacrylate membranes, possibly explained by the high cytokine adsorption capacity of this membrane (10, 11).

UP may cause mechanical skin damage through persistent scratching resulting in superimposed infections and various lesions such as lichen simplex, prurigo nodularis and keratosis papules (12). UP also has a major negative impact on the quality of life causing a decline in physical and mental capacity, anxiety, depression and sleep disturbances (6, 7, 13). Sleep disturbances are described as difficulty falling asleep, nocturnal awakenings, remaining awake at night, daytime sleepiness and chronic fatigue. Recently UP has been associated with an increased mortality rate in several studies (5, 6). The Dialysis Outcomes and Practice Patterns Study (DOPPS), which assessed more than 18,000 patients, reported a correlation between UP and increased mortality (6). However this effect disappeared after adjusting for sleep disturbances underlining the importance of this factor in CKD patients.

### **Pathophysiology**

The pathophysiology of uremic pruritus is multifactorial and poorly understood which in part explains the lack of an effective treatment. There are several hypotheses trying to explain the development of UP: dermatological abnormalities, metabolic abnormalities, neurological abnormalities, a proinflammatory state and an imbalance in the opioid system. It is probable that all of these systems play a role in the development of UP and that there is no single etiological factor.

### **Xerosis**

Xerosis (dry skin) is present in the majority of patients undergoing dialysis. It is caused by the atrophy of sweat glands, impaired sweat secretion and disturbed dermal hydration (14, 15). Some studies have shown a correlation between xerosis and pruritus, with pruritic patients undergoing dialysis having a significantly lower hydration than those without UP, while others have not confirmed this (16, 17, 18, 19, 20). In fact, one study showed transdermal water loss to be normal in dialysis patients (21).

### **Parathyroid Hormone and Divalent Ions**

There is controversy as to the effect of parathyroid hormone on UP. Itching is frequently encountered in patients with hyperparathyroidism and a high calcium phosphorus product (3). Even though parathyroid hormone (PTH) is not pruritogenic,

it causes mast cells to release histamine and precipitation of calcium and magnesium salts in the skin (22). In a study by Narita et al. intact PTH levels were independently associated with the development of severe pruritus, with lower levels being associated with reduced risk (5). Other studies have reported disappearance of itching after parathyroidectomy, supporting the role of PTH in the development of UP (23, 24). However not all patients with severe hyperparathyroidism have pruritus and most studies have failed to show a relationship between PTH levels and UP (25, 26).

Several studies, including the DOPPS study, showed that CKD patients with UP have higher calcium and phosphorus levels (5, 6, 8, 26). Furthermore uremic patients have higher calcium, phosphorus and magnesium concentrations in the skin (27). These divalent ions in the skin may form microprecipitations causing itching. Calcium may also have a direct role on itching by degranulation of mast cells (28). Lowering dialysate calcium and magnesium concentrations have proven useful in decreasing UP (28, 29).

### **Mast Cells and Autacoids**

Mast cells release histamine, a potent mediator for itching. Uremic patients have increased levels of mast cells in the skin as well as increased histamine levels (30, 31). Despite increased levels, most studies have failed to show any correlation between histamine levels and UP (28). Furthermore, while some studies showed reduction of UP with antihistaminic therapy, most studies could not confirm a benefit (4, 28). It is unlikely that histamine alone has a major pathogenetic role since antihistaminic therapy is usually ineffective for treating UP. Reduction of UP with the use of mast cell stabilizers, molecules that inhibit degranulation of mast cells and the release of histamine and leukotrienes, and leukotriene antagonists, has recently been reported, however these findings need to be confirmed in large clinical trials (32-34).

Serotonin (5-hydroxytryptamine, 5-HT), which is pruritogenic when injected into skin, has recently attracted attention because of elevated levels in patients on dialysis therapy (35, 36). Serotonin may cause itching by stimulating 5-HT<sub>3</sub> receptors. However, the use of selective inhibitors of the 5-HT<sub>3</sub> receptor, ondansetron and granisetron, has shown conflicting results regarding effectiveness in patients with UP (28).

### **Neuropathic Mechanisms**

Pruritus is thought to originate in the terminal branching of afferent nonmyelinated C fibers distinct from those involved with pain that are located in the lower epidermis or dermal-epidermal junction (37). The C fibers enter the spinal cord through the dorsal root and travel up the spinal cord by the contralateral spinothalamic tract reaching the superior central nervous system. From here they reach the thalamus and hypothalamus via the reticular formation to the cerebral cortex. Certain neurogenic

abnormalities have been reported in uremic patients. Abnormal innervation patterns as well as a reduced number and diminished functional activity of cutaneous fibers were shown in these patients (15, 38). Mast cells in the dermis lie adjacent to afferent C neuron terminals and interactions between these structures may play an important role in UP (39). Proteases are pruritogenic substances and protease receptors have been described in the distal end of C fibers. The stimulation of these receptors causes a central pruritus sensation and releases substance P that in turn sensitizes mast cells (40). Capsaicin is an agent that degrades substance P and is being used with success in UP treatment (41). The majority of CKD patients with pruritus have neuropathy and the successful use of gabapentin for UP in this patient population underlies the importance of neuropathic mechanisms in UP development (42, 43, 44).

### **Immune System and Inflammation**

There is substantial evidence that UP is a systemic inflammatory disease rather than a local skin entity. Uremic patients with pruritus have significantly lower albumin levels, a negative acute phase reactant, than those without this symptom (1). Serum levels of inflammatory biomarkers such as CRP, IL-6 and white blood cell counts are also increased in patients with UP (6, 45). Patients with UP exhibit alteration of the immune system by causing deranged T helper (Th) lymphocyte differentiation that favors inflammation. Th<sub>1</sub> cytokines are associated with an inflammatory state because they recruit and activate inflammatory leukocytes whereas Th<sub>2</sub> cells secrete anti-inflammatory cytokines. The proportion of Th<sub>1</sub>/Th<sub>2</sub> cells is increased in patients with UP, favoring inflammation (45). Several treatment modalities also support the role of inflammation in UP pathogenesis. Ultraviolet B (UVB) therapy decreases Th<sub>1</sub> lymphocytes while favoring Th<sub>2</sub> differentiation which results in decreased IL-2 levels (46). Thalidomide inhibits TH<sub>1</sub> activation while tacrolimus suppresses T lymphocyte activation (2). UP almost never recurs after renal transplantation which may be explained by the immunosuppression used in this patient population. Since inflammation is associated with increased mortality in patients undergoing dialysis, this may explain the increased mortality rate reported in patients with UP.

### **Opioid System**

Recent evidence suggests that opioid system derangement might have a significant role in UP development. Different receptors of the opioid system have different effects on itching. While  $\mu$  receptor agonists such as morphine induce pruritus,  $\kappa$  receptors inhibit this symptom. Hemodialysis patients have an increased serum  $\beta$ -endorphin to dynorphin A ratio which increases with the severity of pruritus (47). This may cause activation of  $\mu$  receptors, while downregulating  $\kappa$  receptors resulting in UP. Some studies have shown naltrexone, a  $\mu$  receptor antagonist, and nalfurafine, a  $\kappa$  receptor agonist, to be effective in UP treatment in accordance with the above (48, 49).

### **Others**

There are several other factors that have been implicated in UP development such as hypervitaminosis A, inadequate removal of middle molecular weight uremic toxins, anemia, high levels of aluminum,  $\beta_2$ -microglobulin, bile acids and a genetic predisposition as suggested by the high prevalence of HLA-B35 reported in this patient population (5, 40, 50-54).

### **Treatment**

The treatment of UP has proven challenging and difficult partly due to the fact that the pathophysiological mechanisms are not completely understood. There are several empirical treatment modalities that are derived from small clinical trials and case reports.

### **General Measures**

General measures include optimization of dialysis therapy, use of more biocompatible membranes, improving the nutritional status of the patient, and treating hyperparathyroidism with control of calcium and phosphorus. Improvement in pruritus was reported with low calcium and magnesium dialysate levels (29, 55).

### **Topical Treatments**

Topical treatments include skin emollients, primrose oil rich in essential fatty acid gamma-linolenic acid (GLA), pramoxine based lotion, capsaicin cream and topical tacrolimus therapy. The majority of patients with CKD have xerosis and skin emollients rich in water content hydrate the stratum corneum. Several reports have proved that these agents are safe and effective in reducing UP (17). In our opinion they should be offered to every patient as first line therapy since they are easily applicable, cost effective and lack serious side effects.

Essential fatty acids and their derivatives have a protective function and influence skin structure and physiological characteristics. GLA is metabolized to dihomogammalinolenic acid that is the immediate precursor of prostaglandin E<sub>2</sub>, an eicosanoid with anti-inflammatory and immunoregulatory properties (56). Recently published trials have shown GLA to be effective in reducing UP in patients with CKD (56, 57). In a small study, a pramoxine-based anti-itch lotion that is also a local anesthetic agent has reduced pruritus significantly (58).

Capsaicin is another local agent used in UP treatment that acts by depleting substance P at the peripheral neurons. When applied to patients undergoing hemodialysis, it significantly reduces itching (41, 59). Burning sensation at the application site has been reported with this agent and the generalized pruritus observed in this patient population makes this agent unpractical for clinical use.

Tacrolimus blocks the differentiation of Th1 lymphocytes, suppressing IL-2 generation (2). There are two studies showing conflicting results for this agent when used as a topical ointment.

One study showed that 6 weeks of treatment with this agent is effective while another study did not show any benefit (60, 61). However prolonged use of tacrolimus creams and ointments caused skin malignancies in animal studies and FDA issued a black box warning for these agents in 2006. We believe the evidence for the use of this agent is limited and given the potential side effects, these agents should not be used as first line therapy if at all.

### **Systemic Therapy**

UVB radiation therapy has been used with success for decades in UP treatment. Several studies have confirmed its efficacy with remissions lasting months after therapy has been stopped (61). The exact mechanism of action is not known but reduced cytokine production by lymphocytes, alteration of divalent ion concentration in the skin, promotion of cutaneous-nerve degeneration, mast cell apoptosis have all been proposed as potential mechanisms (1, 2). Even though the most reported side effect is sunburn, the potential carcinogenic effect raises concerns. Recently narrow band UVB therapy that is less erythemogenic has proven effective and is being used for UP treatment (63).

Recently gabapentin, a  $\gamma$ -aminobutyric acid analog anticonvulsant, has attracted considerable attention as a therapeutic agent. In a randomized placebo controlled double blind trial, gabapentin given at a dose of 300 mg after each hemodialysis session proved effective in reducing pruritus associated with UP (43). A similar study confirmed these findings and suggested that a much lower dose of 100 mg should be started and titrated slowly to decrease the risk of gabapentin-induced neuropathy and coma in CKD patients (44).

Even though the opioid system seems to play an important role in UP pathogenesis, agents aiming the components of this system such as  $\mu$ -receptor antagonists and  $\kappa$ -reduced agonists have shown disappointing results. Naltrexone, an oral  $\mu$ -opioid receptor antagonist, reduced UP in a small trial but a large placebo controlled trial failed to confirm these results (48, 64). In a multicenter randomized placebo controlled double blind trial, treatment with nalfurafine, a  $\kappa$  opioid receptor agonist, for two weeks resulted in a significant decrease in worst itch symptoms but this effect disappeared when treatment was continued for another two weeks (49).

Selective inhibitors of the 5-HT<sub>3</sub> receptor, ondansetron and granisetron have been implicated in UP treatment. Even though ondansetron was effective in a small study, a randomized placebo-controlled double-blind trial showed that it was not superior to placebo (35, 65). Granisetron was shown to be effective in reducing pruritus in a single case report and a small noncontrolled study, however these results need to be confirmed (66, 67).

Classical antihistamines are widely used even though they are not very effective. There are several anecdotal reports that describe successful treatment with mast cell stabilizers ketotifen and cromolyn as well as with the leukotriene antagonist montelukast (32-34). However large, randomized, placebo controlled trials are needed before the routine administration of these agents can be recommended.

Other therapies including erythropoietin, oral activated charcoal, heparin, cholestyramine, nicergoline, lidocaine, parathyroidectomy, acupuncture and balneological and sauna therapy have been reported to decrease itching in small clinical trials (28, 52, 68-72).

In conclusion, uremic pruritus is a frustrating, frequent symptom associated with CKD that has a significant negative impact on quality of life and mortality. The pathophysiological mechanisms are not completely understood and definitive whereas successful treatment modalities are lacking. New agents as well as large, randomized, placebo controlled trials are needed.

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