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Review Article

Uremic Pruritus Pathogenesis, Revisited

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Abstract

Introduction: Uremia is the most important systemic cause of pruritus. Uremic pruritus (UP) was found to affect 50-90% of patients undergoing dialysis and about 25% of patients with chronic kidney disease (CKD). Despite its high prevalence, morbidity and the marked influence on quality of life, UP remains poorly characterized.

Review: Triggering factors for UP may include cutaneousxerosis, uremic toxins, systemic inflammation and associated common co-morbidities such as diabetes mellitus, endocrinopathies,viral hepatitis and somatic neuropathy. Moreover, high pre-dialysis levels of blood urea nitrogen (BUN), β2-microglobulin, calcium and phosphate, as well as parathyroid hormone (PTH) were found to be related to UP. A new hypothesis of glycation, with advanced glycation end products (AGEs) accumulation in stratum corneum has been proposedas a possible underlying cause of UP.

Common treatments used for UP include antihistamines, steroids, emollients, charcoal, erythropoietin and phototherapy (UVB). Other treatments with some reported efficacy are serotonin antagonists, selective serotonin reuptake inhibitors (SSRI), mast cell stabilizers, leukotriene receptor antagonists, κ-opioid agonists and nicotinamide. Many non-pharmacological treatments, including acupressure, are also used. In addition, improvement of dialysis modalities could relieve patients of UP. The future use of anti-glycation preparations for treatment of UP is supported by recent researches.

Conclusion: Recent researches on the process of glycation as a possible cause of UP may open the way for treatment with anti-glycation preparations. Nevertheless, associated co-morbidities with possible role should be concurrently treated.

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Introduction

Pruritus is defined as an uncomfortable sensation that elicits the desire to scratch [1]. Of all systemic disorders, uremia is the most important cause of this uncomfortable sensation. Among the dermatological abnormalities associated with end-stage renal disease (ESRD), uremic pruritus (UP) is the most prevalent, distressing and depressing symptom [2, 3]. Despite its high prevalence, morbidity and marked influence on quality of life, UP remains poorly characterized and the molecular pathogenesis of pruritus in ESRD remains to be elucidated.

Clinical Background

The intensity and distribution of UP varies significantly over time. Intense UP is defined as a score of >10 mm on a 100-mm visual analogue scale (VAS). Itch intensity fluctuates andappears to be somewhat cyclical in some patients, but it does not entirely settle. It ranges from sporadic discomfort to complete restlessness during day and night. In general, UP intensity is worse for night-time than for daytime. In 25% of patients with UP, pruritus is most severe during or immediately after dialysis, probably due to antigen sensitization from dialysis membranes. Initially, patients with UP do not show any changes in skin appearance. Excoriation with or without impetigo can occur as a secondary phenomenon. Rarely, prurigonodularis or Kyrle's disease is observed. There are inter-individual differences in the distribution of UP. Studies have shown that generalized pruritus was the dominant mode of UP presentation in 25–50% of patients, while in the remaining patients it predominantly affected the back, the face and the fistula arm, in this order of frequency. Although UP distribution was highly variable

from patient to patient, manifestation of symmetry was common in all of them [2, 4].

The magnitude of the problem

A global cross-sectional study in more than 300 dialysis units in twelve countries involving more than 18,000 hemodialysis patients reported a 42% prevalence of moderate to severe UP, and this was strongly associated with sleep disturbance, depression, impaired quality of life, and mortality [5]. A logistic regression analysis revealed that severe UP was an independent predictive factor for death even after adjusting for other clinical risk factors (including diabetes and low albumin) [10].

Current implicated factors

A number of different factors and mechanisms have been proposed to explain the pathogenesis of UP, but none of these is completely convincing. At least four main hypotheses have been put forward: dermatological abnormalities, an immune-system derangement that results in a pro-inflammatory state, an imbalance of the endogenous opioidergic system, and a neuropathic mechanism. Moreover, an array of other triggering factors may include uremic toxins, systemic inflammation, cutaneous xerosis and associated common co-morbidities such as diabetes mellitus, endocrinopathies and viral hepatitis [6]. Theoretically, the accumulation of pruritogenic substances that are less efficiently removed by dialysis might influence itch centers or receptors. This is supported by the finding that itching was less in patients who receivedbetter dialysis (assessed by Kt/V) [7].

During hemodialysis, the exposure of blood to any extra-corporeal artificial surface may result in the activation of several pathways within the body, including those involved in coagulation and complement activation. In this setting, studies have shown clinical implications for using biocompatible membranes in adsorption hemodialysisfor UP [8]. Another technique is push/pull hemodiafiltration (HDF), characterized by alternate filtration and back filtration while dialysate is flowing through a hemodiafilter. Thus, blood is concentrated and diluted many times (approximately 25 times) before it leaves the hemodiafilter. These aforementioned modalities could relieve patients of uncomfortable dialysis-related symptoms including UP [9].

Multiple factors have been suggested as pruritogenic substances in UP, including parathyroid hormone (PTH) [1]. In fact, Narita *et al* have publicized that the development of severe UP is associated with multiple clinical and laboratory disturbances, including high pre-dialysis blood urea nitrogen (BUN), calcium, phosphate, PTH, as well as high β2-microglobulin levels [10]. Although hyperparathyroidism can stimulate mast cells to release histamine (known mediator in itch scratch cycle) and can promote microprecipitation of calcium and magnesium salts in the skin, neither serum phosphate nor other tests of bone and mineral status were found to be significant predictors of UP at any point in time or over time [11].

The relationship between somatic neuropathy and UP, as well as the relationship between UP and peripheral sensorimotor neuropathy and/or dysautonomia were also proposed. Therefore, local therapy with capsaicin creams, gabapentin and the novel k-opioid-agonist nalfurafine may be helpful in treatment [12-14].

Current treatments

Common treatments used for UP include antihistamines, steroids, emollients, charcoal, erythropoietin, and phototherapy (UVB). Particularly, serotonin antagonists like ondansetron and granisetron were found to be fairly effective, safe, and well tolerated [15]. Several studies have revealed that the selective serotoninre-uptake inhibitors (SSRI), such as sertraline, could reduce the severity of pruritus [16]. Similarly, mast cell stabilizersalso gave encouraging results [17]. Montelukast; a leukotriene receptor antagonist, is considered another safe and effective treatment option in UP patients [18]. In addition, gabapentin therapy has been tried with good results [13]. Nalfurafine; a κ-opioid agonist, may also reduce itching [14]. Moreover, it has been shown that thalidomide is effective in the therapy of UP, at least to a certain degree [19].

Nicotinamide, also known as niacinamide and nicotinic acid amide, is the amide of nicotinic acid (vitamin B3/ niacin), and it is a member of the vitamin B family. Nicotinamide has anti-inflammatory action and it is considered generally safe as a food additive or as a component in cosmetics and medications. Thus, it can be regarded as a potential therapeutic option in the treatment of UP [20].

Sericin is a novel moisturizer; a water-soluble biopolymer protein with a high molecular weight that is obtained from the silkworm (Bombyxmori). It is characterized by the presenceof 32% serine, which is the main amino acid of thenatural moisture factor (NMF) in human skin, and can suppress the release of proinflammatory cytokines. Therefore, it has a high potential for reducing UP in hemodialysis patients [21]. Because of fish oil effect in reducing inflammation, free radicals, and leukotriene B-4, plus its effect in supporting the immune system, omega-3 fatty acids (fish oil) supplements could also improve UP [22]. Simply applying chilled or un-chilled

'baby oil' may also improve UP [23]. 'Baby oil' is safe, inexpensive and can easily be applied [23].

Today, many non pharmacological treatments, including acupressure, are used to relieve the discomfort experienced by patients due to pruritus. Acupressure has been proven to reduce the intensity of pruritus when it is used alone or in combination with pharmacologic methods [24].

After kidney transplantation, patients almost never complain of UP even when a substantial loss of transplant function occurs as long as immunosuppressive therapy is administered [25].

New implicated factors

Carbonyl stress

One of the factors currently implicated in the pathogenesis of UP is insulin resistance (IR) and carbonyl stress. IR is characterized by a functional defect in insulin hormone despite high plasma levels, leading to a series of biochemical alterations [26]. Like other chronic diseases, CKD demonstrates low-grade systemic inflammation marked by elevated levels of pro-inflammatory cytokines, and oxidative stress [27]. Liao *et al*reviewed mechanisms of IR in CKD. They concluded that the etiology of IR in CKD patients is multifactorial and associated with a complex network. Not only chronic inflammation and oxidative stress, but also vitamin D deficiency, anemia, and malnutrition are involved. These factors are associated with elevated inflammatory cytokines, and adipokines, leading to an acquired defect of the insulin receptor-signaling pathway[28]. In CKD patients, IR is linked to metabolic and cardiovascular complications [29]. Therefore, IR is a key therapeutic target for reduction of mortality and morbidity in CKD patients.

Numerous factors have been implicated in the pathogenesis of IR occurring before the initiation of dialysis therapy; including anemia, dyslipidemia, uremia, malnutrition, excess PTH, vitamin D deficiency, and metabolic acidosis. After the initiation of dialysis, this situation is partially corrected. Nevertheless, peritoneal dialysis exposes patients to a glucose load that could worsen IR in patients with ESRD. Disturbances of carbohydrate metabolism seem to be even more obvious in non-diabetic patients [30]. Furthermore, the plasma phosphate levels showed a positive correlation with IR. Hence, a reduction of phosphate in diet can improve the degree of IR in ESRD patients [31].

Previous studies reported changes in glucose homeostasis in CKD, with IR and carbonyl stress, irrespective of the presence of diabetes; the well-known cause of accumulated advanced glycation end products (AGEs) [32]. AGEs are formed via Maillard reaction; a non-enzymatic reaction between sugar and lipid adducts with proteins, leading to glycated proteins formation [33]. Oxidative stress also leads to autoxidation of glucose and formation of AGEs [34]. Moreover, AGEs accumulation can be caused by decreased renal clearance of glycated proteins in renal insufficiency [35]. It is possible that AGEs, affecting skin barrier structure and function, and enhancing cytokine production, could be a mechanism for UP.

Skin barrier defect

All dry and itchy skin conditions require restoration of the skin barrier and some studies indicated the involvement of skin barrier dysfunction in UP [36]. The complex network of chronic inflammation, oxidative stress, and altered metabolism in uremia leads to IR and carbonyl stress. This could possibly alter skin barrier structure and function, and correlate with the biochemical changes detected in ESRD and dialysis patients. The stratum corneum (SC) is the outermost layer of the epidermis and is characterized by a 'brick and mortar' complex; the corneocytes form the 'bricks', while the intercellular lipid bi-layer represents the 'mortar'. Abnormalities of such a complex are associated with both dry skin and loss of cutaneous barrier (protective) function, reflected by rapid loss of water through the skin [36]. Yosipovitch *et al* assessed the function and structure of the skin barrier in patients with ESRD and correlated findings with UP [37]. They found that SC integrity was impaired in ESRD. Yet, there was no consistent correlation between pruritus and either dry skin, SC integrity, glycerol content or surface pH. However, their study only involved twenty ESRD patients and SC and AGEs were not assessed. No study has examined whether biochemical abnormalities, in the context of carbonyl stress within the SC, could account for UP in ESRD.

Future implications

AGEs cannot be easily measured in clinical practice because they are difficult to analyze in complex body fluids such as blood, and the assessment of more significant tissue-bound compounds hadpreviously required biopsy [38]. However, since the SC can easily be sampled by stripping, AGES contents of the SC can be measuredwithout difficulty. Recently, the presence of N (ε)-(Carboxymethyl) lysine (CML); an AGE structure, was detected in the epidermis. Furthermore, characterization of the CML-modified proteins in the epidermis was also done. K10 was suggested to be one of the target molecules for CML modification [39]. In the context of pruritus, investigators believe that SC is an appropriate sampling target rather than dermal collagen, for detection of AGEs. Several researchers collected SC samples easily and non-invasively by adhesive tape

stripping, and subsequently determined their carbonyl groups [40, 41].

The SC is the interface of body and environment, and is continuously exposed to oxidative stress, resulting in carbonyl modification of proteins. Assessment of carbonyl protein level in the SC was developed and applied to various kinds of skin [41]. This revealed a link between the SC carbonylated protein (SCCP) level and water content in the SC. These data suggested the involvement of oxidative modification of the SC protein, at least in part, in generation of xerotic skin in inflammatory cutaneous disorders as well as dry skin in healthy subjects [41]. Eventually, pharmacological chaperones with significant impact on the treatment of chronic diseases associated with increased oxidative stress and the formation of AGEs will hopefully be marketed in the near future.

Conclusion

Despite best attempts at prevention and control, many ESRD patients continue to be affected by chronic, intense pruritus. The current treatment of UP has not been investigated well, and no drugs have been approved by the US Food and Drug Administration (FDA) for UP treatment. Lack of enough data on UP and paucity of relevant measurement tools have been obstacles to progress. The recent researches with regard to glycation as a possible cause of UP may open the way for treatment with anti-glycation preparations. Nevertheless, associated co morbidities with possible role should be concurrently treated.

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