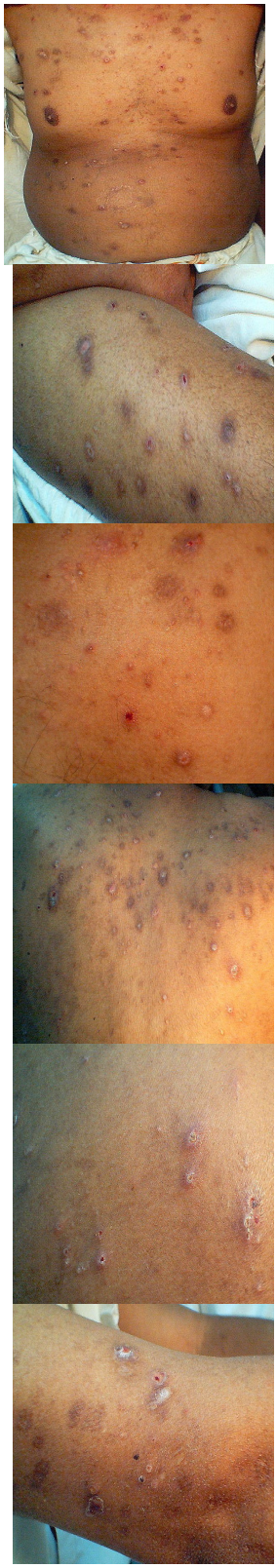

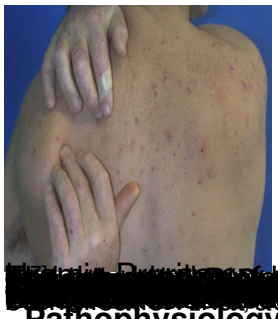

Pathophysiology

The pathophysiology of UP is complex and many uremic and nonuremic factors contribute to its development. Two hypotheses on the underlying pathophysiological mechanisms of UP have been postulated -- the immunohypothesis and the opioid hypothesis -- and these have been strengthened somewhat by the results of clinical trials.

The immunohypothesis considers UP to be an inflammatory systemic disease rather than a local skin disorder. This idea is supported by studies that have demonstrated beneficial effects of ultraviolet B (UVB) radiation exposure on UP, and those that have shown amelioration of UP with thalidomide treatment or calcineurin inhibitors such as tacrolimus.[4,8] UVB phototherapy has been shown to attenuate the development of T

H

1-type lymphocytes in favor of T

H

2-type lymphocyte differentiation, and hence to decrease the production of interleukin (IL) 2.
[11]

The number of CXC chemokine receptor 3 (CXCR3)-expressing and interferon γ secreting CD4

+

cells (which indicate T

H

1 cell differentiation) is significantly higher in patients on dialysis with UP than in those without UP.
[12]

In addition, serum levels of inflammatory biomarkers, such as C-reactive protein and IL-6, are increased in patients with UP, which confirms the inflammatory nature of the disease.
[12]

The increased mortality risk associated with UP that was observed in epidemiological surveys might be explained by the inflammatory state, and implicates UP as a potentially novel marker of malnutrition inflammation atherosclerosis (MIA) syndrome, a known risk factor for death in dialysis populations.
[13]

The opioid hypothesis proposes that UP is partly a result of changes in the endogenous opioidergic system, with overexpression of opioid μ-receptors in dermal cells and lymphocytes.[14]

Overactivity of the opioid μ-receptor (and concomitant downregulation of opioid κ-receptors) might be caused by the increased serum β-endorphin to dynorphin A ratio observed in patients with CKD and could explain the development of UP.
[15]

Activation of the κ-opioid system by administration of a κ-receptor agonist such as nalfurafine reduces the severity of pruritus in patients on hemodialysis.
[16]

Use of naltrexone, a μ-receptor antagonist, has also shown beneficial effects, as described below.
[17]

Parathyroid hormone and divalent ions (e.g. calcium, phosphate and magnesium ions) have also been implicated in the pathogenesis of UP, as itching frequently accompanies severe secondary hyperparathyroidism and an elevated calcium-phosphate product. The lack of consistent correlation between levels of parathyroid hormone, calcium and phosphorus and UP severity, however, indicates that other factors are more important in the pathogenesis of UP.[18-20]

Histamine, which is released from mast cells in response to substance P, has also been implicated in UP; the number of dermal mast cells is increased in patients with CKD and increased plasma levels of tryptase and histamine have been reported in individuals with severe UP.[21,22] The role of elevated plasma serotonin (5-hydroxytryptamine [5-HT]) levels in patients on dialysis with UP is still being debated, however, as clinical trials of selective inhibitors of the 5-HT $_3$ receptor have yielded conflicting results.[23,24]

Xerosis (dry skin) can facilitate the development of UP in patients with CKD. Xerosis is caused by atrophy of sweat glands and sebaceous glands, impaired sweat secretion, disturbed dermal hydration, and abnormal arborization of free, cutaneous type C nerve fibers.[25,26]

The pathophysiological processes that underlie UP are clearly very complex and remain largely unknown. An improved understanding of these mechanisms is urgently required to enable the development of efficient therapeutic strategies for this distressing ailment.

Treatment

General measures to control UP in patients on dialysis include optimization of dialysis efficacy, use of biocompatible dialysis membranes and improvement of the nutritional status of the patient. Adequate control of plasma levels of calcium and phosphorus and the concomitant treatment of secondary hyperparathyroidism can ameliorate pruritus symptoms in some cases.[19]

In patients with CKD, cases of pruritus caused by liver diseases (e.g. hepatitis), primary skin diseases (e.g. atopic dermatitis, contact dermatitis, psoriasis and urticaria) and endocrine disorders (e.g. Graves disease, hypothyroidism and diabetes mellitus) require specific treatments. Available treatment options for UP include both topical and systemic therapies

Topical Treatments. Topical treatments for UP include skin emollients, capsaicin cream and tacrolimus. The primary therapy in patients with CKD who have UP is the application of skin emollients with a high water content to hydrate the stratum corneum. [27,28]
The use of simple emollients that do not contain perfumes or other additives is preferable. Many other topical preparations have shown beneficial effects on UP and they can be tried in cases where simple emollients fail. Such preparations include evening primrose oil (which is rich in essential fatty acids such as γ-linolenic acid), fish oil, olive oil, safflower oil, bath oil that contains polidocanol and creams that contain natural lipids and endocannabinoids.
[29-31]

Capsaicin (trans-8-methyl-*N*-vanillyl-6-nonenamide), a natural alkaloid found in the chili pepper plant (genus *Capsicum*), reduces levels of substance P in cutaneous type C sensory nerve endings. Clinical studies have shown that the application of a 0.025% capsaicin cream significantly alleviated UP in patients on dialysis while exhibiting no adverse effects. [32,33] Although topical capsaicin might be useful for the treatment of localized disease, it is impractical for large areas or generalized pruritus.

Tacrolimus blocks the differentiation of T_H1-type lymphocytes and, therefore, suppresses the production of IL-2. A single-center pilot study in 25 patients on chronic dialysis with UP showed that 6 weeks of treatment with tacrolimus ointment (0.03% for 3 weeks and 0.1% for 3 weeks) significantly reduced the severity of UP without detectable systemic exposure or serious adverse effects. [34] However, a subsequent, smaller vehicle-controlled trial showed that relief of UP was the same with the vehicle and with the active drug. [35] An FDA black-box warning was issued in 2006 against the prolonged topical use of tacrolimus creams and

ointments, on the basis of results from animal studies that showed an increased risk of skin malignancies following use of these agents.
[36]

To date, an excess number of skin malignancies has not been observed with the chronic use of tacrolimus ointment in over 9,800 patients with atopic dermatitis.
[37,38]

The results of larger placebo-controlled trials are awaited, but, in the meantime, use of tacrolimus ointment or cream is not advised for prolonged periods or as a first-line therapy for UP.

Systemic Treatments. Systemic treatments that have been used in UP include ultraviolet light, gabapentin, opioid receptor antagonists and agonists, antihistamines, activated charcoal, 5-HT
3
antagonists, immunomodulators and erythropoietin.

Ultraviolet light, particularly broadband UVB (wavelength 280-315 nm) is an effective treatment for UP and is well tolerated aside from occasional instances of sunburn.[39] The duration of the antipruritic effect of thrice-weekly, total-body, UVB phototherapy (8-10 sessions in total) is variable but can last for several months. The potential carcinogenic effect of ultraviolet radiation requires serious consideration, particularly in patients with a fair complexion (skin phototypes I-II). Narrow-band UVB therapy is less erythemogenic than broadband UVB and also seems to be effective for UP. [40
,41]

Gabapentin, a γ-aminobutyric acid analog used as an anticonvulsant, significantly reduces the severity of CKD-associated pruritus when given at a dose of 100-300 mg after each dialysis session.[42,43] Attention must be paid to neurotoxic adverse effects such as dizziness, somnolence and coma, and a low starting dose of 100 mg is advocated. Other reported adverse effects of gabapentin include fatigue and nausea.

Naltrexone, an oral μ-opioid-receptor antagonist, effectively reduced the severity of UP in a randomized, cross-over trial in patients on dialysis.[17] A large placebo-controlled trial could not, however, confirm a significant difference in efficacy between naltrexone and placebo treatments. [44] In 2005, a κ-opioid-receptor agonist, nalfurafine, was investigated for the treatment of UP in two randomized, double-blind, placebo-controlled trials that included 144 patients on dialysis. Itching intensity, excoriations and sleep disturbances were significantly but modestly reduced in patients who received 2 weeks of treatment with the active compound and no excess of drug-related adverse effects occurred

with nalfurafine compared with placebo.
[16]

Continued nalfurafine treatment for 4 weeks did not alleviate 'worst itch' symptoms significantly more than placebo, which suggested a possible attenuation in the beneficial effects of the drug with continued use. Disadvantages of nalfurafine include the fact that it is currently only available in an intravenous formulation, that symptom relief is potentially incomplete during the interdialytic interval, and that its use is associated with adverse effects of the central nervous system such as sleepiness, vertigo, insomnia, headaches, drowsiness and nausea. In a case series of patients without CKD affected by pruritus, intranasal administration of butorphanol, a κ-opioid-receptor agonist and μ-opioid-receptor antagonist, reduced the severity of intractable pruritus.
[4]

Classical antihistamines have a limited beneficial effect in UP that probably results predominantly from their sleep-inducing side effect.[45]

Oral use of activated charcoal has been shown to completely resolve or significantly reduce pruritus symptoms in patients on chronic dialysis.[46,47] This well tolerated and inexpensive substance can be considered in patients with therapy-resistant UP.

Ondansetron, a selective 5-HT_3 antagonist, was used successfully in a small group of patients on peritoneal dialysis with UP, but a subsequent, larger, randomized, placebo-controlled study in hemodialysis patients failed to prove efficacy of ondansetron in the treatment of UP.
[23,24]

Granisetron, another selective 5-HT

3
antagonist, was effective and well tolerated for UP in a small noncontrolled study.
[48]

Administration of thalidomide, an immunomodulator, reduced the intensity of UP by 80% in patients on hemodialysis in a placebo-controlled, cross-over study.[49] Owing to its teratogenic properties, however, thalidomide should probably be reserved for individuals with therapy-resistant UP who are not of reproductive age. In addition, prolonged use of thalidomide can cause severe polyneuropathy.

A small, 10-week, placebo-controlled, crossover study in patients receiving dialysis who had severe pruritus showed that administration of erythropoietin induced a reversible reduction in plasma histamine concentrations and a simultaneous decrease in pruritus score.