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Five Things to Know About. . .

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Five Things to Know About Pruritus in Patients on Dialysis

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1. Chronic kidney disease–associated pruritus, although highly prevalent is underreported, associated with poorer health-related quality of life, and increased mortality.

Chronic kidney disease–associated pruritus, which we will call "pruritus" from here on, is defined as itching directly related to kidney disease, without any other comorbid condition to explain the itching.[1] Dialysis Outcomes and Practice Patterns Study (DOPPS) reported that most patients (~65%) on hemodialysis (HD) experience pruruitis,[2] with 37% being moderately bothered and 7% being extremely bothered.[3] Pruritus can be debilitating and has been associated with decreased recovery time post sessions,[3] insomnia,[4] reduced quality of life,[5] depression,[6] missed HD sessions,[7] and withdrawal from dialysis.[3] It is underreported with 17% of symptomatic patients not reporting symptoms to health care providers,[8] and it is underappreciated by healthcare professionals in HD units.[9]

2. Pruritus can be severe, risk factors are: older age, higher comorbidity, lower hemoglobin and albumin, and higher C-reactive protein.

Symptoms from pruritus can vary from mild discomfort to unremitting and refractory and can occur at any time in relation to dialysis.[5] In most patients, symptoms are most noticeable at night and involve bilateral, symmetrical, large nondermatomal areas of skin.[5] Compared with those without pruritus, patients with pruritus tend to be slightly older, had greater comorbidity, were more likely to dialyze with a central venous catheter, had higher C-reactive protein, and had lower hemoglobin and serum albumin levels.[3] Sex, ethnicity, years on dialysis, and etiology of kidney failure have not consistently been shown to be risk factors for pruritus.[5]

3. The pathogenesis of pruritus is unclear. There is some support for mechanisms involving stimulation of opioid receptors and immune dysregulation in a uremic milieu.

Pruritus is likley to involve cross talk between keratinocytes, immune system, and neurons in a uremic environment.[10] Markers of mineral metabolism (calcium, phosphorus, parathyroid hormone)[11] and dialysis efficiency (uremic toxins)[11,12] have been proposed, but causality has not been determined. Opioid imbalance (overstimulation of central μ-opioid receptors (MORs), antagonism of peripheral κ-opioid receptors (KORs), or a discrepancy of stimulation and antagonism of MOR and KOR), immune system dysregulation (microinflammation,[13] elevated interleukin levels),[14,15] elevated levels of histamine[16] and tryptase,[17] peripheral neuropathy, and dry skin have been proposed as etiological and/or contributing factors (Figure 1).

4. Low-quality evidence exists for optimizing the hemodialysis prescription and medium cutoff (MCO) dialyzers. Consider parathyroidectomy for severe hyperparathyroidism. Kidney transplantation reverses pruritus in most patients

In a randomized controlled trial (RCT) of 22 HD patients with severe pruritus,[12] increased small solute clearance (mean Kt/V, 1.28) led to a decrease in pruritus scores (12.6 ± 5.1 to 6.3 ± 3.2). In comparison, when the HD prescription was left unchanged (mean Kt/V, 1.09), pruritus scores remained unchanged (12.3 ± 4.7 to 12.7 ± 6.4).[11] Ko et al[18] also found a kT/V >1.5, and use of high-flux dialyzers was associated with less itching. However, other studies have not shown a similar relationship between kT/V and pruritus,[19] implying that middle molecules and not small molecules play a role in pruritus.

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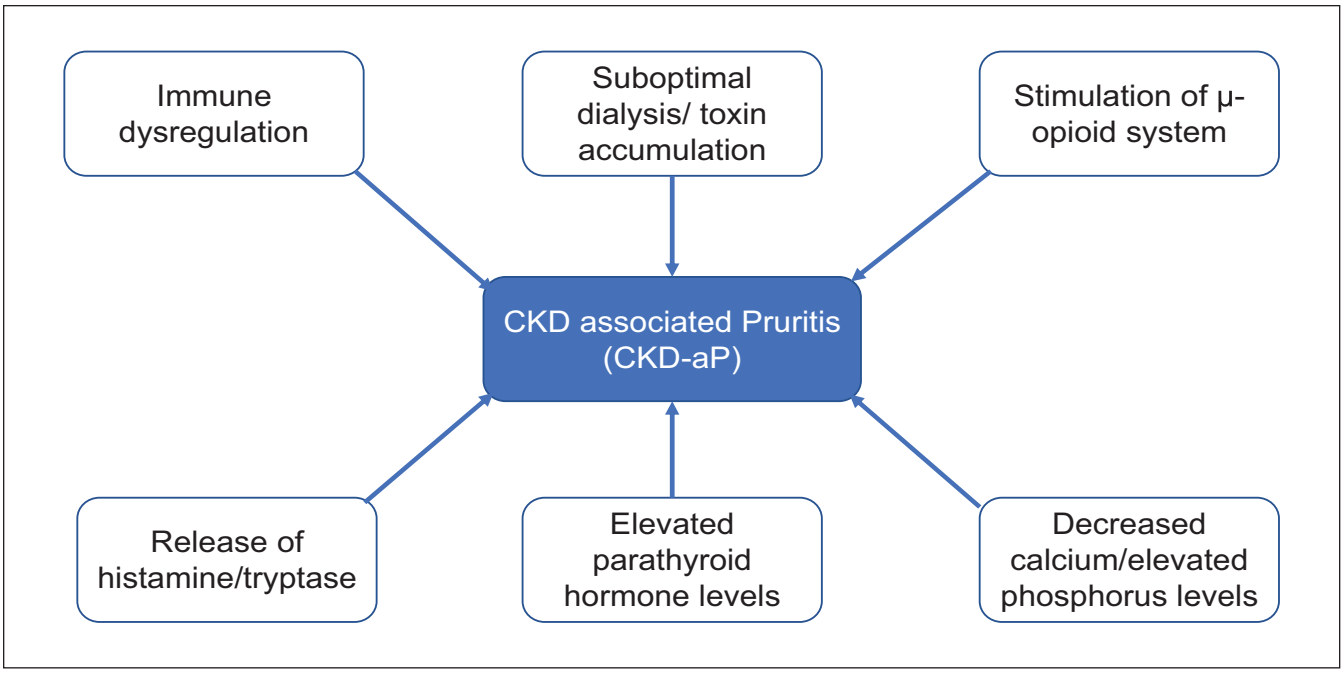

Figure 1. Risk factors and proposed mechanisms for pruritus.
CKD = chronic kidney disease.

Unfortunately, none of the trials comparing short daily or nocturnal HD with incenter HD evaluated pruritus as an outcome measure. We identified only 1 RCT comparing MCO dialyzer (n = 24) with high-flux dialyzer (n = 25). Patients with MCO dialyzers had better pruritus scores (1.29 ± 0.46 vs 1.64 ± 0.64, $P = .034$) and sleep, reflecting a relationship between efficient elimination of middle molecules and symptom relief.[20]

Parathyroidectomy has been found to be consistently associated with itch reduction. A prospective, uncontrolled study of 37 HD patients (22 had symptomatic pruritus) with a mean parathyroid hormone level of 156 pmol/L showed a significant decrease in visual analog scale (VAS) score before and after parathyroidectomy (5.4 ± 3.2 to 1.8 ± 1.5, $P < .001$).[21] A couple of other pre/post parathyroidectomy studies from the mid-1960s have shown similar reduction in pruritus.[22-24]

Kidney transplantation has consistently shown to provide substantial symptom relief. In a prospective study of 1298 HD patients and 521 transplant recipients, pruritus (of the 11 symptoms measured) had the greatest improvement after transplant.[25]

5. Consider the following therapeutic options:
A. Topical options:
Emollients with low pH and/or high water content have been found to be helpful as xerosis exists in 50% to 85% of patients and is an aggravating factor of pruritus.[26] There are several over-the-counter (OTC) options for the clinicians:

a. Consider a cream containing 2.2% gamma linolenic acid (GLA): In a double-blind, placebo-controlled, crossover study (n = 17) with refractory pruritus, a cream containing 2.2% GLA significantly improved pruritus compared with a placebo.[27] Gamma linolenic acid is an essential fatty acid that is metabolized to a prostaglandin precursor with known anti-inflammatory properties and is available OTC as evening primrose oil.

b. Consider a cream containing 1% pramoxine: In a randomized, double-blind, controlled comparative trial with 28 patients using 1% pramoxine lotion versus placebo, there was 61% reduction in pruritus scores in comparison with 12% in the placebo group.[28] The cream is available OTC in 0.5% to 1.0% concentrations as CeraVe, Gold Bond, and Aveeno Anti-Itch cream. Both topical GLA and pramoxine show promise and should be attempted initially in the management of pruritus.

c. Topical cannabinoids can be effective, but more data is needed: A single study of 21 patients showed that topical cannabinoids were effective in reducing xerosis and pruritus and were well tolerated.[29] The baseline itch intensity measured by VAS was 6.24 ± 2.19 and had improved by day 21 (1.29 ± 1.41).[29] The long-term effects of cannabis use, particularly in CKD, are yet unknown, and there are no data on systemic absorption. In the absence of randomized trials, a recent Canadian review on the topic suggested caution regarding its use until further independent and controlled studies were undertaken.[10]

d. OTC baby oil is inexpensive and can be effective: In a study of 70 Turkish HD patients (n = 35 in the intervention vs 35 in the control group), patients who applied baby oil to the affected areas reported a positive impact on itching, quality of life, and sleep quality.[30] A prospective pre-post-test study looking at chilled/unchilled baby oil showed improvement in pruritus scores and quality of life.[31]

B. Oral and intravenous options:
a. Consider using gabapentin/pregabalin: In an RCT involving 42 HD patients, 21 received gabapentin and 21 received pregabalin. Both medications produced a significant difference in itching intensity.[32] Another study reported significant reduction in mean pruritus score before and after administration of 300 mg of oral gabapentin post-HD over 4 weeks in HD patients with pruritus (8.4 ± 0.94 vs 1.2 ± 1.8) (P = .0001), with no demonstrable side effects at that dose.[33] While initially approved to treat epilepsy, use of gabapentin and pregabalin in patients with pruritus is supported by European Dermatology Guidelines and a recent Cochrane systematic review.[34,35]

b. Consider using a selective KOR agonist (difelikefalin): In the largest multicenter RCT in HD patients with pruritus, difelikefalin (0.5 mg/kg of dry body weight) or placebo was administered intravenously, 3 times per week post-HD for 12 weeks. In all, 378 HD patients with moderate to severe uremic pruritus (Worst Itching Intensity Numerical Rating Scale [WI-NRS] >4 points) were randomized 1:1 to a placebo. Difelikefalin significantly reduced WI-NRS compared with placebo (49.1% vs 27.9%) and led to significant improvements in quality of life.[36] It has been approved by Food and Drug Administration for use in the United States and is under review at Health Canada.[37]

c. Consider using MOR antagonists (naltrexone): A placebo-controlled, double-blind, crossover trial (n = 15) showed administration with oral naltrexone 50 mg once a day for 1 week led to an almost complete resolution of itching with few side effects.[38] However, another double-blind, placebo-controlled crossover study of 23 patients over 4 weeks failed to show a statistically significant reduction in itch scores.[39] Naltrexone is approved for use in Canada only for alcohol and opiate use disorder and used as a component of an alcohol counseling program.

d. Consider using a selective KOR agonist (nalfurafine) if available: A meta-analysis of 2 randomized, double blind, placebo-controlled studies on 144 HD patients showed nalfurafine administered intravenously postdialysis reduced worst itching (P = .02) and itching intensity (P = .04).[40] In a study of 337 patients on HD with pruritus, participants were randomized 1:1:1 to 5.0 μg of nalfurafine, 2.5 μg of nalfurafine or placebo, and followed for 2 weeks. Both 5.0 and 2.5 μg of nalfurafine significantly improved pruritus intensity compared with placebo.[41] This drug is approved for use in Japan for management of pruritus, but not in Canada.

e. Consider using a combination of KOR agonists and MOR antagonists (nalbuphine): A multicenter, randomized, double-blind, placebo-controlled trial of 373 HD patients with moderate to severe pruritus demonstrated that the group receiving nalbuphine 120 mg extended-release tablets twice a day for 8 weeks reported significantly decreased pruritus.[42] Nalbuphine is approved for use in Canada for pain management and as a surgical anesthesia supplement.

f. Antihistamines are best avoided, mast cell stabilizers may help: While antihistamines are routinely prescribed in clinical practice, most studies have been unsuccessful.[43] Medications such as hydroxyzine cannot be recommended as first-line use[44] due to discouraging trial results and the likelihood for side effects in the elderly patients (over sedation). Orally administered mast cell stabilizers such as montelukast, cromolyn sodium, and zinc sulfate all probably reduce pruritus, but additional high-quality evidence is required before a decisive conclusion can be made.[35]

C. Nonpharmacological therapies:
a. Trial phototherapy (UVB radiation), if available at your institution: Eighteen HD patients with severe pruritus randomized to UVB (290-nm to 320-nm wavelength) or UVA therapy light showed a greater reduction (4-week follow-up) in the UVB therapy group (80% vs 20%).[45] Gilchrest et al[46] showed that side effects of narrow-band UVB radiation were less frequent and just as effective as treatment using broad-band UVB. Phototherapy appears to be the most promising nonpharmacological therapy available to clinicians.

b. Acupuncture has been trialed, but more evidence is needed. A review of 3 RCTs and 3 uncontrolled observational trials found that acupuncture reduced itching in all trials. However, due to a high risk of bias in these studies, there is insufficient evidence to recommend acupuncture.[47]

c. While there are data on benefits of exercise in CKD patients with pruritus,[48] there are no trials yet looking at intradialytic exercise on itch reduction.

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All authors consent for publication.

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