Uremic Pruritus Excerpt

Executive Summary

Uremic pruritus or chronic kidney disease-associated pruritus (CKDaP) refers to itching associated with chronic kidney disease which is not attributable to other causes of itching. Prevalence rates of up to 97.8% have been reported with an average rate of 55%.[1] In clinical practice, clinicians often underestimate the prevalence of CKDaP leading to undertreatment.

CKDaP significantly impacts patient outcomes and is ranked as the second most common symptom in a survey of symptom distress, quality of sleep, and quality of life among patients on maintenance hemodialysis.[2] The severity of symptoms is variable, and CKDaP may present as a mild intermittent form. In other cases, CKDaP presents as a severe, persistent, and disturbing disease. Hemodialysis patients with CKDaP are shown to be at increased risk of depression, poor sleep, non-adherence, and worse clinical outcomes.[3]

Traditionally, elevated calcium, phosphate, and parathyroid hormone levels have been implicated, but recent data do not support their role. Current proposed pathophysiologic mechanisms include skin alteration, inflammation, nociceptive receptor dysfunction, and opioid receptor dysfunction.[3] As such, several therapies targeting these pathophysiologic mechanisms have been explored.

In clinical practice, management strategies have included antihistamines and phosphate binders but these are not shown to be beneficial in trials. Other management strategies include the use of emollients and gabapentinoids. Several studies support the use of emollients, but their efficacy is limited. Gabapentin and pregabalin target nociceptive receptor dysfunction and studies have demonstrated their efficacy among CKD patients with pruritus. Although emollients and gabapentinoids are effective in mild to moderate symptoms, they are often insufficient for patients with more severe symptoms. Furthermore, gabapentin and pregabalin carry a risk of falls in frail patients and should be prescribed cautiously in patients with CKD. Considering the risk of non-adherence and negative clinical outcomes linked with uraemic pruritus, there is a need for additional effective therapies.

Opioid receptor agonists are newly approved therapies effective in the management of uraemic pruritus. Nalfurafine is a κ-opioid-receptor agonist while naltrexone is a μ-opioid-receptor antagonist. Difelikefalin is a selective kappa-opioid receptor agonist approved by the US Food and Drug Administration for the treatment of moderate to severe CKDaP in adult patients undergoing hemodialysis. These agents, which are not widely used, may pose challenges to clinicians who are unaware of dosing, tolerability, efficacy, and safety.

Our proposed educational program targeted at nephrologists will combine didactic review of available data with case studies to promote recognition of CKDaP, assessment of its impact on patients, and identification of patients who would benefit from newer therapies. At the end of

the program, learners will walk away with the confidence and skills to recognize, evaluate, and manage patients with CKDaP.

Identified gaps in practice

Gap 1	Clinicians may be unaware of the burden of CKD-associated pruritus
Current Practice	Pruritus is prevalent among patients with CKD, especially end-stage renal disease. It is also present in patients undergoing hemodialysis and peritoneal dialysis. Despite the reported high prevalence, surveys show that clinicians frequently underestimate the prevalence of CKDaP. As such, clinicians may not be exploring the presence of pruritus and offering treatment to patients with CKD
Best Practice	Clinicians must recognize that pruritus is not only common but linked to poor sleep, depression, non-adherence, and poor outcomes
Learning objective	Describe the prevalence of pruritus and its impact on the overall health of patients with CKD.

Supporting literature

A diagnosis of CKDaP should only be made after excluding other disease conditions that cause itching, such as eczema, liver disease, and atopy. CKDaP may be localized or generalized. Morphologic skin lesions may be absent, but CKDaP may be associated with dry skin, papules, and ulcers. The severity and pattern of itching in CKDaP are variable. While some patients report mild and intermittent symptoms, others report irritatingly persistent symptoms.[4] In one survey of symptom distress, quality of sleep, and quality of life performed in 301 maintenance hemodialysis patients, itching was the most severe symptom.[2]

In various studies, the reported prevalence of CKDaP varies between 18% and 97.8%.[1] Despite the high prevalence of CKDaP and its impact on patients' lives, it is often underreported and untreated.[5-7] To illustrate, only 32.4% of participants in one study had received treatment for chronic itch.[5] In another study, 17% did not report their itch to their healthcare professionals.[6] Reports suggest that patients often accept it as something to live with and prioritize other health concerns.

In addition, nephrologists often underestimate the prevalence of CKDaP. For example, when data from 6256 patients and 268 medical directors in 17 countries from 2012 to 2015 were analyzed, medical directors underestimated the prevalence of pruritus in 69 facilities.[6]

The impact of CKDaP is profound as it increases the risk of depression, poor sleep, and non-adherence. A participant in one study considered stopping hemodialysis because of the itch saying, "*it controls my life. It drives me mad.*"[8] Given patients' reluctance to report itching, it is important that clinicians enquire about pruritus and treat it.

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