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Chronic kidney disease–associated pruritus (CKD-aP)

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Chronic kidney disease-associated pruritus (CKD-aP), historically termed uraemic pruritus, is a common, persistent and distressing symptom affecting patients with advanced CKD, particularly those undergoing maintenance haemodialysis (HD). This multifactorial condition substantially impairs patients' wellbeing and may even be correlated with increased mortality rates.

CKD-aP prevalence

The reported prevalence of CKD-aP exhibits considerable variability across studies, ranging from 20% to as high as 90%. Although more recent international studies suggest that the prevalence of severe pruritus has declined over the past two decades, likely due to enhancements in dialysis facilities and practices, the burden of this condition remains substantial. Data from the largest international study of CKD-aP prevalence in HD patients, the Dialysis Outcomes and Practice Patterns Study (DOPPS), revealed that approximately 42% of HD patients experience moderate-to-extreme pruritus, with considerable variation across countries and dialysis facilities. Nevertheless, healthcare professionals frequently underestimate its prevalence, as many patients fail to report symptoms.

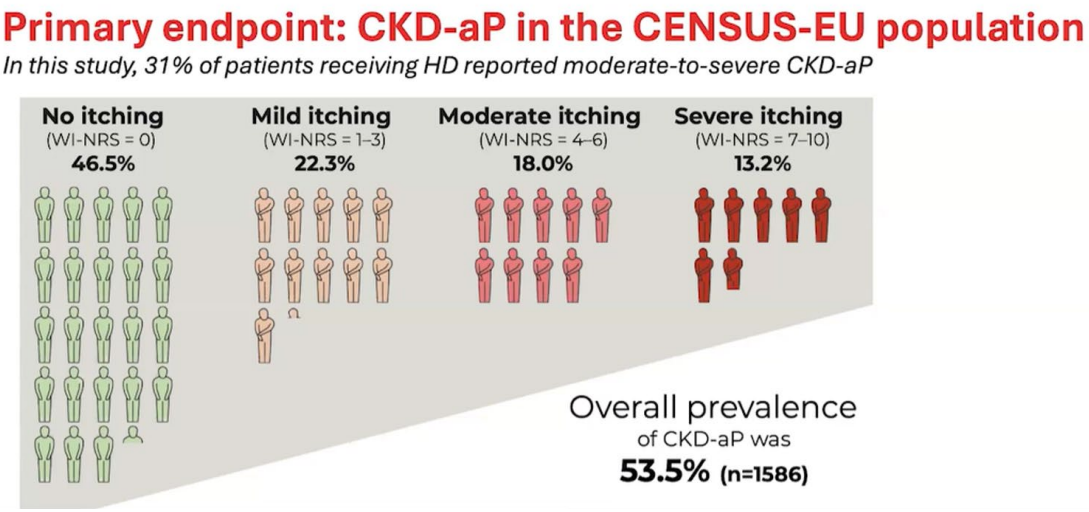

Figure 1.
CKD-aP prevalence among maintenance HD patients (from ref. 4)

The largest contemporary European investigation of CKD-aP, the CENSUS-EU study, recently provided important real-world data on CKD-aP prevalence and clinical burden among patients receiving maintenance HD. This multicentre, cross-sectional study included 2,963 patients from seven European countries who completed validated patient-reported outcome measures assessing itch severity, health-related quality of life (HRQoL), sleep, psychological wellbeing and treatment patterns. Using the Worst Itching Intensity Numerical Rating Scale, CKD-aP was reported by 53.5% of participants, with 22.3% experiencing mild, 18.0% moderate and 13.2% severe pruritus. Overall, nearly one-third of patients (31.2%) claimed moderate-to-severe symptoms. Pruritus severity was strongly associated with impaired HRQoL, including greater sleep disturbance, higher depression scores, increased disability and a greater adverse impact

nearly one-third of patients (31.2%) claimed moderate-to-severe symptoms. Pruritus severity was strongly associated with impaired HRQoL, including greater sleep disturbance, higher depression scores, increased disability and a greater adverse impact on daily, social and occupational activities. The study also highlighted persistent under-recognition and undertreatment of CKD-aP in routine clinical practice, as more than one-quarter of patients with pruritus had not reported their symptoms to any healthcare professional, while approximately 41% of patients with current or previous severe pruritus were not receiving any treatment at the time of assessment. These findings reinforce previous evidence that CKD-aP remains highly prevalent despite advances in dialysis care and highlight the importance of routine symptom assessment.

CKD-aP prevalence

The pathophysiology of CKD-aP remains incompletely understood and is thought to involve multiple interacting mechanisms. Current evidence suggests that this condition results from an interplay of skin barrier dysfunction, systemic inflammation, immune dysregulation, metabolic and mineral disturbances, peripheral and central neural sensitisation, and altered endogenous opioid signalling. Systemic inflammation is increasingly recognised as a central mechanism, with patients exhibiting elevated concentrations of inflammatory biomarkers, including C-reactive protein, interleukin (IL)-2, IL-6 and IL-31, alongside increased T-helper 1 cell activity. Skin barrier impairment also appears to contribute, as xerosis is commonly seen in patients with CKD. Clinical studies have further identified associations between pruritus and accumulation of uraemic toxins, disturbed calcium-phosphate homeostasis, hypoalbuminaemia, hepatitis C infection, increased white blood cell count, reduced dialysis adequacy (low Kt/V), advanced CKD and several comorbid conditions, including congestive heart failure, pulmonary and neurological disease. Female sex, older age, diabetes mellitus and comorbid cardiovascular, pulmonary and neurological disease have also been associated with greater symptom burden. Despite these recognised associations, no single factor independently explains the occurrence of CKD-aP, highlighting the complex and incompletely elucidated pathogenesis of this condition and the need for continued research into its underlying mechanisms.

Clinical presentation and significance of CKD-aP

The clinical presentation of CKD-aP is heterogeneous, although certain characteristic features are consistently described. Pruritus is typically persistent, recurrent and bilaterally symmetrical, occurring daily or almost daily, affecting large, discontinuous areas of skin, predominantly the back, trunk and limbs, with a tendency to migrate over time. Symptoms often exacerbate overnight, contributing to sleep disturbance, and may be heightened by heat, dry skin, stress, physical activity, showering or dialysis. While primary skin lesions are generally absent, secondary changes resulting from chronic scratching, such as excoriations, crusting, papules, prurigo nodularis and secondary infection, are common. Xerosis frequently coexists and may escalate symptom severity.

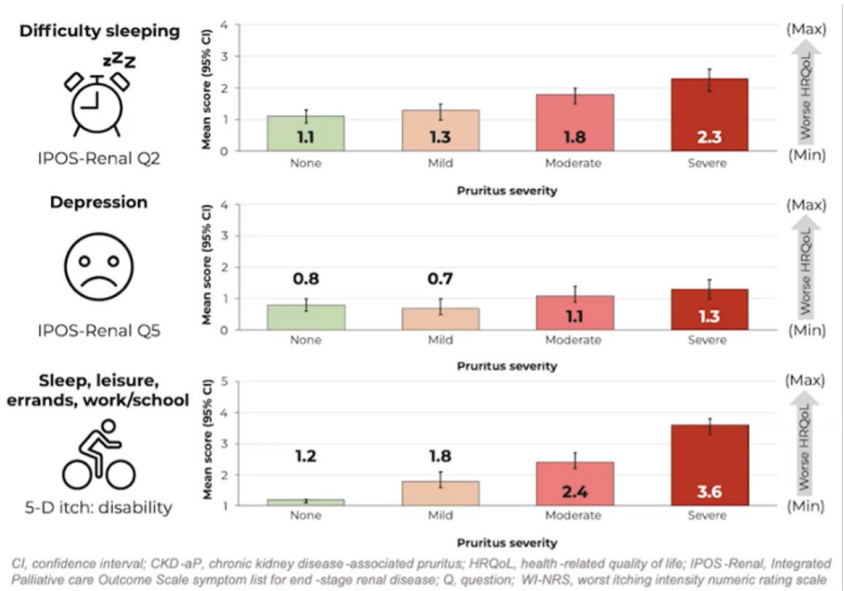

Figure 2.
Impact of pruritus severity on health-related quality of life (from ref. 4)

Current and emerging treatment options of CKD-aP

The management of CKD-aP is multimodal and should be tailored to symptom severity, underlying mechanisms and patient characteristics. Topical treatments are recommended as a first-line approach, particularly in patients with concomitant xerosis. Emollients enhance skin hydration and barrier function, alleviating pruritus, while pramoxine and capsaicin may provide additional symptom relief in selected patients. Evidence for topical tacrolimus is still inconsistent.

Among systemic therapies, gabapentin and pregabalin have demonstrated the most consistent efficacy and are widely regarded as the pharmacological treatments of choice, although dose adjustment and monitoring for neurological adverse effects are necessary. Modulation of the endogenous opioid system has also shown promise, particularly with κ-opioid receptor agonists. By contrast, conventional antihistamines generally have limited efficacy and are not routinely recommended. Optimising dialysis adequacy and correcting mineral metabolism disturbances may further reduce symptom burden. Complementary approaches, including acupuncture, herbal therapies like turmeric and gamma-linolenic acid, and ultraviolet B phototherapy, have demonstrated potential benefits in some studies, but require further high-quality trials to establish their role in CKD-aP management.

Recent advances in CKD-aP management have focused on selective κ-opioid receptor agonists, reflecting growing evidence that dysregulation of the endogenous opioid system plays a central role in the pathogenesis. Unlike conventional antipruritic therapies, these agents target a key mechanistic pathway, achieving significant reductions in itch severity alongside improvements in quality of life.

Difelikefalin, a peripherally restricted selective κ-opioid receptor agonist, was evaluated in the phase III KALM-1 trial involving 378 HD patients with moderate-to-severe CKD-aP. Intravenous difelikefalin (0.5 μg/kg) administered three times weekly for 12 weeks produced significantly greater reductions in itch intensity than placebo, with 51.9% of treated patients achieving at least a three-point improvement in the Worst Itching Intensity Numerical Rating Scale (WI-NRS), compared with 30.9% in the placebo group. Significant improvements were also observed in itch-related quality of life, as assessed by the 5-D Itch and Skindex-10 questionnaires. The most frequently reported adverse events were diarrhoea, dizziness and vomiting. A pooled analysis of the KALM-1 and KALM-2 studies, comprising 851 patients, confirmed the rapid onset of benefit, with improvements evident from the first week of treatment and sustained efficacy across diverse patient subgroups. Furthermore, favourable effects on itch-related quality of life persisted for up to 64 weeks.

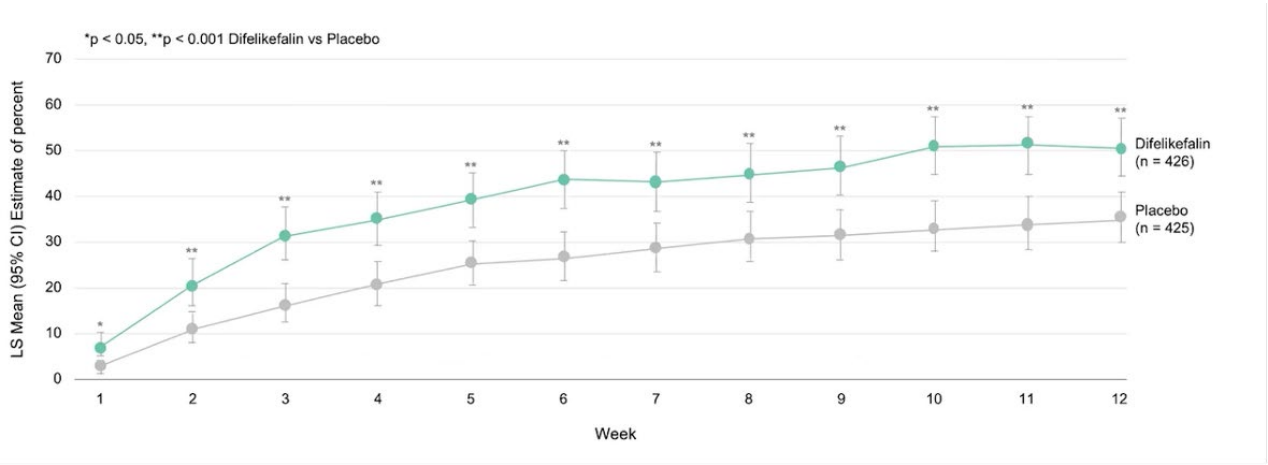

Figure 3.
Achievement of ≥3 point improvement of the WI-NRS in maintenance HD patients over 12 weeks (from ref. 14)

More recently, the novel k-opioid receptor agonist anrikefon demonstrated similarly encouraging results in a multicentre phase III trial involving 545 HD patients in China. At 12 weeks, 37% of patients receiving anrikefon achieved a clinically meaningful reduction of at least four points on the WI-NRS, compared with 15% receiving placebo, while improvements in both the 5-D Itch and Skindex-10 scores confirmed a substantial benefit in HRQoL. Sustained efficacy was maintained throughout the 40-week open-label extension phase, and treatment was generally well tolerated, with mild-to-moderate dizziness representing the most common adverse event. These studies establish selective k-opioid receptor agonists as an important therapeutic advance in the treatment of moderate-to-severe CKD-aP.

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KEY POINTS

1 CKD-aP is still highly prevalent, especially in advanced CKD and among HD patients. Nevertheless, it remains overlooked and undertreated in this population.

2 Routine symptom screening, improved patient–clinician communication and timely implementation of effective antipruritic therapies are essential measures to reduce the CKD-aP burden.

3 Novel agents selectively targeting k-opioid receptors, difelikefalin and anrikefon, showed promising results in terms of alleviating CKD-aP in the HD population.

Written by Jasna Trbojevic-Stankovic.
The speaker reviewed and approved the content.

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Further readings

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