

The burden and management of symptoms in chronic kidney disease (CKD) patients on haemodialysis: an insight into CKD-associated pruritus

Exploring symptom burden in hemodialysis patients

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Clinicians tend to focus on hard clinical endpoints from trials, this session centers on what matters to patients.

Great achievements have been accomplished in dialysis so far. The dialysis population achieve a significantly older age, which brings more comorbidities and requires more supportive care. (Li 2017) With a changing population, should the goals of care also change?

Many studies in nephrology looking at hard clinical endpoints fail. This includes studies on normalizing hemoglobin, aiming for higher Kt/V, dialysis modalities and blood pressure management, as well as studies investigating specific treatments. Moving away from study endpoints that focus on mortality to look more closely at symptoms and patient reported outcomes will help make physicians more aware of what is also troublesome for patients and significantly affects their daily activities and wellbeing.

A study from 2007 shows the discrepancy between symptoms reported by patients and the awareness from healthcare professionals of the number of patients experiencing these symptoms. (Weisbord 2007)

In order to bring symptom-based management to the clinic, it is necessary to identify the goals of care through shared decision-making. There are several components that contribute towards setting this goal together with patients including life expectancy, individual wishes, the burden of the disease and the burden of treatment. Quantity of life vs. quality of life can also be an important consideration when looking at goals of care. If the wish is to extend life for as long as possible, then targets like dialysis dose, laboratory results and blood pressure will be among the management goals. But if quality of life is more important, a focus on managing symptoms such as pain, sleep and anxiety will be at the core of the goals. Of course, many patients will want both quantity and quality of life, but it is still important to have the discussion about their priorities.

Physical and emotional symptoms are common in maintenance hemodialysis patients who experience a mean of 10 symptoms ranging from dry skin and itching, tiredness and bone or joint pain. The symptoms can be severe and are directly correlated with significantly impaired quality of life and depression. (Weisbord 2007)

It is often thought that optimizing dialysis will reduce the burden of these symptoms, however, a study at a recent KDIGO Controversies Conference found that the majority of factors determining patient wellbeing are not directly affected by dialysis delivery (see fig 2). (Chan 2019)

The Frail and Elderly Patient Outcomes on Dialysis (FEPOD) study has shown that frailty is a key predictor for patients at risk of a high symptom burden. (Iyasere 2016)

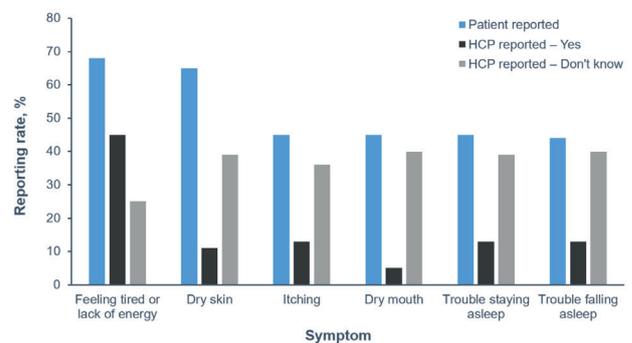


Figure 1.

Patient and HCP reports of symptoms. Adapted from Weisbord SD, et al. Clin J Am Soc Nephrol 2007;2:960-7

Uncovering the complexities of CKD-associated Pruritus

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Chronic pruritus is a debilitating condition that can be defined as an unpleasant sensation of the skin leading to the desire to scratch, with symptoms present for more than 6 weeks. It has a variety of underlying causes: dermatological conditions present with primary skin lesions, but these are absent when the underlying cause is psychogenic, neuropathic or systemic, as for chronic kidney disease. (Stander 2007)

CKD-associated Pruritus does not usually start with a skin lesion. The skin lesions in CKD-associated Pruritus are secondary and are often a consequence of chronic scratching. Where primary skin lesions are present, differential diagnoses should be considered as CKD-associated Pruritus is primarily a diagnosis of exclusion.

CKD-associated Pruritus is a condition with intense symptoms that markedly impair patients' quality of life. Its appearance is variable, but it is often bilateral and symmetrical. (Mathur 2010)

The estimated prevalence of CKD-associated Pruritus is approximately 70% among patients undergoing hemodialysis, (Rayner 2017) with varying degrees of severity. A large study of 68,426 patients on hemodialysis found that 39.8% were 'not at all' bothered by itching, but that 30.2%, 15.4%, 9.3% and 5.3%, respectively, reported being 'somewhat', 'moderately', 'very much', or 'extremely' bothered by itching. (Ramakrishnan 2014)

CKD-associated Pruritus is associated with adverse outcomes including reduced quality of life, poor sleep quality, increased healthcare costs, depression and an increased risk of mortality. (Ramakrishnan 2014, Sukul 2020)

Quality of life in hemodialysis patients deteriorates with an increase in CKD-associated Pruritus severity. Self-reported pruritus is strongly associated with both physical and mental components of health-related quality of life scores, and both progressively decrease as the severity of pruritus increases. (Sukul 2020)

The majority of patients with CKD-associated Pruritus suffer from disturbed or restless sleep, with the likelihood of experiencing restless sleep increasing as the severity of CKD-associated Pruritus increases. (Rayner 2017)

Patients with CKD-associated Pruritus are more likely to be diagnosed with depression compared with hemodialysis patients who are not bothered by pruritus. A significantly greater Beck Depression Index score was seen in patients with more severe pruritus vs. less severe/no pruritus, and the use of treatments for depression was greater among patients with more severe pruritus vs. less severe/no pruritus. (Mathur 2010)

Bacteremia and septicemia are more common in patients with severe itch vs patients without itch (Ramakrishnan 2014) and this may be due to the effect of scratching on the integrity of the skin barrier. Furthermore, patients with severe itch are more likely to be hospitalized for cardiovascular, infection and skin-related complications than those not bothered by itch (see fig 3). (Sukul 2020)

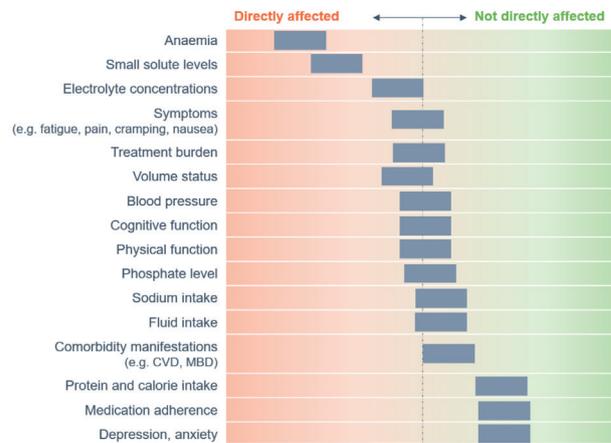


Figure 2.

Factors affected by dialysis treatment or dialysis unit care. Adapted from Chan CT, et al. Kid Int 2019;96:37-47.

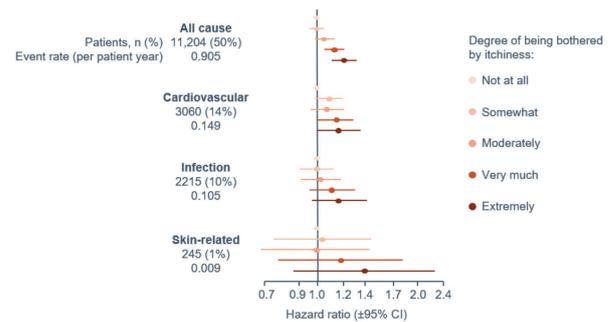


Figure 3.

Incidence of hospitalization according to CKD-associated Pruritus severity (DOPPS 2009-2018; N=23,260). Adapted from Sukul N, et al. Kidney Med 2020;3:42-53.

Severe CKD-associated Pruritus has been associated with an increased risk of mortality in patients undergoing hemodialysis. In a study of 1773 hemodialysis patients who were followed until death or for 24 months, severe pruritus was associated with a worse prognosis than mild or moderate pruritus ($p=0.0001$). Severe pruritus was also an independent predictive factor for death, even after adjusting for other factors ($HR=1.595$; $p=0.0084$).^(Narita 2006)

The pathogenesis of CKD-associated Pruritus is multifactorial.^(Verduzco 2020)

- Abnormalities related to uremia (implicated toxins: vitamin A, aluminum, calcium, phosphorus, magnesium)
- Peripheral neuropathy/paresthesia (abnormal nerve conduction: pattern of cutaneous innervation and nerve conduction)
- Endogenous opioid dysregulation (Imbalanced mu opioid receptor [MOR] and kappa opioid receptor [KOR] activity)
- Immune system dysregulation (pro-inflammatory state: increase in T-helper 1 (Th1) cells, C-reactive protein (CRP), IL-6, IL-2)

Uremic toxins have previously been implicated in CKD-associated Pruritus,^(Hu 2019, Hiroshige 1995) but their contribution appears to be limited when managed according to current standards. No association was observed between CKD-associated Pruritus and CKD-related laboratory values in a recent, large DOPPS study.^(Sukul 2020)

Dry skin (xerosis) is present in 50-85% of CKD-associated Pruritus patients and is likely to be a significant contributor to the condition, but not the only cause.^(Sharizian 2017) Xerosis frequently aggravates pruritus^(Coombs 2015) and predisposes patients to poor wound healing,^(Sharizian 2017) although many patients with xerosis do not suffer from pruritus.^(Mettang 2015) Moisturization and skin rehydration improve symptoms and should be a mainstay of therapy.^(Mettang 2015)

CKD-associated pruritus may be the result of an upregulated inflammatory state. An enhanced proportion of Th1 cells and increased serum levels of IL-6 and CRP have been reported among patients with CKD-associated Pruritus compared to patients without CKD-associated Pruritus.^(Mettang 2015, Kimmel 2006) IL-2 and IL-31 have also been associated with CKD-associated Pruritus.^(Fallahzadeh 2011, Ko 2014)

We now know there is an imbalance between kappa opioid receptor (KOR) and mu opioid receptor (MOR) expression in CKD-associated Pruritus and that this plays a central role in the etiology and pathogenesis of CKD-associated Pruritus. In a study of MOR and KOR receptor expression, KOR expression was significantly lower in patients with CKD-associated Pruritus compared to those without,^(Wieczorek 2020) although MOR expression was similar in both groups. KOR expression was negatively correlated with CKD-associated Pruritus severity.^(Wieczorek 2020) Activation of KORs on peripheral sensory neurons is being investigated as a new therapeutic approach to reduce pruritic signaling.

Evolving management horizons in CKD-associated Pruritus

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People with CKD frequently experience unpleasant symptoms which often occur in clusters, with one as the lead symptom and others as secondary symptoms. Uremic toxins are often considered to be the main cause of CKD-associated symptom burden, but treatment of uremia by dialysis often fails to resolve them and can engender additional symptoms.^(Kalantar-Zadeh 2022)

People with CKD, including those who depend on dialysis or transplantation, should feel actively supported in their symptom management through the identification and targeting of unpleasant symptoms via a tailored palliative care approach. Such an approach may help minimize the burden and consequences of kidney disease, and lead to improved patient outcomes, including HR-QoL and better life participation.^(Kalantar-Zadeh 2022) This was the focus of the 2021 World Kidney Day campaign *Living Well with Kidney Disease*.

The relationship between CKD and pruritus is often not well understood by patients, and many fail to report it to their healthcare providers for a variety of reasons.^(Aresi 2019)

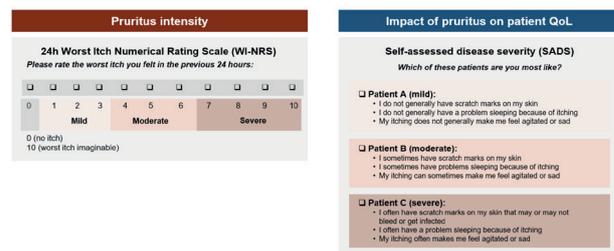


Figure 4.

Simple validated instruments to assess pruritus severity. Adapted from Mathur VS, et al. Clin J Am Soc Nephrol 2010;5:1410-19; Phan NC, et al. Acta Derm Venereol 2012;92:502-7

- Unaware that itch is a symptom associated with CKD
- Lack of awareness around treatment options
- Acceptance of itch as inevitable
- Lack of prompting by healthcare professionals
- Time with nephrologist is too limited, and other health issues are prioritized
- Perceived trivialization of itch by nephrologists
- History of unsuccessful treatments
- Fear of additional medications

The prevalence of itch is underestimated by nephrologists: 69% of nephrologists participating in the DOPPS survey underestimated the prevalence of pruritus in their dialysis facility. (Rayner 2017)

Alleviating the burden of CKD-associated Pruritus requires the proactive identification of patients. Simple validated instruments can then be used to assess pruritus severity: the Worst Itch Numerical Rating Scale (WI-NRS) to assess pruritus intensity and Self-Assessed Disease Severity (SADS) to determine the impact on quality of life (see figure 4). (Mathur 2010, Phan 2012)

A range of agents are used to manage itching, but with the exception of nalfurafine (available in Japan and South Korea) (Locatelli 2021) and difelikefalin (approved in the US and the EU) there are no other approved treatments for CKD-associated Pruritus. Off-label treatments may have limited evidence of efficacy and adverse effects that may be of concern for patients with CKD. (Weisshaar 2019)

An analysis from DOPPS showed that antihistamines are the most commonly used first-line treatment for patients with CKD-associated Pruritus who are not referred to a specialist, 10 but this is not recommended by current guidelines. (Weisshaar 2019)

Gabapentinoids (gabapentin and pregabalin) are also used to treat CKD-associated Pruritus, however, there is a lack of evidence for their long-term use and the adverse effects associated with gabapentin – including dizziness, somnolence, weight gain, angio-edema and increased suicide risk – may limit use in CKD-associated Pruritus. (Verduzco 2020)

A number of investigational treatments, including KOR agonists and MOR antagonists are in development for CKD-associated Pruritus. Difelikefalin is the first of the KOR agonists to be approved in the US and the EU for the treatment of CKD-associated Pruritus. It is administered three times per week by intravenous bolus injection into the venous line of the dialysis circuit at the end of the hemodialysis treatment.

Difelikefalin treats CKD-associated Pruritus by activating KORs on peripheral sensory neurons and immune cells. In the peripheral nervous system, KOR activation leads to direct pruritic signal suppression and is also thought to regulate the response of C-fibers to pruritogens. Difelikefalin also reduced secretion of pro-inflammatory cytokines TNF- α , IL-1 β , IL-8, and G-CSF following stimulation of primary human macrophages. (Spencer IASP 2010)

Two phase 3 double-blind, placebo-controlled multicenter trials (KALM-1 in the US; KALM-2 global) assessed the efficacy and safety of difelikefalin over 12 weeks vs placebo followed by a 52-week open label extension phase. Patients were at least 18 years of age with ESRD and moderate-to-severe pruritus. All patients had been receiving hemodialysis treatment ($\geq 3 \times$ per week) for at least three months prior to enrolment. (Fishbane NEJM 2020, Wooldridge ASN 2020)

Both studies showed that a significantly greater proportion of patients achieved a ≥ 3 -point improvement from baseline in the weekly mean of the daily WI-NRS score with IV difelikefalin vs placebo, (Fishbane NEJM 2020, Wooldridge ASN 2020) and pooled data from KALM-1 and KALM-2 showed a clinically meaningful improvement in 5-D Itch and Skindex-10 total scores with difelikefalin treatment. (Topf, Kidney Med 2022) Improvement in 5-D Itch response with difelikefalin was maintained over the 52-week open-label extension of KALM-1 and KALM-2, and emerged in patients that switched from placebo (see figure 5), and the efficacy of difelikefalin was consistent among subgroups stratified according to baseline use of anti-pruritic medications. (Topf, Kidney Med 2022)

Pooled safety data from KALM-1 and KALM-2 showed that treatment-emergent adverse events were generally mild-to-moderate in the 12-

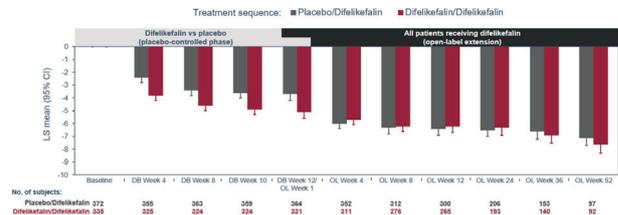


Figure 5.

Improvement in 5-D Itch response with difelikefalin. Adapted from Topf J, et al. *Kidney Med* 2022. doi:<https://doi.org/10.1016/j.xkme.2022.100512>

week placebo-controlled phase, with diarrhea, dizziness, nausea, gait disturbances, including falls, hyperkalemia, headache, somnolence and mental status changes being the most common.^(Fishbane, Kidney Med 2022)

A multicenter, open-label study of difelikefalin in patients with moderate-to-severe CKD-associated Pruritus demonstrated an association between improvement in itch and sleep quality, providing an insight into the potential real-world effectiveness of difelikefalin in this group of patients.^(Weiner ERA 2021)

Now that there is a medication that is approved for patients with moderate to severe CKD-aP, a person-centered approach to care would suggest that this should now be considered as the first line itch therapy for this group of patients, used before any off-label treatments.

Further readings

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