

CKJ REVIEW

Epidemiology and burden of chronic kidney disease-associated pruritus

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ABSTRACT

Chronic kidney disease-associated pruritus (CKD-aP) is a common, yet underrecognized condition in patients with CKD and end-stage kidney disease (ESKD). Real-world observational studies indicate that CKD-aP affects up to 80% of ESKD patients undergoing haemodialysis (HD), with ~40% experiencing moderate to severe itch. CKD-aP can negatively impact patients' mental and physical health-related quality of life (HRQoL) and is also associated with sleep disturbance and depression. Several studies have found that CKD-aP is a predictor of adverse medical outcomes, including an increased risk of hospitalizations and mortality. In this article we review the literature relating to the epidemiology of CKD-aP to describe its prevalence across the treatment spectrum of CKD (non-dialysis, HD, peritoneal dialysis and transplant recipients) and to summarize potential risk factors associated with its development. We also review key data from studies that have evaluated the impact of CKD-aP on HRQoL and medical outcomes.

Keywords: chronic kidney disease, end-stage kidney disease, itch, quality of life, uraemic pruritus

INTRODUCTION

Chronic kidney disease-associated pruritus (CKD-aP) is defined as itch secondary to kidney disease, unexplained by alternate causes. Differential diagnoses such as hypersensitivity reactions, primary dermatological disorders, infection, haematological malignancies and cholestasis must be excluded [1]. The nomenclature has recently shifted away from 'uraemic pruritus' due to the non-linear relationship between itch and the degree of uraemia [2]. Several factors are thought to contribute to CKD-aP, including an immune-mediated response and nociceptive stimulation. However, its complex pathophysiology remains poorly understood [1]. CKD-aP is reported to affect up to 80% of patients with end-stage kidney disease (ESKD), with 40% experiencing moderate to severe itch [3].

The clinical manifestations of CKD-aP are heterogeneous with variable intensity and unpredictable timing around

dialysis [4]. The pattern of distribution is also inconsistent, but up to half of patients with CKD-aP experience generalized itch [4], while others notice localized areas of pruritus, most notably the back or the fistula arm. Several associated skin abnormalities have been reported, of which the most common is xerosis (seen in up to 85% of patients), as well as less frequent superimposed lesions such as impetigo, crusting, papules, ulceration and nodules [5].

Exacerbating factors of CKD-aP include extremes in temperature, dry skin or showering. The reported sequelae of CKD-aP are poor quality of life (QoL), disturbed sleep patterns, low mood, increased infective complications, more frequent hospitalization and greater mortality [6]. The approach to therapy typically includes a combination of topical treatments, gabapentinoids, μ -opioid receptor antagonists and κ -agonists, antidepressants, alterations to dialysis and

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Table 1. Summary of studies evaluating epidemiology of CKD-aP and its impact on patient outcomes

Study	Study design	Prevalence	Risk factors	Impact of CKD-aP on outcomes
Sukul et al. [8] (DOPPS 4-6)	n = 23 264, HD International	No itch: 33%; mild: 30%; moderate: 18%; moder- ate-severe: 12%; extreme: 7%	Older age, higher serum phosphate, lower hae- moglobin and lower se- rum albumin	Higher mortality, cardiovascular and infection-related mortality and hospitalizations, greater risk of skin infections, increased rate of withdrawal from dialysis, reduced QoL
Ting et al. [9]	n = 108 679, HD Taiwanese health database	Total: 13.5%	Older age, PD > HD, hy- pertension, diabetes, increased medication use	Increased infection-related hospi- talizations, catheter-associated infections, heart failure, major adverse cardiac events, parathyroidectomy
Rehman et al. [10]	n = 354, HD Pakistan, two centres	Total: 74%; mild: 53.4%; <6 h/day: 64.5%	Male sex	Reduced QoL
Sukul et al. [11] (CKDopps and CKD-REIN)	n = 3780, non-dialysis CKD Brazil, USA, France	At least moderate: 24%; severe: 10-13%; severe: 19%; higher in Stage 5 CKD compared with Stage 3	Older age; female sex; his- tory of lung disease, diabetes or depression; higher serum phos- phate and lower haemoglobin	Increased depression (almost 2- fold with moderate pruritus, 2.5- fold with severe pruritus), rest- less leg syndrome, disturbed sleep, reduced QoL
Rayner et al. [12] (DOPPS 1-5)	n = 35 452, HD International (17 countries)	No itch: 26-31%; mild: 28-31%; moderate: 18- 20%; moderate-severe: 11-16%; extreme: 7-12%	Older age, elevated CRP, low serum albumin, hepatitis B and C	Restless sleep (60%)
Min et al. [13]	n = 425, HD; n = 223, PD Korean registry	HD: 48.3%; PD: 62.6%	Higher BMI, lower K_t/V , hypertension, hyperli- pidaemia and PD	No impact on mortality
Li et al. [14]	n = 362, PD China, single centre	Mild-moderate: 52.5%; severe: 12.7%	Elevated PTH, longer dialysis vintage	Sleep disorder, depression
Weiss et al. [15] (GEHIS)	n = 860, HD German, multicentre	Total: 25.2%	Age <70 years, longer di- alysis vintage	Greater anxiety, poor sleep quality
Ramakrishnan et al. [16]	n = 73 124, HD and PD US dialysis provider	Total: 60%; severe: 14.5%	Female sex, younger age, diabetes mellitus, mul- tiple medical comorbid- ities, increased EPO and IV iron use	Increased infective complications and antibiotic use, poor QoL, in- creased number of missed dialy- sis sessions
Kimata et al. [17]	n = 6480, HD Japan, multicentre	Moderate-severe: 44%	Older age, male sex, hy- pertension, ascites, hepatitis C, higher se- rum calcium-phos- phate, elevated PTH, lower serum albumin, recent history of smoking	Poor sleep quality, poor QoL, 23% higher mortality risk
Lopes et al. [18] (PROHEMO)	n = 980, HD Brazil, multicentre	Mild: 24.4%; severe: 19.4%	Older age, lower serum al- bumin, heart failure	Difficulty sleeping, depression
Mathur et al. [19] (ITCH)	n = 103, HD US, multicentre	Daily-near daily itch: 84% Duration >1 year: 59%	Younger age	Lower mood, poor social relation- ships, poor sleep quality
Pisoni et al. [3] (DOPPS 1-2)	n = 18 801, HD International	No itch: 26% (DOPPS 1), 29% (DOPPS 2); mild: 29%; moderate: 18%; moderate-severe: 15% (DOPPS 1), 14% (DOPPS 2); extreme: 12% (DOPPS 1), 10% (DOPPS 2)	Male sex, lung disease, congestive cardiac fail- ure, neurological dis- ease, higher serum calcium and/or phos- phate, lower serum al- bumin, ascites, hepatitis C, leucocytosis	Poor sleep (45%), increased odds of depression (OR 1.3-1.7), in- creased mortality, poorer QoL

(continued)

Table 1. (continued)

Study	Study design	Prevalence	Risk factors	Impact of CKD-aP on outcomes
Narita et al. [20]	n = 1773, HD Japan, multicentre	Total: 72.9%; severe: 25.5%	Male sex, longer dialysis vintage, elevated PTH, elevated calcium and phosphate, elevated CRP	Increased mortality, trend towards increased death due to infection (not statistically significant), independent predictor for death, poor sleep

CKD-REIN, Chronic Kidney Disease–Renal Epidemiology and Information Network; OR, odds ratio; PROHEMO, Prospective Study of the Prognosis of Chronic Hemodialysis Patients.

phototherapy. However, treatment responses to these therapies are variable [1, 7].

This update outlines the epidemiology and risk factors for CKD-aP and its impact on health outcomes and QoL. A summary of the key studies reviewed is provided in Table 1.

EPIDEMIOLOGY OF CKD-AP

The reported prevalence of CKD-aP in ESKD is widely variable, ranging from 18 to 80% [2, 16]. This variability may be reflective of inconsistent patient reporting and physician awareness [21]. As a result, the true prevalence of CKD-aP may be underestimated. In the Dialysis Outcomes and Practice Patterns Study (DOPPS), a large multicentre international prospective cohort study of adult haemodialysis (HD) patients, Rayner et al. [12] found that 17% of patients experiencing severe constant pruritus had not previously disclosed this to a healthcare professional. Underrecognition of CKD-aP by healthcare providers was also common, with 65% of medical directors estimating that <5% of patients in their dialysis centre experienced severe pruritus, well below the actual numbers [12]. In several centres where severe pruritus was documented in 21–50% of patients, only 1% of physicians accurately estimated this prevalence [12].

HD

The DOPPS recruited 51 062 participants from 21 countries across five study phases (DOPPS 1–5) between 1996 and 2015 [10] and 23 264 participants across DOPPS 4–6 between 2009 and 2018 [11]. Patients were asked to self-report via questionnaire the presence and severity of pruritus over a 4-week period. In the DOPPS 1 cohort, 26% had no itch, 29% had mild itch and 45% had moderate to extreme itch. In the DOPPS 2 cohort, 29% had no itch, 29% had mild itch and 42% had moderate to extreme itch [3]. The proportion of patients with moderate to extreme itch in DOPPS 1 and 2 (45 and 42%, respectively) was similar to that in DOPPS 4–6, where the overall prevalence of moderate to extreme itch was 37%, with no significant difference across study phases [8]. One reported difference was that participants noted less severe itch in DOPPS 5 (2012–2015) compared with DOPPS 1 (1996–2001) [10], which may suggest improvements in managing CKD-aP over time. A study of the Japanese DOPPS cohort (JDOPPS) showed that overall, 44% of patients experienced moderate to extreme pruritus, but the prevalence varied widely across centres, ranging from 20% to 70% [17].

There is still a recognizable divergence in the reported prevalence of CKD-aP in the literature. Ramakrishnan et al. [16] conducted a retrospective cohort study involving 73 124 participants with ESKD on HD or peritoneal dialysis (PD), 60% of whom reported itch, whereas the German Epidemiology HD Itch Study (GEHIS) of 860 HD patients found that only 25.2% experienced CKD-aP [15].

PD

The reported incidence of CKD-aP in PD patients is similarly variable, ranging between 10 and 70% [22]. In a single-centre Chinese observational study with 362 patients on PD, 52.5% had either mild or moderate itch and 12.7% had severe itch [14]. In a cohort study of South Korean ESKD patients undergoing HD (n = 425) or PD (n = 223), Min et al. [13] found patients on PD were more prone to itch, with 62.6% of patients reporting symptoms compared with 48.3% of HD patients. However, the PD patient cohort was older with a higher body mass index (BMI) and higher serum levels of creatinine, phosphate, calcium-phosphate product, parathyroid hormone (PTH), β 2-microglobulin and ferritin. Following adjustment for confounding variables including age, BMI and dialysis modality, PD was still an independent risk factor for CKD-aP. However, there was no adjustment for biochemical parameters, potentially influencing these results.

Conversely, Wu et al. [23] found that patients on PD had less severe or frequent itch compared with patients on HD, with an observed prevalence of 28.6 and 38.2%, respectively. The relationship between reported itch and dialysis modality is unclear, with no discernible reasons to account for the observed differences between PD and HD patients.

Non-dialysis

The prevalence of pruritus among non-dialysis CKD patients was evaluated by an analysis of the international Chronic Kidney Disease Outcomes and Practice Patterns Study (CKDopps) [11]. From a total of 5658 non-dialysis patients with Stages 3–5 CKD enrolled from the USA, Brazil and France, 3780 participants responded to the pruritus question from the Kidney Disease Quality of Life Short Form (KDQOL-SF) questionnaire. The proportion of patients with moderate to extreme pruritus was 24%, with 10–13% experiencing severe to extreme pruritus. Patients with Stage 5 CKD reported a 19% greater prevalence of moderate to extreme itch compared with those with Stage 3 CKD.

The suggested trend of greater pruritus prevalence and severity with worsening kidney function is confirmed by other studies. Murtagh et al. [24] conducted a small survey of 66 patients with Stage 5 CKD on a conservative care pathway and found 74% experienced pruritus, with 32% describing it as distressing. However, a study by Solak et al. [25] of 402 pre-dialysis patients with Stages 2–5 CKD observed a relatively low prevalence of CKD-aP in the overall study cohort (18.9%) and no significant differences in pruritus prevalence between CKD stages.

Transplant

Renal transplantation has been identified as a definitive treatment for CKD-aP, with one study showing resolution of pruritus

in 73.7% of HD patients post-transplantation [26]. However, transplant recipients still experience itch, and there is limited understanding surrounding this. A literature review of eight studies found a variable prevalence of itch in transplant patients ranging between 12 and 32%. While these rates of pruritus are lower compared with the dialysis patient population, they are higher than in the general healthy population [27]. Skin biopsies following transplantation have shown resolution of skin abnormalities, including xerosis. However, connective tissue changes may persist, which may account for persistent itch [27].

POTENTIAL RISK FACTORS FOR CKD-aP IN DIALYSIS PATIENTS

Several potential risk factors for CKD-aP have been identified, some of which may guide therapeutic options. However, these require further research as the current data remains conflicted.

Calcium-phosphate

There has previously been a focus on calcium-phosphate balance in the treatment of CKD-aP, as earlier phases of the DOPPS reported an association between higher calcium-phosphate product concentration and itch severity in HD patients [12]. This finding was not seen in the later phases of the DOPPS and no itch relief was seen following the normalization or lowering of serum phosphate [12]. There was also no association between the use of calcium- versus non-calcium-containing phosphate binders and the occurrence of moderate to severe pruritus [3]. Sukul *et al.* [11] did observe that greater itch intensity was associated with higher serum phosphate levels in non-dialytic CKD patients, but acknowledged confounding factors, as worsening hyperphosphataemia generally reflects lower kidney function.

While Ramakrishnan *et al.* [16] did show a correlation between elevated PTH and CKD-aP, it was small in magnitude and a number of other studies have shown no relationship [3, 19, 28].

Age

In the DOPPS, younger patients experienced less severe pruritus than older patients [12] and a meta-analysis of 42 studies involving a total of 11 800 adult dialysis patients indicated that younger age was a protective factor [2]. However, Ramakrishnan *et al.* [16] found that patients who reported greater itch severity tended to be younger, while the GEHIS study further showed that patients <70 years of age experienced more frequent itch compared with those ≥ 70 years [15].

Sex

There are also discrepancies regarding the impact of sex on CKD-aP. However, this is an area of research interest, based on evidence of sex-specific differences in itch-related mechanisms, including mast cell activation and regulation of the opioid cannabinoid and the neurokinin 1 systems [1]. A number of observational studies, including DOPPS, have shown a greater prevalence of CKD-aP in males undergoing HD [3, 10]. However, Ramakrishnan *et al.* [16] found a higher prevalence of pruritus in females.

Race and country of residence

While it has been documented that perception and experience of itch differ according to ethnicity, there are no studies that have explored the direct influence of race on the severity of CKD-aP [1, 16]. An analysis of the DOPPS Phases 4–6 (2009–18)

found some variations of CKD-aP severity by country. However, the significance of this finding is unclear [8]. The proportion of patients who reported moderate to extreme pruritus was lowest in Germany (27%) and highest in the UK (47%).

Comorbidities

Multiple comorbidities have been associated with an increased risk of severe itch, including concurrent cardiovascular disease, congestive cardiac failure, lung disease, liver disease and neurological disease [3, 16]. Diabetes mellitus is also reported to be associated with worse itch, with poor glycaemic control and a higher haemoglobin A1c correlating with greater symptom burden [29]. However, the converse was seen in the GEHIS study, with a lower prevalence of itch in diabetic patients [28]. Akhyani *et al.* [30] performed a small study with 167 dialysis patients in Iran and found that neuropathy was associated with CKD-aP. Hepatitis C infection has also been shown to correlate with increased itch [3, 17].

Dialysis characteristics

Increased severity of itch has been associated with longer dialysis vintage [15, 16]. The GEHIS study found that HD patients experiencing itch had a mean dialysis duration of 68.9 months, compared with 50.8 months for those with no itch [15]. As outlined above, Min *et al.* [13] found that PD was an independent risk factor for CKD-aP, but the data relating to this association are inconsistent [23].

Hu *et al.* [2] found that shorter dialysis duration and greater dialysis adequacy were protective factors for itch. While DOPPS 1 also indicated lower odds of itch with greater dialysis adequacy (defined as $K_t/V > 1.5$), this finding was not replicated in DOPPS 2 or DOPPS 5 [10]. Ko *et al.* [31] also found an HD $K_t/V > 1.5$ coincided with less itch. However, the ITCH study showed no correlation between itch and HD adequacy [19], and Li *et al.* [14] found no differences in K_t/V between PD patients with and without pruritus. There are also discrepancies in the literature surrounding the impact of dialyser membrane and high-flux dialysers on itch [3, 28, 31]. There is no documented relationship between itch and residual renal function [3].

Anaemia

DOPPS 1 showed lower odds of moderate to severe itch with a higher haemoglobin level, but this was not observed in later phases of the study [12]. Ramakrishnan *et al.* [16] also demonstrated an association between increased itch severity and worse anaemia. However, this relationship was not observed in the ITCH study [19]. Pisoni *et al.* [3] also found higher serum ferritin levels were associated with a lower likelihood of moderate to severe itch, but transferrin saturation was not associated with pruritus severity [3].

While Ramakrishnan *et al.* [16] found increased monthly recombinant erythropoietin (EPO) and intravenous (IV) iron requirements in HD patients with greater itch severity, no such differences were reported in the DOPPS [3].

Inflammatory markers

Lower serum albumin has been consistently associated with greater odds of moderate to severe pruritus [3, 12, 16, 17], potentially reflective of a chronic inflammatory state and malnutrition.

Elevated C-reactive protein (CRP) [3, 12, 32] and leucocytosis [3, 33] have both been shown to have a significant correlation with itch severity, again suggestive of an association between pruritus and an inflammatory response. HD patients with moderate to severe CKD-aP and an elevated CRP level also have higher mortality and worse outcomes [34]. Increased rates of eosinophilia have also been observed in non-dialysis patients with CKD-aP [25]. A relationship between pruritus and various other inflammatory cytokines including interleukin-13 (IL-13) [35] and IL-31 [36] has been identified, which may have implications on future therapeutic options.

IMPACT OF CKD-aP ON HEALTH-RELATED QOL (HRQOL) AND MEDICAL OUTCOMES

CKD-aP is associated with poor QoL and adverse medical outcomes, including increased mortality [2]. Key data from studies evaluating the impact of CKD-aP on these aspects are summarized below.

Impaired physical and mental health-related QoL (HRQoL)

Data consistently demonstrate that CKD-aP has a negative impact on QoL [37]. Most studies employ the 36-item Short Form Health Survey (SF-36) or modified versions of this questionnaire (SF-12, KDQOL-36), as it is a validated tool to assess HRQoL. These surveys include a physical component summary (PCS) and mental component summary (MCS), integrating various domains such as physical function, pain, general health, social functioning, vitality and emotional well-being [38].

Several studies show lower PCS and MCS scores with greater itch severity [8, 16, 17, 39]. In the GEHIS study, female HD patients with itch reported significantly lower MCS scores compared with males [37]. In the DOPPS, patients with pruritus were more likely to report feeling washed out, poor sleep quality and depressive symptoms than patients with no pruritus [8]. Patients with itch also had 2- to 5.8-fold greater odds of 'feeling drained' compared with those with no itch [8, 17]. The GEHIS study also observed that HD patients with pruritus are more likely to complain of pain than those without pruritus [3]. Li et al. [14] found that PD patients with severe pruritus had significantly lower PCS QoL scores than those with mild to moderate or no pruritus, although this association was no longer significant following adjustment for sleep quality and depression.

Mortality

Higher mortality rates have been reported in patients with CKD-aP, with a poorer prognosis for those with severe itch [20]. In DOPPS 4–6, a greater rate of all-cause mortality was found in patients with extreme itch compared with those with no itch [hazard ratio (HR) 1.24] [8] as well as increased rates of cardiovascular-related death (HR 1.29) and infection-related death (HR 1.44). There were also increased rates of withdrawal from dialysis for those patients with extreme itch (HR 1.5) [8]. Other studies support the link between CKD-aP and cardiovascular mortality. Ting et al. [9] showed a slight increase in major cardiovascular adverse events (HR 1.05) and heart failure (HR 1.08) and Weng et al. [40] found that CKD-aP was a predictor for 2-year cardiovascular mortality in HD patients (HR 3.164).

Sleep disturbance may contribute to the association between pruritus and mortality. In DOPPS 1 and 2, although the presence of pruritus was associated with a 17% greater mortality risk

($P < 0.0001$), the statistical significance was lost following adjustment for sleep disorders [3]. However, Kimata et al. [17] showed that Japanese HD patients with moderate to severe pruritus had a 23% greater risk of mortality than patients without pruritus ($P = 0.09$), and this difference remained significant event after adjustment for poor sleep.

Other potential contributing factors were highlighted in the GEHIS study, which found increased mortality in patients with CKD-aP who had skin lesions, elevated CRP, lower PCS and depression [41]. There was one study that showed no relationship between pruritus and mortality for HD or PD patients, which was hypothesized to be due to very low numbers of patients with severe pruritus [13].

Sleep disturbance

CKD-aP has a negative impact on sleep quality and quantity, with a meta-analysis showing the prevalence of disturbed sleep secondary to pruritus ranging between 9 and 76%, with a pooled effect of 50% [42]. In the DOPPS, 45% of patients with moderate to severe pruritus reported poor sleep quality compared with 29% of those with mild or no pruritus [3]. Those with moderate to severe itch had 1.4- to 4-times greater odds of having insufficient sleep, daytime somnolence or difficulty sleeping at night. Of these patients, 33.1% were prescribed a sleeping pill. A Malaysian study of 334 HD patients found a 5.47-fold increased risk of poor sleep quality in patients with moderate to severe pruritus compared with those with mild or no itch [43]. These findings are similarly noted in PD patients, with increased sleep disorders associated with increased severity of itch [14]. In the GEHIS study, >50% of HD patients with itch had poor sleep quality, but there was no correlation between grade of pruritus severity and sleep quality [15].

Poor dialysis and medication adherence

Ramakrishnan et al. [16] found that patients with worse itch were less adherent to HD sessions, with 56.2% of those with no itch missing dialysis sessions compared with 63.2% of those with severe itch. Sukul et al. [8] also found that patients who had extreme itch were more likely to miss dialysis sessions and reported a longer time for recovery after dialysis, which remained significant following adjustment for sleep quality.

Hospitalization

The impact of CKD-aP on hospitalizations among HD patients was evaluated by an analysis of the DOPPS 4–6 cohorts [8]. The study observed that patients with severe itch had a greater risk of being hospitalized for cardiovascular-, infection- and skin-related complications compared with those with no itch [8]. Patients with extreme itch also had a greater rate of hospitalization for mental status change or confusion (HR 1.84), however, the overall incidence of this remained relatively low (1%).

Risk of infection

Dialysis patients with itch are reported to have increased infection-related events, including sepsis and bacteraemia [9]. Sukul et al. [8] found an increased risk of skin-related infections in HD patients with extreme itch (HR 1.41). Ting et al. [9] conducted a large study on 14760 dialysis patients with CKD-aP and found increased infection-related hospitalization (HR 1.13) and catheter-associated infection (HR 1.16) compared with a control group of dialysis patients without pruritus [9]. A large

retrospective cohort study in 73 124 patients with ESKD found that increased IV antibiotic use was also associated with greater itch severity in HD patients, particularly those dialysing via a central venous catheter (CVC) [16]. Among HD patients with a CVC, the rate of IV antibiotic use was higher in those with extreme itch (28.5%) compared with those who were itch-free (21.8%) [16]. Among PD patients, IV antibiotic use ranged from 9.1 to 11.6% across the itch categories evaluated [16].

Depression

Patients with greater itch severity are more likely to experience depressive symptoms [3, 18, 39]. Pisoni *et al.* [3] found that HD patients with moderate to extreme pruritus had 1.3–1.7 times higher odds of being diagnosed with depression. Of these patients, 14.4% were prescribed a benzodiazepine and 8.4% were prescribed an antidepressant. Sukul *et al.* [11] found that non-dialysis CKD patients with moderate and severe pruritus experienced, respectively, 1.8 and 2.5 times the number of depressive symptoms, compared with patients without itch [11]. Furthermore, an analysis of the JDOPPS suggested that depressive symptoms may have been predictive for future development of severe pruritus in HD patients during the 0.5- to 2.5-year follow-up period [44].

The GEHIS study of German HD patients found no significant association between depression and itch, but it did show that patients with pruritus suffered from higher levels of anxiety [15, 45].

CONCLUSION

CKD-aP is a common yet underrecognized condition that affects patients with CKD and ESKD regardless of whether they are undergoing conservative care, HD, PD or have received kidney transplantation. Observational studies in the HD population show the prevalence of CKD-aP has decreased slightly during the past 20 years; however, a significant proportion of HD patients (~40%) still experience moderate to severe symptoms. The clinical presentation of CKD-aP is highly variable in terms of its pattern of distribution, intensity and persistence over time. The subjective nature of itch presents a challenge for diagnosis of CKD-aP and its identification relies on healthcare provider recognition and patients reporting their symptoms. Several studies have demonstrated that CKD-aP markedly impairs patients' physical and mental HRQoL and that it is also associated with sleep disturbance and depression. In addition, CKD-aP has also been linked with worse clinical outcomes, including an increased risk of infections, hospitalizations and mortality. An improved understanding of the pathophysiology of CKD-aP and ongoing research into pharmacological therapies that target the underlying disease mechanisms are important to guide the management of this condition and help reduce the symptom burden of CKD-aP on patients.

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CONFLICT OF INTEREST STATEMENT

D.K. has no conflicts of interest to declare. C.P. is Chair of the Australian Advisory Board for difelikefalin. She is also on the advisory boards for Vifor, AstraZeneca, Janssen Cilag, Otsuka, Boehringer Ingelheim, Eli Lilly and Novartis.

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