





Pruritus associated with chronic kidney disease with and without renal replacement therapy.

Santiago David Silva Tobar ¹ , Santiago Martín Camacho Pedroza ² .


1. Nephrology Service, Ambato Provincial General Teaching Hospital, Solca Núcleo Tungurahua, Ambato, Ecuador.
2. Dermatology Service, "Piel Sana" Dermatological and Dermato-Oncological Surgery Center, Ambato, Ecuador.

Received: June 12, 2022
Accepted: July 30, 2023
Published: August 16, 2023
Editor: Dr. Franklin Mora Bravo.

Cite:

Silva S, Camacho S. Pruritus associated with chronic kidney disease with and without renal replacement therapy. REV SEN 2023;11(2):98-109.

DOI: <http://doi.org/10.56867/55>
SOCIEDAD ECUATORIANA DE NEFROLOGÍA DIÁLISIS Y TRASPLANTE.
ISSN-L: 2953-6448

 Copyright 2023, Santiago David Silva Tobar, Santiago martin Camacho Pedroza. This article is distributed under the [Creative Commons CC BY-NC-SA 4.0 Attribution License](https://creativecommons.org/licenses/by-nc-sa/4.0/), which allows the use and redistribution, citing the source and the original author for noncommercial purposes.

Abstract

Introduction: Pruritus associated with chronic kidney disease (CKD) affects quality of life adherence to treatment and increases mortality in patients with chronic kidney disease with and without extracorporeal renal replacement therapy (hemodialysis or peritoneal dialysis). Its prevalence and intensity of symptoms are higher in peritoneal dialysis (PD) than in hemodialysis (HD). The diagnosis is made using scores that avoid subdiagnosis. Its treatment is related to the intensity of the symptoms, from mild to moderate, topical treatment, and, in severe symptoms, systemic. It usually presents as large, symmetrical, reddened areas of skin, often at night.

Objective of the review: The aim is to review the main pathophysiological aspects and establish an algorithm for diagnosing and treating pruritus in patients with chronic kidney disease with and without requiring renal replacement therapy (hemodialysis and peritoneal dialysis).

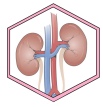
Essential points of the review: There are several diagnostic scores, such as the visual analog scale that measures the intensity of itching, the Pauli-Magnus scale that relates to the quality of sleep, and the 5-D itching scale that evaluates the quality of life, however, the KDQoL-36, WINRS, and SADS are more practical at the time of assessment. The most recent treatment is Nalfurafine, a k-opioid receptor agonist, which has reduced the severity of symptoms by 95%.

Conclusion: The objective of the review is to review the main pathophysiological aspects and establish an algorithm for diagnosing and treating pruritus in patients with chronic kidney disease with and without requiring renal replacement therapy (hemodialysis and peritoneal dialysis).

Keywords:

MeSH: Pruritus; Renal Dialysis; Continuous Renal Replacement Therapy; Peritoneal Dialysis; Renal insufficiency, Chronic.

* Corresponding author



Chronic kidney disease has increased over time, making it a public health problem worldwide [1, 2]. End-stage chronic kidney disease (ESRD) is defined as the need for renal replacement therapy (RRT) (hemodialysis, peritoneal dialysis, or kidney transplant) due to advanced kidney damage, which corresponds to stage 5 chronic kidney disease [2].

According to an epidemiological study, it is estimated that by 2030, approximately 2 million people in the United States will receive dialysis [3]. According to data from the Ministry of Health, the prevalence of CKD in Ecuador reaches 1,074 patients per million inhabitants [4].

The prevalence of pruritus associated with chronic kidney disease (PA-CKD) ranges between 18% and 55% [5, 6]. It is related to poor quality of life, depression, anxiety, sleep disorders, and increased mortality. Its incidence is decreasing thanks to improvements in dialysis treatments, while the pathogenesis is poorly understood. The interaction between unmyelinated C fibers and dermal mast cells is essential in precipitation and sensory stimulation [5, 6].

The diagnosis of pruritus in hemodialysis is made using scales. Among the most effective due to their simplicity are the KDQoL-36, WINRS, and SADS [7].

For the initial screening in the diagnosis of chronic pruritus in this age group, question 20 of the KDQoL-36 is used, as it provides notable and sufficient information [7]. Hemodialysis pruritus usually presents as large symmetrical red areas of the skin, often at night. Its treatment is challenging [7].

Epidemiology

According to an epidemiological review study, by 2003, it is estimated that approximately 320,000 people in the United States were receiving dialysis, with expected increases of 650,000 by 2010 and 2 million by 2030; in the same study, mortality from cardiovascular disease (CVD). It was 10 to 30 times higher in these patients than in the general population [3].

In Ecuador, according to the 2022 situation report on renal replacement therapy issued by the Ministry of Public Health, an incidence rate of 55.53 patients per million inhabitants and a prevalence rate of 1,074 patients per million inhabitants were obtained [4].

The prevalence of PA-ERC diagnosed by the visual pruritus scale (VPS) was 55%, according to a meta-analysis of 42 cross-sectional studies from Asia, Africa, North America, South America, and Europe 5. In comparison, in other studies, it ranges between 18% and 55% [6, 8].

In the same multinational meta-analysis comparing renal replacement therapy modalities, there was a higher prevalence among

patients with PD (56%, 95% CI 44-68, I² = 89.9%) compared to HD (55%, 95% CI 49 -62, I² = 97.9%) [5].

In the retrospective Dialysis Outcomes and Practice Patterns Study (DOPPS), patients with moderate to extreme pruritus were more likely to have exhaustion (adjusted odds ratio (AOR) = 2.3-5.2, P < 0.0001), poor sleep quality (AOR = 1.9-4.1; P = 0.0002), more significant depression (AOR = 1.3-1.7; P 0.004), and mental and physical quality of life (QoL) composite scores 3.1-8.6 points lower (P < 0.0001) than patients without pruritus or with mild pruritus [9].

The last major study on the prevalence of pruritus associated with CKD, DOPPS-III data, mainly from Japan, observed an incidence of moderate to extreme pruritus of 44% between 1996 and 2008 [10]. Pruritus in HD patients was also associated with a 17% risk of mortality (P < 0.0001), which was no longer significant after adjusting for sleep quality measures [9]. There is no described epidemiology of pruritus related to CKD in patients on renal replacement therapy in our country.

Concept and diagnosis

Pruritus is defined as burning or itching of the skin and represents the most common skin symptom in ESRD, which is why it is commonly known as “uremic pruritus.” However, there is no proven correlation between cause and effect with uremia [1, 5].

For this reason, pruritus is generally not observed in patients with acute kidney injury (AKI) and is difficult to distinguish from pruritus in other pathologies (thyroid disease, malignancies, and hematological neoplasms) [1, 5].

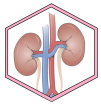
For this reason, the definition of pruritus associated with CKD (PA-CKD) is appropriate to refer to the pruritus presented by patients suffering from chronic kidney disease who do or do not require RRT.

The diagnosis of PA-CKD can be based on different scales, but the most commonly used is the visual analog scale of pruritus (VAS), which evaluates pruritus in an objective and unidimensional manner (intensity only) from a value of 0 (absence) of itching) to 10 (severe itching) [11].

Other scales also evaluate the distribution of itch and its impact on sleep; this would be the case for the modified Pauli-Magnus scale. The “5-D itching scale” test also evaluates the effect of itching on quality of life. Finally, the Skin Index 10 adds to pruritus's emotional, social, and occupational impact on patients' lives [11].

Another classic score is the itch severity scale or Itch Severity Scale (ISS), developed and validated in 2007 by Majeski. et al., in patients with psoriasis, made it possible to diagnose the intensity of the itch objectively, observe its effect on the patient, and evaluate the effectiveness of the treatment [11].

The limitation of the scales described above is the difficulty they present for the patient's understanding at the time of evaluation. For this reason, we have based ourselves on the KDQoL-36, WINRS, and



SADS scales used for the diagnosis and assessment of the severity of pruritus recommended by the Information and Consensus Document for the diagnostic and therapeutic management of pruritus associated with chronic kidney disease in patients in hemodialysis in Spain due to its ease of application [7, 36, 37].

For the screening of chronic pruritus, question number twenty of the KDQoL-36 scale was initially used since it covers sufficient information to make decisions ("In the last four weeks, to what extent have you felt discomfort caused by having itching?, as answers: nothing, somewhat, a lot, a lot or a lot") [7].

This gives us a better idea of the presence of itching and its intensity quickly and efficiently, as it can be applied by doctors and nursing staff. If the patient responds "somewhat, quite a bit, a lot, or a lot" as a second step, a differential should be made with other causes of pruritus [7]. This screening will be performed every three months in patients whose pruritus associated with CKD has not been diagnosed [7].

Etiopathogenesis

To explain the pathophysiology of PA-CKD, several hypotheses have been proposed, which have yet to be demonstrated, but it is clear that it is a multifactorial etiology [11, 12].

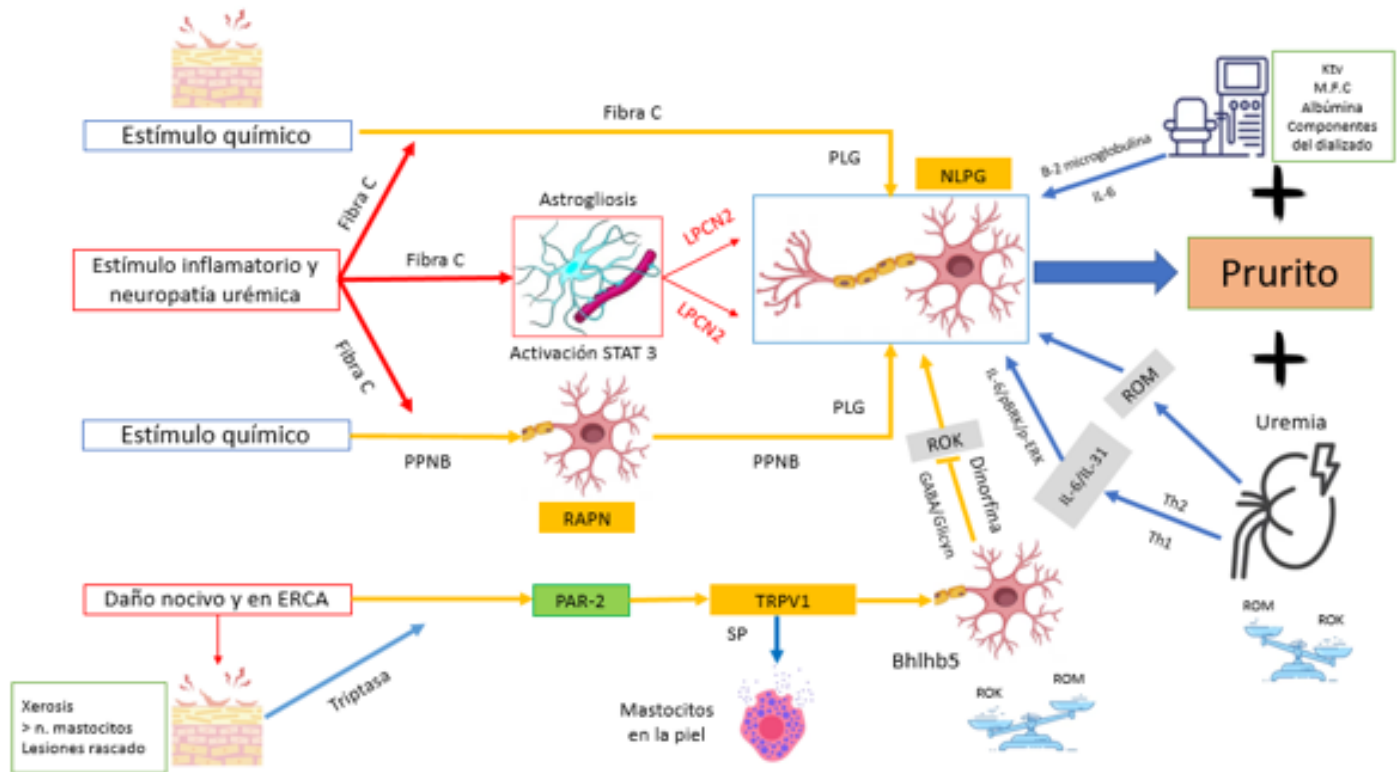
Skin changes: In CKD, there is an increase in dermal mast cells and levels of tryptase, which is produced by dermal cells. Tryptase activates proteinase-activated receptor 2 (PAR-2) on itch-generating afferents. The activation of PAR-2 sensitizes the ion channels of the transient receptor potential vanilloid 1 (TRPV1) in the afferent nerves, activating the adjacent ones and transmitting the itch signal to the dorsal root ganglion and dorsal horn of the spinal cord [12, 13, 17].

TRPV1 sensitization further causes a retrograde release of substance P from nerve endings, which, in turn, activates dermal mast cells and keratinocytes to release more cytokines, worsening pruritus [12, 17].

In the skin of patients with chronic kidney disease, there is a more significant inhibition of kappa (κ) opioid receptors (due to upregulation), which causes their activity to decrease, statistically correlated with the severity of pruritus in kidney disease. Chronic, since the activation of kappa opioid receptors has an antipruritic effect. (These receptors appear on the surface of dermal mast cells, keratinocytes, and the dorsal horn.) [14].

Loss of regulation of the opioid system: This hypothesis is the most important since this system at the level of the central nervous system controls pain and itching in such a way that when the μ -opioid receptor (ROM, a receptor for β -endorphin), there is more significant itch, while if the κ -opioid receptor (ROK, a dynorphin receptor) is activated, it is inhibited [1, 12, 15].

This hypothesis explains why dynorphin released by basic helix-loop-helix b5 (Bhlhb5) neurons inhibits the ROK at the level of the receptor of the neurons that release gastrin peptide (NLPG) in the spinal cord, which is directly responsible for itch. All this worsens if there is a loss of regulation by the inhibitors of these neurons (Figure 1) [12]. This clinical picture worsens in patients with CKD since, in addition to the above, there is hyperstimulation of the ROM, which worsens much more in the case of extracorporeal therapies since it has been shown that, in patients on hemodialysis, the intensity of the pruritus was positively correlated with serum β -endorphin concentration and the more significant amount of ROM agonist relative to ROK agonist [15].

Figure 1. Pathophysiology of Pruritus Associated with Chronic Kidney Disease


STAT3.- Signal transduction and transcription activation 3; PPNB: Natriuretic Polypeptide B; PLG: Gastrin-releasing peptide; NLPG: Neurons that release the peptide gastrin; RAPN: Natriuretic peptide receptor A LPCN2: Lipocalin 2; Bhlhb5: Basic helix-loop-helix b5 neurons; PAR-2: Proteinase-activated receptor 2; TRPV1: transient receptor potential vanilloid 1; SP: Substance P; ROK: Kappa opioid receptor; ROM: mu opioid receptor; Th1: T helper one lymphocyte; Th2: T helper 2 lymphocytes; IL-6: Interleukin 6; IL-31: Interleukin 31; IL-6/pBRK/p-ERK: Interleukin 6/Phosphorylated Bruton Tyrosine Kinase Receptor/Extracellular Signal Regulated Kinase Pathway; MFC: Phosphocalcium metabolism.

Taken and modified from Kim, J.C., Shim, W.S., Kwak, I.S., Lee, D.H. et al. Pathogenesis and Treatment of Pruritus Associated with Chronic Kidney Disease and Cholestasis. *Int J Mol Sci.* 2023, Jan 13;24(2):1559. doi:10.3390/ijms24021559

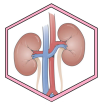
Uremic neuropathy: In patients with uremia, the peripheral nerve endings are reduced, and some branches are irregular in the epidermis, which paradoxically increases the excitability of the nerve, generating itching, and with scratching, neurogenic inflammation and destruction of the epidermal nerves are caused ("cycle of itching-scratching"), which produces astroglial activation in the spinal cord, overexcitability of NLRP3 neurons and aggravates the cycle [12]. This would probably explain the higher prevalence of pruritus in these patients and the reason for the excellent response to drugs for neuropathic pain [12, 15].

Altered calcium and phosphorous metabolism: Classically, alterations such as hyperparathyroidism, increased calcium/phosphorus product, and hyperphosphatemia have been responsible for pruritus in HD patients since when they are corrected pharmacologically or through parathyroid surgery, the pruritus is the site [12, 15]. However, the DOPPS study, a multivariate analysis with 6256 patients, showed conflicting results. There was no significant correlation between CKD-associated pruritus and the concentration of phosphorus, calcium,

calcium-phosphorus products, or parathyroid hormone (PTH) [9]. Various studies also demonstrated that uremia in patients with CKD was correlated with the retention of multiple solutes not yet elucidated that cause uremic syndrome [12, 15]. Finally, an experimental study showed that when injecting calcium phosphate in rats, pruritus increased secondarily to the release of interleukin 6 (IL-6) [12].

Loss of regulation of the immune system: In chronic kidney disease, there is a significant change in the expression of "naïve Th" lymphocytes to Th1 lymphocytes. Additionally, there is an increase in cytokines produced by Th1 cells, including interferon- γ (IFN- γ), interleukin-6 (IL-6), and tumor necrosis factor- α (TNF- α). TNF- α enhances the expression of Th1 lymphocytes. IL-6 triggers a cascade called pruritus induced by IL-6/pBRK/p-ERK signaling [13].

This hypothesis is supported by increased levels of serum C-reactive protein (serum CRP) ($P = 0.010$), IL-6 ($P = 0.019$), IFN- γ ($P = 0.026$), and CD4 receptor 3-producing TCD4 cells. CXC chemokine (CXCR3) ($P = 0.016$) in hemodialysis patients with pruritus [11,



[12] and to the excellent response of immunomodulatory therapies such as ultraviolet (UV) therapy and tacrolimus to reduce pruritus and effect that is also observed with cyclosporine in kidney transplant patients, including those whose kidney function has been affected [12].

It is also evident that there is an increase in interleukin-31 (IL-31), a pruritogenic cytokine of Th2 lymphocytes, as well as indirect growth in leukotriene B4, a highly pruritogenic cytokine [14].

A higher concentration of the highly pruritogenic β 2-microglobulin protein has also been documented in both the serum and skin of patients with CKD, as well as an increase in extracellular free calcium levels in the basal layer of the epidermis, which would also contribute to the stabilization of pruritus [14].

Xerosis occurs with atrophy of the sebaceous glands and thickening of the skin's basement membrane, causing dryness of the stratum corneum and increased pH. Furthermore, itch relief by moisturizing the skin suggests that xerosis is involved in the pathogenesis of CKD-associated pruritus [12].

Neuropeptide Natriuretic Polypeptide B (NPPB): NPPB is a neuropeptide released by primary terminal afferent neuronal fibers. Mishra et al. studied NPPB knockout mice and elicited potent scratching when NPPB was injected intrathecally, demonstrating that this neuropeptide causes pruritus when released from somatosensory neurons. For this reason, NPR1 inhibition is now a novel strategy for patients with CKD [12, 15].

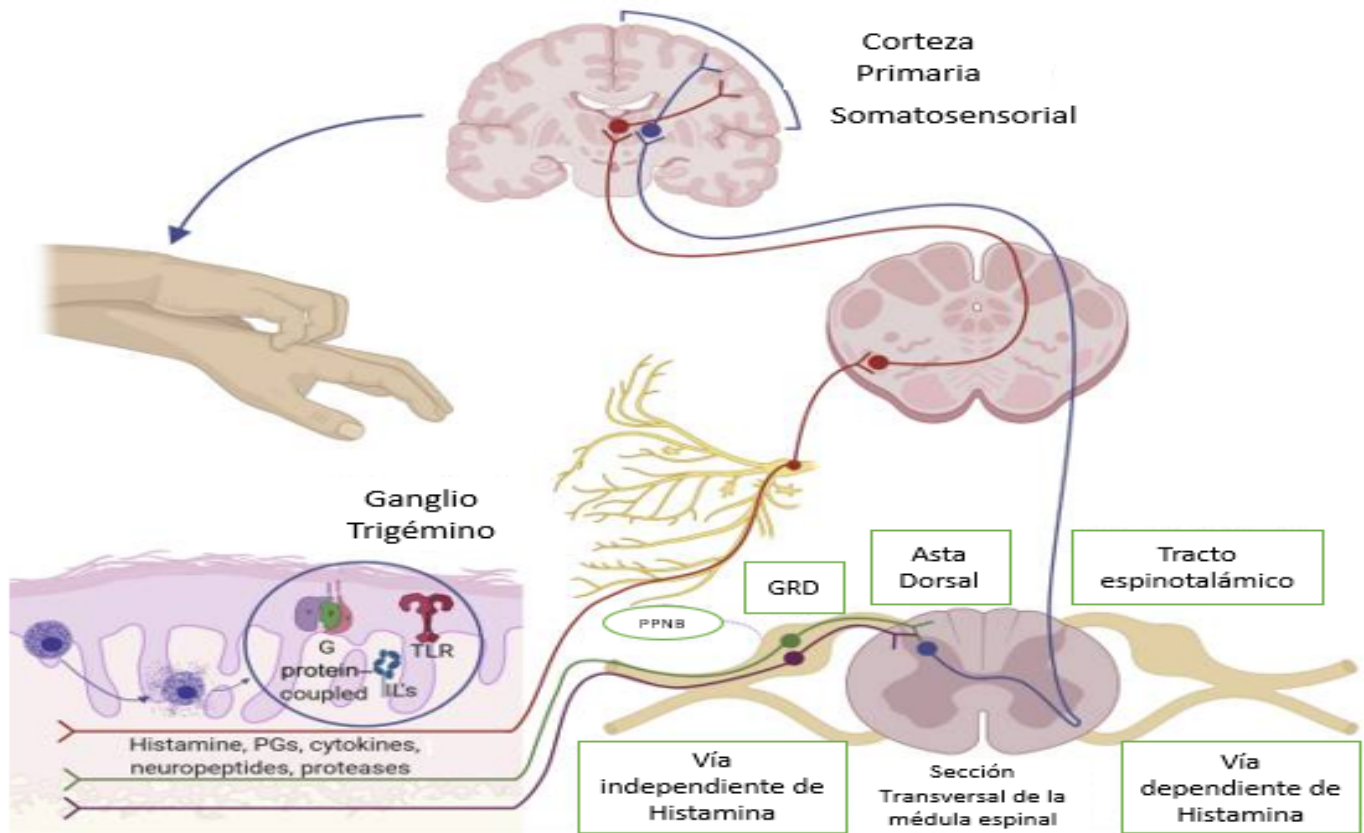
Underdialysis: Dialysis quality has also been linked to pruritus, as urea Kt/V levels less than 1.5 have been associated with severe pruritus over time [12]. However, there are discrepancies on this issue since differences in the DOPPS-I study were found in the prevalence of pruritus depending on Kt/V but not in the DOPPS-II study [9, 15]. This is related to pruritogenic molecules, among which the most important in CKD are aluminum, calcium, phosphate, parathyroid hormone, blood urea, and beta-2 microglobulin [9].

Other contributing factors: In some studies, lower serum albumin levels and higher white blood cell counts had significantly higher odds of having moderate to extreme pruritus. Furthermore, anemia, low erythropoietin levels, high ferritin levels, and low transferrin levels have also been explored as possible risks of related pruritus [8].

In this way, keratinocytes, immune cells, and neighboring neurons in the skin release pruritogens (such as histamine, prostaglandins, cytokines, neuropeptides, and proteases). These pruritogens activate histamine pathway-dependent or -independent primary afferent sensory neurons in the dorsal root and trigeminal ganglia cell bodies through G protein-coupled, Toll-like, or interleukin receptors [12, 35].

These sensory neurons then propagate the itch signal to secondary neurons in the dorsal horn of the spinal cord. Spinal interneurons then modulate itch through specific neurotransmitters (e.g., B-natriuretic polypeptide) and activate projection neurons that transmit the signal through the spinothalamic tract to the cerebral cortex [12, 35].

Figure 2. Somatosensory pathway of pruritus.



DRG: Dorsal root ganglia, PPNB: Natriuretic polypeptide B, PGs: Prostaglandins, TLR: Toll-like receptor

Taken and modified from Verduzco HA, Shirazian S. CKD-Associated Pruritus: New Insights Into Diagnosis, Pathogenesis, and Management. *Kidney Int Rep* 2020 May 8;5(9):1387-1402. doi: 10.1016/j.ekir.2020.04.027. PMID: 32954065.

Differential diagnosis

Pruritus is usually classified classically, depending on its duration, clinical manifestations, and etiology [16]. According to its time, it must be differentiated between acute and chronic itching, with acute itching lasting less than six weeks. In contrast, the chronic type refers to symptoms of longer duration [16, 18].

Chronic pruritus is more complex to treat and can be exhausting for the patient; available therapies provide temporary relief that generally does not cover the underlying causes of such pruritus [16, 18]. In chronic pruritus, it is mandatory first to differentiate primary versus secondary skin lesions so that if they are direct, they are of dermatological cause [17].

If the causes of chronic pruritus are not due to primary skin lesions, it is due to nondermatological reasons, including diseases with systemic, neuropathic, or psychogenic causes [17].

The experts who are members of the International Forum for the Study of Pruritus [16] have proposed a classification system of two groups:

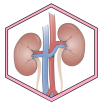
The *first group* does not have an established diagnosis and consists of three subgroups:

- Subgroup I: pruritus plus skin inflammation.
- Subgroup II: pruritus plus the absence of inflamed skin, such as stage 5 chronic kidney disease, cholestatic or neuropathic syndrome [16].
- Subgroup III: pruritus presenting with severe, chronic, secondary scratching lesions, such as prurigo nodules associated with chronic kidney disease or excoriations secondary to severe itching in patients with pruritus related to systemic diseases or neuropathic pruritus [16, 17].

Skin biopsy is necessary to diagnose patients belonging to group I since a primary skin disease can be analyzed [17, 18]. Biopsy is generally useless in group II or III patients [16, 17].

The *second group* knows the origin of the itching and is divided into the following categories:

- Dermatological: This subgroup is characterized by pruritus with skin disorders. Examples include xerosis, atopic dermatitis, psoriasis, urticaria, and skin infections, i.e., the same lesions as those in subgroup I patients in the first group. [16, 17].
- Systemic: Consists of pruritus secondary to organic disorders, for example, chronic renal failure, liver disease, hematological or lymphoproliferative disorders, endocrine disorders such as diabetes, thyroid disorders, and malignancy. Drug-induced pruritus also falls into this category [16].



- **Neurological:** Includes pruritus related to disorders of the peripheral or central nervous system, for example, notalgia paresthetica (chronic sensory neuropathy characterized by intense pain and pruritus), brachioradial pruritus and multiple sclerosis [16].
- **Psychogenic:** examples of this type of pathology are psychiatric disorders such as depression, anxiety, psychogenic excoriation, and delusional infestation (also called delusional parasitosis) [16].
- **Mixed:** pruritus attributed to more than one cause is placed in this category [16].

Treatment

Due to a limited understanding of the pathogenesis of PA-CKD, current treatments for uremic pruritus still need to be discovered. There was no Food and Drug Administration (FDA)-approved treatment for uremic pruritus until difelicephalin was supported in the United States in 2021 [19].

Conventional treatments include emollients, topical agents (steroids, tacrolimus, and liquid paraffin), antihistamines, modification of normal dialysis parameters, phototherapy, and serotonin receptor antagonists. Recently, more evidence suggests that gabapentin, pregabalin, opioid receptor agonists and antagonists, and biologics play essential roles in uremic pruritus [19].

Topical Treatments

Moisturizers: Xerosis is found in 50-85% of patients with uremic pruritus and aggravates pruritus. Several emollients, such as glycerol, paraffin, 10% urea and dexpanthenol, physiological lipids, and baby oil, decrease xerosis and pruritus in patients with uremic pruritus [9].

Topical calcineurin inhibitor (tacrolimus, pimecrolimus): Tacrolimus, a calcineurin inhibitor, is used for its anti-inflammatory effects by inhibiting T lymphocytes [8].

Capsaicin, a compound found in chili peppers, is an agonist of transient potential vanilloid member 1 (TRPV1) raptor, is used for pain relief and neuropathy, and has also been used in pruritus [8].

Pramoxine is a topical anesthetic with antipruritic effects [20].

Hemodialysis: Since uremic toxins are suggested as possible pruritogenic toxins, increasing the efficiency of dialysis and modifying the hemodialysis prescription is a potential strategy for treating uremic pruritus. Hemodialysis, including high-flux hemodialysis, hemodiafiltration with hemodialysis, and high-permeability hemodialysis, has shown significant decreases in pruritus intensity [21].

Phototherapy: By modulating the differentiation of Th1 and Th2 lymphocytes, they attenuate Th1-mediated responses. Broadband ultraviolet B phototherapy was effective in patients with uremic pruritus compared with ultraviolet A phototherapy [22].

Oral Drugs.

Antihistamines mainly target the histamine H1 receptor; they are not satisfactory for treating uremic pruritus. Additionally, the side effects of antihistamines, such as dizziness, sedation, and urinary retention, are of concern [23].

Gabapentin, Pregabalin: Both pregabalin and gabapentin, analogs of gamma-aminobutyric acid, are neurotransmitter modulators, possibly acting by decreasing the release of pruritogenic neurotransmitters. The incidence of adverse effects with gabapentin, including dizziness and drowsiness, should always be considered [24].

Naloxone: It is an agonist/antagonist of opioid receptors. Intravenous injection of naloxone, a mu receptor antagonist, is effective in some instances; frequent adverse effects, such as nausea and sleep disorders, have been reported with these medications [24].

Nalfurafine: A new selective agonist of the kappa receptor, proved to be very effective in uremic pruritus [27], as demonstrated by the prospective phase III study, canonized double-blind against placebo, where Kumagai H et al. showed that nalfurafine hydrochloride at a dose of 2.5 mcg orally decreased pruritus by VAS scale significantly about placebo ($P = 0.0001$), and at a quantity of 5 mcg, it was more effective ($P = 0.0002$) [25].

Difelicephalin: Difelicephalin is a selective kappa opioid receptor agonist restricted to the periphery; it demonstrated its effectiveness in treating uremic pruritus at a dose of 0.5 µg per kilogram or placebo for 12 weeks. Common adverse events included diarrhea, dizziness, and vomiting, but no adverse events of dysphoria, hallucinations, euphoria, or discontinuation-related malaise were reported in the difelicephalin group. The FDA approved difelicephalin in the United States in 2021 [26].

Nalbuphine is a dual-action drug, an antagonist of the kappa opioid receptor and an agonist of the mu-opioid receptor, which is beneficial for uremic pruritus. The regimen is 120 mg of nalbuphine twice daily for eight weeks [27].

Mast cell stabilizer: Mast cell stabilizers, which prevent degranulation of mast cell inflammatory mediators, are effective in uremic pruritus and include topical sodium cromoglycate, oral sodium cromoglycate, ketotifen, and zinc sulfate. Mast cell stabilizers are safe and potentially effective in uremic pruritus, but more studies are needed [28].

Montelukast: Leukotriene B4, released mainly by macrophages and leukocytes, is involved in pruritus and can cause scratching. The drug montelukast is a leukotriene receptor antagonist. It can be used at a dose of 10 mg of montelukast daily for 30 days [28].

Ondansetron: 5-HT3 receptor antagonists have been studied for their effectiveness in treating uremic pruritus [22].



Nemolizumab: Due to the higher concentration of IL-31 in hemodialysis patients with uremic pruritus, the role of nemolizumab, an IL-31 receptor alpha antibody, in treating uremic pruritus is suggested [29].

Dupilumab: As the possible involvement of IL-31 was implicated in uremic pruritus, the role of T-helper 2, which is the uphill regulator of IL-31, in uremic pruritus has been suggested. Dupilumab, an IL-4 receptor alpha-blocker, was reported to successfully treat cases with intractable uremic pruritus [30].

Other treatments

Acupuncture, Acupressure: Defined by the insertion of acupuncture needles into specific points on the skin as a treatment, acupuncture has long been used for various symptoms, such as acute or chronic pain, sleep disorders, and poor quality of life in East Asia. Acupuncture is believed to act by modulating the endogenous opioid system [5].

Active Charcoal: Given the hypothesis of nondialyzable uremic toxins as possible pruritogens, adequate removal of potential toxins by charcoal is a reasonable therapeutic option. A daily dose of 6 g of activated charcoal can be used for eight weeks [31].

Parathyroidectomy: Calcium multiplied by phosphate level is reported to correlate with the extent of pruritus after parathyroidectomy, and intractable pruritus improves after parathyroidectomy in some cases [32].

Thalidomide is an immunomodulator and neuromodulator that can reduce dialysis patients' pruritus [33].

Renal transplantation: kidney replacement therapy significantly decreased or cured chronic pruritus in patients with uremic pruritus [34].

Dietary changes: Exogenous protein catabolism can lead to the retention of protein-bound molecules. Therefore, protein-restrictive diets and probiotics may serve as potential treatments for uremic pruritus [35].

Discussion

Pruritus associated with CKD is a term that applies to CKD in patients with and without requiring renal replacement therapies (hemodialysis, peritoneal dialysis, and transplantation) [1-3].

In those who do not require renal replacement therapy, it generally occurs with greater intensity and prevalence in advanced stages, which is called advanced chronic kidney disease (ACKD) (stages 3b, 4 and 5), as confirmed by the prospective study by Kendra E et al. in 3685 patients with CKD who did not undergo RRT and who were assessed with the KDQoL-36 scale, where there was a greater intensity and prevalence of pruritus symptoms associated with CKD in stages

3b, 4 and 5. Furthermore, the association between the estimated glomerular filtration rate (eGFR) and the uremia symptom severity score was not linear. When starting with a lower initial eGFR, for every 5 ml/min/1.73 m² decrease, it was associated with a better progression and intensity of uremic symptoms, including pruritus [38].

We believe that this concept does not apply to patients with ARF since in these patients, elevated urea does not have a significant association with pruritus, according to several studies, which forces us to consider other causes of pruritus in these cases [1, 2, 5].

This concept, in turn, allows us to realize that the pathophysiology of pruritus in this age group is not exclusively due to the uremic state but also to other toxins that have not yet been elucidated, which also have to do with phosphorus/calcium metabolism and dialysis quality (KTV) in the case of patients on RRT. Regarding uremia, pruritus occurs secondary to atrophy and loss of peripheral nerve endings at the skin level, which paradoxically increases nervous excitability [12, 16].

Our criteria in this regard are that this pathophysiological process responds only to chronic uremic states since the atrophy and neuronal damage of peripheral nerves, especially at the level of the dermis, occurs with sustained damage over time and does not occur in the short term, similar to what happens in Alzheimer's disease, which is a neurodegenerative disease that usually develops slowly and progressively worsens over time.

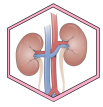
Among the pathophysiological mechanisms of CKD-related pruritus are skin alterations related to the increase in the number of mast cells and the production of tryptase by epidermal cells, which ends in the stimulation of the responsible neurons that release the peptide gastrin [13].

Other mechanisms involved are the overexpression of inhibitors of k-type opioid receptors (counteracting pruritus) and the increase in m-opioid receptors (pruritus generators) that exacerbate pruritus by further stimulating the neurons that release the peptide gastrin at the spinal cord level [13, 14]. All of this is also enhanced by xerosis (loss of sebaceous glands that causes skin dryness), alteration of phosphorus/calcium metabolism, and poor quality of dialysis (especially regarding B2 microglobulin), which patients may experience with CKD [14, 16].

In this regard, significant advances have been made in removing small and medium-sized molecules through RRT, especially molecules such as B2 microglobulin and interleukins that have to do with the pathophysiology of CKD-associated pruritus.

With this assertion, the CONVINCE TRIAL was carried out, a multinational, randomized controlled study that compared the benefits of hemodiafiltration (convection volume of 25.3 liters) versus high-flow hemodialysis, obtaining better benefits in favor of hemodiafiltration in terms of lower all-cause mortality [39].

For this reason, we believe that with the use of hemodiafiltration, we can even remove molecules that have not yet been elucidated and that have to do with the complications of CKD, including pruritus, not in vain an indication for admitting a patient to hemodiafiltration. Pruritus is not controlled with clinical treatment.



The immune system is also involved in the development of pruritus in CKD through an increase in the number of Th1 lymphocytes (cytokine generators) that produce IL6 and Th2 lymphocytes that produce IL31, which further enhance the itch mechanism along with the activation of inflammation [15].

We believe at this point that the pathophysiology of pruritus associated with CKD is multifactorial in which neuronal (opioid system), inflammatory, immunological, local dermal, and metabolic mechanisms involve uremia and phosphorus/calcium metabolism (which acts chronically), and finally, the quality of dialysis in the case of patients on RRT. Thus, since it is a multifactorial syndrome, we must act at the level of more than one pathophysiological mechanism to effectively control pruritus development.

As it has a multifactorial etiology, its diagnosis is also complex, so we propose a simple algorithm based on question 20 of the KDQOL™-36 to begin by considering the intensity of the itching, continuing with the next step, which is to differentiate the type of skin lesions (primary or secondary) and finally the differential diagnosis with other types of pruritus (systemic, dermatological, neurological, psychogenic or mixed) (Figure 2).

We based ourselves on question 20 of the KDQOL™-36 scale because it is a simple question and one that makes it easier for both the patient and the examiner to approach and respond to when diagnosing pruritus, as confirmed by the study carried out by the Information and consensus document for the diagnostic and therapeutic management of pruritus associated with CKD in patients on HD in Spain [7].

Furthermore, we justify the use of this question because it has the advantage that it takes less time and provides the necessary information to continue with the next steps of the algorithm, with other scales for diagnosing pruritus that are more complex, taking much more time to answer them adequately is cumbersome for both the patient and the interviewer.

Although the number of treatments for pruritus of uremic origin is progressing and more specific treatments are being deployed, it still needs to be studied due to the large number of affected patients. Many of the treatments described need more evidence obtained through randomized, controlled, and blinded studies, and to date, there have been very few studies comparing the different treatment options with each other [40].

All patients should be dialyzed optimally according to objectives. If pruritus persists, a trial of retargeting dialysis dose escalation may be considered; this can be achieved by increasing the time and frequency of dialysis. Conversion to peritoneal dialysis may be considered [30, 41, 31].

Comorbid medical conditions, independent and associated with CKD (e.g., hyperparathyroidism), should be monitored. Emollients with high water content should be recommended for all patients. Adding pramoxine to an emollient regimen may be recommended for additional relief. Topical therapies should be first-line in mild and localized PAERC [2].

Systemic treatments should be sought in generalized disease or moderate to severe and refractory intensity. Until now, gabapentinoids

(gabapentin and pregabalin) had the most evidence supporting their safety and efficacy in these patients and were therefore considered first-line, with caution regarding dosing [26].

With the recent FDA approval and discovery of new drugs, selective KOR agonists such as diphelicaphalin and more unique, selective agonists such as nalfurafine can be considered a safe and effective alternative to gabapentinoids.

Alternative and adjuvant treatments such as fatty acid supplementation, phototherapy, activated charcoal, cannabinoids, and acupuncture/acupressure should be considered on a patient-by-patient basis based on accessibility, practicality, financial status, and other comorbidities [43].

More studies are needed to investigate the pathophysiology of PA-CKD, compare the available and in-development treatments, and analyze patient outcomes to successfully address this pressing, debilitating, and understudied condition [44].

Conclusions

Pruritus associated with chronic kidney disease is a complication with implications for the patient's quality of life and is probably a secondary epiphenomenon to underdialysis that adds more significant mortality. Its diagnosis and treatment are challenging, as is elucidating its entire pathophysiology. We propose a protocol to address its early management and treatment, which will reduce its underdiagnosis. The therapy is multifactorial, and the advances are promising, giving rise to various combinations that allow a more favorable improvement in less time.

Abbreviations

PD: Peritoneal dialysis.

CKD: Chronic kidney disease.

HD: Hemodialysis.

PA-CKD: pruritus associated with chronic kidney disease.

RRT: Renal replacement therapy.

Supplementary information

Supplementary materials have not been declared.

Acknowledgments

Does not apply.

Author contributions

Santiago David Silva Tobar: conception, bibliographic search, writing of the article, analysis of conclusions.

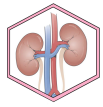
Santiago Martín Camacho Pedroza: bibliographic search, article writing, and graph review.

Both authors read and approved the final version of the article.

Financing

The source of the funding for this article was our resources.

Availability of data or materials



Does not apply.

Statements

Ethics committee approval and consent to participate

Does not apply.

Consent for publication

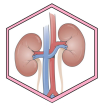
Does not apply when images or photographs of the physical examination or X-rays/CT scans/MRI of patients are not published.

Conflicts of interest

The authors declare that they have no conflicts of interest.

References

1. Patel TS, Freedman BI, Yosipovitch G. An update on pruritus associated with CKD. *Am J Kidney Dis.* 2007 Jul;50(1):11-20. doi: [10.1053/j.ajkd.2007.03.010](https://doi.org/10.1053/j.ajkd.2007.03.010). PMID: 17591521.
2. Hu X, Sang Y, Yang M, Chen X, Tang W. Prevalence of chronic kidney disease-associated pruritus among adult dialysis patients: A meta-analysis of cross-sectional studies. *Medicine (Baltimore).* 2018 May;97(21):e10633. doi: [10.1097/MD.00000000000010633](https://doi.org/10.1097/MD.00000000000010633). PMID: 29794739; PMCID: PMC6392722.
3. Nolan CR. Strategies for improving long-term survival in patients with ESRD. *J Am Soc Nephrol.* 2005 Nov;16 Suppl 2:S120-7. doi: [10.1681/ASN.2005060662](https://doi.org/10.1681/ASN.2005060662). PMID: 16251247.
4. Viceministerio de Atención Integral en Salud Subsecretaría Nacional de Provisión de Servicios de Salud Dirección Nacional de Centros Especializados INFORME TÉCNICO: DNCE-0070-2022 FECHA: 3 de junio de 2022. SITUACIÓN ACTUAL DE TERAPIA DE REEMPLAZO RENAL EN EL ECUADOR. Disponible en: salud.gob.ec/
5. Hu X, Sang Y, Yang M, Chen X, Tang W. Prevalence of chronic kidney disease-associated pruritus among adult dialysis patients: A meta-analysis of cross-sectional studies. *Medicine (Baltimore).* 2018 May;97(21):e10633. doi: [10.1097/MD.00000000000010633](https://doi.org/10.1097/MD.00000000000010633). PMID: 29794739; PMCID: PMC6392722.
6. Bello AK, Okpechi IG, Osman MA, Cho Y, Htay H, Jha V, Weinstein M, Johnson DW. Epidemiology of hemodialysis outcomes. *Nat Rev Nephrol.* 2022 Jun;18(6):378-395. doi: [10.1038/s41581-022-00542-7](https://doi.org/10.1038/s41581-022-00542-7). Epub 2022 Feb 22. PMID: 35194215; PMCID: PMC8862002.
7. Buades JM, -Nart IF,Goicoechea M y col. Documento de información y consenso para el manejo diagnóstico y terapéutico del prurito asociado a la enfermedad renal crónica en pacientes en hemodiálisis en España, *Nefrología*,2023. Doi: <https://doi.org/10.1016/j.nefro.2023.04.006>.
8. Rayner HC, Larkina M, Wang M, Graham-Brown M, van der Veer SN, Eccer T, Hasegawa T, Kleophas W, Bieber BA, Tentori F, Robinson BM, Pisoni RL. International Comparisons of Prevalence, Awareness, and Treatment of Pruritus in People on Hemodialysis. *Clin J Am Soc Nephrol.* 2017 Dec 7;12(12):2000-2007. doi: [10.2215/CJN.03280317](https://doi.org/10.2215/CJN.03280317). Epub 2017 Sep 18. PMID: 28923831; PMCID: PMC5718267.
9. Pisoni RL, Wikström B, Elder SJ, Akizawa T, Asano Y, Keen ML, Saran R, Mendelssohn DC, Young EW, Port FK. Pruritus in hemodialysis patients: International results from the Dialysis Outcomes and Practice Patterns Study (DOPPS). *Nephrol Dial Transplant.* 2006 Dec;21(12):3495-505. doi: [10.1093/ndt/gfi461](https://doi.org/10.1093/ndt/gfi461). Epub 2006 Sep 12. PMID: 16968725.
10. Ring T, Merkus MP, Krediet RT. Physical symptoms and quality of life in patients on chronic dialysis: results of the Netherlands cooperative study on adequacy of dialysis (NECOSAD). *Nephrol Dial Transplant.* 2000 Feb;15(2):280-1. doi: [10.1093/ndt/15.2.280](https://doi.org/10.1093/ndt/15.2.280). PMID: 10648684.
11. Santos-Alonso C, Maldonado Martín M, Sánchez Villanueva R, Álvarez García L, Vaca Gallardo MA, Bajo Rubio MA, Del Peso Gilsanz G, Ossorio González M, Selgas Gutiérrez R. Pruritus in dialysis patients. Review and new perspectives. *Nefrologia (Engl Ed).* 2021 Mar 8;S0211-6995(21)00032-1. English, Spanish. doi: [10.1016/j.nefro.2020.12.010](https://doi.org/10.1016/j.nefro.2020.12.010). Epub ahead of print. PMID: 33707097.
12. Kim JC, Shim WS, Kwak IS, Lee DH, Park JS, Lee SY, Kang SY, Chung BY, Park CW, Kim HO. Pathogenesis and Treatment of Pruritus Associated with Chronic Kidney Disease and Cholestasis. *Int J Mol Sci.* 2023 Jan 13;24(2):1559. doi: [10.3390/ijms24021559](https://doi.org/10.3390/ijms24021559). PMID: 36675074; PMCID: PMC9864517.
13. Balaskas EV, Chu M, Uldall RP, Gupta A, Oreopoulos DG. Pruritus in continuous ambulatory peritoneal dialysis and hemodialysis patients. *Perit Dial Int.* 1993;13 Suppl 2:S527-32. PMID: [8399656](https://pubmed.ncbi.nlm.nih.gov/8399656/).
14. Rhee EP, Guallar E, Hwang S, Kim N, Tonelli M, Moe SM, Himmelrath J, Thadhani RI, Powe NR, Shafi T. Prevalence and Persistence of Uremic Symptoms in Incident Dialysis Patients. *Kidney360.* 2020 Feb;1(2):86-92. doi: [10.34067/kid.0000072019](https://doi.org/10.34067/kid.0000072019). PMID: 32529191; PMCID: PMC7289028.
15. Kimmel M, Alscher DM, Dunst R, Braun N, Machleidt C, Kiefer T, Stülten C, van der Kuip H, Pauli-Magnus C, Raub U, Kuhlmann U, Mettang T. The role of microinflammation in the pathogenesis of uremic pruritus in hemodialysis patients. *Nephrol Dial Transplant.* 2006 Mar;21(3):749-55. doi: [10.1093/ndt/gfi204](https://doi.org/10.1093/ndt/gfi204). Epub 2005 Oct 25. PMID: 16249205.
16. Fazio SB, Yosipovitch, Dellavalle R. et al. Pruritus: Etiology and patient evaluation. 2023 UpToDate.
17. Ständer S, Weisshaar E, Mettang T, Szepletowski JC, Carstens E, Ikoma A, Bergasa NV, Gieler U, Misery L, Wallengren J, Darsow U, Streit M, Metzke D, Luger TA, Greaves MW, Schmelz M, Yosipovitch G, Bernhard JD. Clinical classification of itch: a position paper of the International Forum for the Study of Itch. *Acta Derm Venereol.* 2007;87(4):291-4. doi: [10.2340/00015555-0305](https://doi.org/10.2340/00015555-0305). PMID: 17598029.
18. Yosipovitch G, Bernhard JD. Clinical practice. Chronic pruritus. *N Engl J Med.* 2013 Apr 25;368(17):1625-34. doi: [10.1056/NEJMcp1208814](https://doi.org/10.1056/NEJMcp1208814). PMID: 23614588.



19. Sukul N, Speyer E, Tu C, Bieber BA, Li Y, Lopes AA, Asahi K, Mariani L, Laville M, Rayner HC, Stengel B, Robinson BM, Pisoni RL; CKDopps and CKD-REIN investigators. Pruritus and Patient Reported Outcomes in Non-Dialysis CKD. *Clin J Am Soc Nephrol*. 2019 May 7;14(5):673-681. doi: [10.2215/CJN.09600818](https://doi.org/10.2215/CJN.09600818). Epub 2019 Apr 11. PMID: 30975656; PMCID: PMC6500934.
20. Kim D, Pollock C. Epidemiology and burden of chronic kidney disease-associated pruritus. *Clin Kidney J*. 2021 Oct 14;14(Suppl 3):i1-i7. doi: [10.1093/ckj/sfab142](https://doi.org/10.1093/ckj/sfab142). PMID: 34987777; PMCID: PMC8702817.
21. Ramakrishnan K, Bond TC, Claxton A, Sood VC, Kootsikas M, Agnese W, Sibbel S. Clinical characteristics and outcomes of end-stage renal disease patients with self-reported pruritus symptoms. *Int J Nephrol Renovasc Dis*. 2013 Dec 19;7:1-12. doi: [10.2147/IJNRD.S52985](https://doi.org/10.2147/IJNRD.S52985). PMID: 24379689; PMCID: PMC3872274.
22. Sherjeena PB, Binitha MP, Rajan U, Sreelatha M, Sarita S, Nirmal C, Deepthi NS. A controlled trial of narrowband ultraviolet B phototherapy for treating uremic pruritus. *Indian J Dermatol Venereol Leprol*. 2017 Mar-Apr;83(2):247-249. doi: [10.4103/0378-6323.198464](https://doi.org/10.4103/0378-6323.198464). PMID: 28164894.
23. Weiss M, Mettang T, Tschulena U, Passlick-Deetjen J, Weisshaar E. Prevalence of chronic itch and associated factors in hemodialysis patients: a representative cross-sectional study. *Acta Derm Venereol*. 2015 Sep;95(7):816-21. doi: [10.2340/00015555-2087](https://doi.org/10.2340/00015555-2087). PMID: 25740325.
24. Weisshaar E, Weiss M, Passlick-Deetjen J, Tschulena U, Maleki K, Mettang T. Laboratory and dialysis characteristics in hemodialysis patients suffering from chronic itch--results from a representative cross-sectional study. *BMC Nephrol*. 2015 Nov 4;16:184. doi: [10.1186/s12882-015-0177-3](https://doi.org/10.1186/s12882-015-0177-3). PMID: 26530958; PMCID: PMC4632673.
25. Kumagai H, Ebata T, Takamori K, Muramatsu T, Nakamoto H, Suzuki H. Effect of a novel kappa-receptor agonist, nalfurafine hydrochloride, on severe itch in 337 hemodialysis patients: a Phase III, randomized, double-blind, placebo-controlled study. *Nephrol Dial Transplant*. 2010 Apr;25(4):1251-7. doi: [10.1093/ndt/afp588](https://doi.org/10.1093/ndt/afp588). Epub 2009 Nov 19. PMID: 19926718.
26. Mathur VS, Lindberg J, Germain M, Block G, Tumlin J, Smith M, Grewal M, McGuire D; ITCH National Registry Investigators. A longitudinal study of uremic pruritus in hemodialysis patients. *Clin J Am Soc Nephrol*. 2010 Aug;5(8):1410-9. doi: [10.2215/CJN.00100110](https://doi.org/10.2215/CJN.00100110). Epub 2010 Jun 17. PMID: 20558560; PMCID: PMC2924419.
27. Kimata N, Fuller DS, Saito A, Akizawa T, Fukuhara S, Pisoni RL, Robinson BM, Akiba T. Pruritus in hemodialysis patients: Results from the Japanese Dialysis Outcomes and Practice Patterns Study (JDOPPS). *Hemodial Int*. 2014 Jul;18(3):657-67. doi: [10.1111/hdi.12158](https://doi.org/10.1111/hdi.12158). Epub 2014 Apr 27. PMID: 24766224.
28. Ting SW, Fan PC, Lin YS, et al. Uremic pruritus and long-term morbidities in the dialysis population. *PLoS One*. 2020 Oct 26;15(10): e0241088. doi: [10.1371/journal.pone.0241088](https://doi.org/10.1371/journal.pone.0241088). PMID: 33104746.
29. Ting SW, Fan PC, Lin YS, Lin MS, Lee CC, Kuo G, Chang CH. Association between uremic pruritus and long-term outcomes in patients undergoing dialysis. *J Am Acad Dermatol*. 2020 Sep;83(3):924-925. doi: [10.1016/j.jaad.2020.01.011](https://doi.org/10.1016/j.jaad.2020.01.011). Epub 2020 Jan 12. PMID: 31940463.
30. Mettang T, Kremer AE. Uremic pruritus. *Kidney Int*. 2015 Apr;87(4):685-91. doi: [10.1038/ki.2013.454](https://doi.org/10.1038/ki.2013.454). Epub 2014 Jan 8. PMID: 24402092.
31. Min JW, Kim SH, Kim YO, Jin DC, Song HC, Choi EJ, Kim YL, Kim YS, Kang SW, Kim NH, Yang CW, Kim YK. Comparison of uremic pruritus between patients undergoing hemodialysis and peritoneal dialysis. *Kidney Res Clin Pract*. 2016 Jun;35(2):107-13. doi: [10.1016/j.krcp.2016.02.002](https://doi.org/10.1016/j.krcp.2016.02.002). Epub 2016 Feb 21. PMID: 27366666; PMCID: PMC4919557.
32. Schricker S, Weisshaar E, Kupfer J, Mettang T. Prevalence of Pruritus in a Single Cohort of Long-term Kidney Transplant Recipients. *Acta Derm Venereol*. 2020 Feb 27;100(4):adv00066. doi: [10.2340/00015555-3421](https://doi.org/10.2340/00015555-3421). PMID: 32052851; PMCID: PMC9128945.
33. Krajewski PK, Krajewska M, Szepietowski JC. Pruritus in renal transplant recipients: Current state of knowledge. *Adv Clin Exp Med*. 2020 Jun;29(6):769-772. doi: [10.17219/acem/122174](https://doi.org/10.17219/acem/122174). PMID: 32573994.
34. Krajewski PK, Olczyk P, Krajewska M, et al. Clinical Characteristics of Itch in Renal Transplant Recipients. *Front Med (Lausanne)*. 2021 Jan 20;7:615334. doi: [10.3389/fmed.2020.615334](https://doi.org/10.3389/fmed.2020.615334). PMID: 33553209.
35. Verduzco HA, Shirazian S. CKD-Associated Pruritus: New Insights Into Diagnosis, Pathogenesis, and Management. *Kidney Int Rep*. 2020 May 8;5(9):1387-1402. doi: [10.1016/j.ekir.2020.04.027](https://doi.org/10.1016/j.ekir.2020.04.027). PMID: 32954065; PMCID: PMC7486142.
36. Vernon M, Ständer S, Munera C, Spencer RH, Menzaghi F. Clinically meaningful change in itch intensity scores: An evaluation in patients with chronic kidney disease-associated pruritus. *J Am Acad Dermatol*. 2021 Apr;84(4):1132-1134. doi: [10.1016/j.jaad.2020.06.991](https://doi.org/10.1016/j.jaad.2020.06.991). Epub 2020 Jun 27. PMID: 32603719.
37. Ricardo AC, Hacker E, Lora CM, Ackerson L, DeSalvo KB, Go A, Kusek JW, Nessel L, Ojo A, Townsend RR, Xie D, Ferrans CE, Lash JP; CRIC Investigators. Validation of the Kidney Disease Quality of Life Short Form 36 (KDQOL-36) US Spanish and English versions in a cohort of Hispanics with chronic kidney disease. *Ethn Dis*. 2013 Spring;23(2):202-9. PMID: 23530302; PMCID: PMC3651651.
38. Wulczyn KE, Zhao SH, Rhee EP, Kalim S, Shafi T. Trajectories of Uremic Symptom Severity and Kidney Function in Patients with Chronic Kidney Disease. *Clin J Am Soc Nephrol*. 2022 Apr;17(4):496-506. doi: [10.2215/CJN.13010921](https://doi.org/10.2215/CJN.13010921). Epub 2022 Mar 4. PMID: 35246460; PMCID: PMC8993474.
39. Blankestijn PJ, Vernooij RWM, Hockham C, Strippoli GFM, Canaud B, Hegbrant J, Barth C, Covic A, Cromm K, Cucui A, Davenport A, Rose M, Török M, Woodward M, Bots ML; CONVINCE Scientific Committee Investigators. Effect of Hemodiafiltration or Hemodialysis on Mortality in Kidney Failure. *N Engl J Med*. 2023 Aug 24;389(8):700-709. doi: [10.1056/NEJMoa2304820](https://doi.org/10.1056/NEJMoa2304820). Epub 2023 Jun 16. PMID: 37326323.



-
40. Wikström B. Itchy skin--a clinical problem for hemodialysis patients. *Nephrol Dial Transplant*. 2007 Jul;22 Suppl 5:v3-7. doi: 10.1093/ndt/gfm292. PMID: 17586843. Wu HY, Peng YS, Chen HY, et al. A Comparison of Uremic Pruritus in Patients Receiving Peritoneal Dialysis and Hemodialysis. *Medicine (Baltimore)*. 2016 Mar;95(9):e2935. doi: [10.1097/MD.0000000000002935](https://doi.org/10.1097/MD.0000000000002935). PMID: 26945400.
41. Mettang T, Pauli-Magnus C, Alscher DM. Uremic pruritus--new perspectives and insights from recent trials. *Nephrol Dial Transplant*. 2002 Sep;17(9):1558-63. doi: 10.1093/ndt/17.9.1558. PMID: 12198205.
42. Narita I, Alchi B, Omori K, Sato F, Ajiro J, Saga D, Kondo D, Skatsume M, Maruyama S, Kazama JJ, Akazawa K, Gejyo F. Etiology and prognostic significance of severe uremic pruritus in chronic hemodialysis patients. *Kidney Int*. 2006 May;69(9):1626-32. doi: [10.1038/sj.ki.5000251](https://doi.org/10.1038/sj.ki.5000251). PMID: 16672924.
43. Manns B, Hemmelgarn B, Lillie E, Dip SC, Cyr A, Gladish M, Large C, Silverman H, Toth B, Wolfs W, Laupacis A. Setting research priorities for patients on or nearing dialysis. *Clin J Am Soc Nephrol*. 2014 Oct 7;9(10):1813-21. doi: [10.2215/CJN.01610214](https://doi.org/10.2215/CJN.01610214). Epub 2014 May 15. PMID: 24832095; PMCID: PMC4186509.

DOI: Digital Object Identifier. PMID: PubMed Identifier.

Editor's Note

REV SEN remains neutral concerning jurisdictional claims over published maps and institutional affiliations.
