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Chronic Kidney Disease-Associated Pruritus: Nomenclature and Treatment – We Need to Take Two Steps Forward

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Effective communication between nephrologists is essential to achieve an integration of datasets, better recognition of gaps in knowledge, and development of treatment in different diseases. For this purpose, the international organization Kidney Disease: Improving Global Outcomes (KDIGO) has developed guidelines promulgating definitions, evaluation, and management of different kidney diseases, including a Consensus Conference on kidney function and disease nomenclature [1].

A complication that affects up to 80% of kidney failure patients undergoing hemodialysis is "uremic pruritus" [2]. However, this prevalence in maintenance dialysis patients is highly variable, ranging from 18 to 80% and therefore, reflecting an underestimation of this pathology and its severity. An international registry reported the prevalence of severe pruritus in 21–50% of patients and this prevalence was only estimated by 1% of their physicians [2, 3].

"Uremic pruritus" is a condition that to be diagnosed requires ruling out other conditions that may explain the pruritus as comorbid liver, hematologic, and skin conditions, and medications such as opioids [4]. In addition to the above, "uremic pruritus" is not observed in acute kidney injury, and there is no relation to uremia, reflecting multiple other factors in addition to uremic toxins to explain the pruritus [5]. For these reasons and the requirement to agree on a definition that allows for grouping, analyzing future studies, and reducing the heterogeneity in the prevalence data, the correct term to use should be chronic kidney disease-associated pruritus (CKD-associated pruritus).

The foregoing is essential to continue generating therapeutic advances in CKD-associated pruritus. For this, an approach based on its pathophysiology is key and efforts should not be focused only on the deregulation of the opioid system and the signaling pathways, independent of difelikefalin trial results (a selective κ opioid receptor agonist) [6, 7]. In addition, the conventional associations between CKD-associated pruritus with the levels of serum parathyroid hormone, serum calcium, and phosphate are inconsistent; therefore, we must go further into the pathophysiological mechanisms [8].

Patients with CKD-associated pruritus present an increase in inflammatory cytokines such as INF-γ, IL-2, IL-4, IL-13, IL-6, IL-31, and TNF-α, along with an increase in skin β_2-microglobulin. This interaction between the immune system and the nervous system activates receptors in sensory neurons, triggering the sensation of itching [9].

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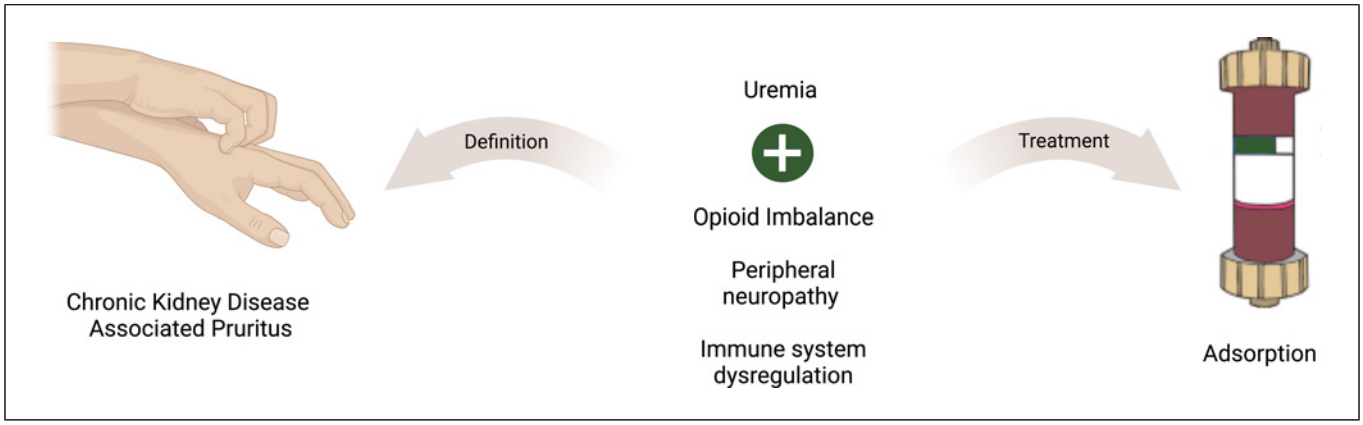

Fig. 1. Pathophysiology and treatment of CKD-associated pruritus.

Currently, there is a direct relationship with respect to inflammatory mediators, the levels of protein-bound uremic toxins, and CKD-associated pruritus [10, 11]. Current therapeutic strategies are not satisfactory in the removal of protein-bound uremic toxins and inflammatory molecules, so new techniques to increase the ability to reduce inflammation are necessary. Hemadsorption overcomes the limitations of other techniques. This has been confirmed by using hemadsorption cartridges combined with hemodialysis (HD) to optimize clearance and correct CKD-associated pruritus and sleep disorders derived from the same problem with good results, regardless of the type of dialysis membrane used (low-flux or high-flux), with greater removal of middle-sized molecules, and large molecular toxins, improving the micro inflammatory state and improve quality of life by significantly improving the intensity of CKD-associated pruritus [12–15]. When comparing hemadsorption + HD versus hemodiafiltration, one study did not show differences between the two techniques in the removal of protein-bound uremic toxins and in middle molecule uremic toxins. However, blood flow, at least 300–350 mL/min, is a crucial factor in achieving the highest efficacy in all HD modalities. Therefore, future studies of hemadsorption + HD on CKD-associated pruritus should maintain the same blood flow as current sessions and not reduce to 200 mL/min as in this study [16]. Consequently, we believe that new studies focused on reducing pruritus with the use of adsorption, with the unification of the definition of CKD-associated pruritus, will allow us to improve the management of this complication (Fig. 1).

The development of new studies with hemadsorption will need a clear determination of the biological plausibility with the use of primary surrogate outcomes (such as the reduction of protein-bound uremic toxins or inflammatory cytokines) and then move forward with trials with longer follow-up, larger sample size, and patient-reported outcomes measures with pruritus scores (e.g., Skindex-10, Kidney Disease Quality of Life 36-item survey, Worst Itching Intensity Numerical Rating Scale, Visual Analogue Scale) [7, 13, 17, 18], to calculate the sample size and improve the clinical outcome that matters most to patients.

Conflict of Interest Statement

C.R. has received funding for lectures and been consultant or advisory board member for Asahi, Astute, B. Braun, Baxter, bioMérieux, Bioporto, CytoSorbents, Estor, Fresenius Medical Care, General Electric (GE), Jafron, Medtronic, and Toray. TR has received funding for lectures and been consultant or advisory board member for AstraZeneca, B. Braun, Baxter, bioMérieux, Boehringer Ingelheim, Contatti Medical (CytoSorbents), Eurofarma, Fresenius Medical Care, Jafron, Lifepharma, and Nova Biomedical. None of the other authors declare any competing interests. The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this article. The authors alone are responsible for the content and writing of this article.

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Author Contributions

G.R.-G., T.R., and C.R. designed the work and drafted the work or substantively revised it; G.R.-G., T.R., and C.C. collected and analyzed the data; and all authors read and approved the final manuscript.

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