End-Stage Renal Disease Chronic Itch and Its Management

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KEYWORDS

• Chronic itch • Chronic kidney disease • Epidemiology • Pathogenesis • Quality of life • Treatment

KEY POINTS

- End-stage renal disease chronic itch is a frequent symptom that bothers patients with advanced stages of chronic kidney disease.
- The pathogenesis of the chronic itch symptom is complex and not yet fully understood and includes many metabolic, immunologic, and neurogenic factors.
- A significant burden of the disease results in decrease of quality of life with sleep impairment, depressive symptoms, and increased mortality of affected individuals.
- No treatment of choice is available; topical therapy (emollients), phototherapy (UV-B), and systemic therapy (antiepileptics, opioid agonists, and antagonists) provide significant relief in varying percentages of patients

INTRODUCTION

Chronic kidney disease (CKD) is a major problem worldwide because it is encountered in approximately 13% of the population (stages 1–5), whereas in 11% it is present in advanced stages 3 to 5.[1] CKD is a problem of growing importance because the elderly population is increasing, along with the number of patients suffering from diabetes or hypertension. CKD is defined as abnormalities of kidney structure or function that are present for more than 3 months.[2] To diagnose CKD, at least one criterion has to be fulfilled: decreased glomerular filtration rate (GFR) (<60 mL/min/1.73 m^2) or markers of kidney damage, such as albuminuria, urine sediment abnormalities, electrolyte and other abnormalities associated with tubular disorders, histologic abnormalities, structural abnormalities detected by imaging, and a history of kidney transplantation. CKD is divided into 5 stages according to GFR, the fifth being characterized by GFR < 15 mL/min/1.73 m^2, also termed end-stage renal disease (ESRD). CKD is associated with numerous complications, such as anemia, hyperlipidemia, nutrition, osteodystrophy, or cardiovascular risk,[3] to mention just a few. Cutaneous manifestations of CKD are profuse and especially marked in ESRD, including skin color alterations, elastosis, ecchymoses, xerosis, and pruritus, but also specific disorders, such as acquired perforating disorders, disorders with metastatic calcification, or bullous disorders of hemodialysis (HD).[4]

Chronic itch (CI) is a frequent symptom in the general population and systemic diseases, posing a high burden and decrease in quality of life (QoL) of an affected individual.[5] CI is defined as an itch that lasts for more than 6 weeks. According to the International Forum for the Study of Itch (IFSI), the etiologic classification of chronic

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pruritus comprises 6 categories: (I) dermatologic, (II) systemic, (III) neurologic, (IV) psychogenic/psychosomatic, (V) mixed, and (VI) others.[6] One of the most important causes of systemic itch is end-stage renal disease–associated chronic itch (ESRDCI). Since its first description in 1932 coined "uremic itch,"[7] it remains a common problem impairing the QoL of patients and a significant therapeutic challenge for physicians specializing in dermatology and nephrology. Although numerous proposed etiologic factors have been explored, the cause is unclear and may involve several mechanisms.

DISCUSSION

Definition

ESRDCI or another more commonly used term, uremic pruritus, is defined as CI observed in patients with CKD with significant abnormal renal function with advanced stages of renal damage.[8] Establishing the diagnosis is based on exclusion of other possible causes. It is necessary to diagnose CKD beforehand. It must be emphasized that acute kidney injury is not considered an eliciting factor of CI.

Epidemiology

Epidemiologic aspects of ESRDCI vary according to data presented in the literature, especially when newer reports are taken into account. In the early 1970s, 85% of patients on dialysis could have suffered from CI, decreasing to 50% to 60% at the end of 1980s.[9] A large multicenter study by Pisoni and colleagues[10] (Dialysis Outcomes and Practice Patterns Study, DOPPS) of 18,801 hemodialysis patients revealed that 42% of them suffered from CI. Interestingly, pruritus was a predictor of a 17% higher mortality. Weiss and colleagues[11] analyzed the data from 860 HD patients attending German dialysis units. The point prevalence of CI was 25%, and 12-month prevalence reached 27%, whereas lifetime prevalence was estimated to be 35%. Interestingly, patients aged less than 70 years complained of CI more often than those aged 70 and older. One Korean study demonstrated that CI was more prevalent among patients on peritoneal dialysis (PD) (n = 223) than those on HD (n = 425), with the prevalence estimated at 62% and 48%, respectively (P = .001).[12] Regarding patients on PD (n = 30), Tessari and colleagues[13] reported that 52.1% of patients suffered from CI, and these figures were similar to those regarding patients on HD (n = 135). A Polish study revealed that among children suffering from CKD (stages 3–5) (n = 103) CI is present in 20.8% of cases.[14] Moreover, the percentages were comparable among different treatment methods: 18.4% in conservative treatment group and 23.5% in the group on dialysis (HD or peritoneal). In a study comprising 171 individuals on HD, Heisig and colleagues[15] reported that 52.6% of patients complained of itch in the past, whereas in 46.2% of itch was present within the last 3 days.

Notwithstanding the abundance of ESRDCI reports focusing on patients on HD or PD, there are also epidemiologic reports focusing solely on patients with CKD not yet on dialysis. Solak and colleagues[16] evaluated 402 predialysis patients with CKD stages 2 to 5 and itch was present in 19%, regardless of CKD stage. Another study demonstrated that in stages 4 to 5 of CKD pruritus was reported by 56% of patients.[17] Murtagh and colleagues[18] evaluated 66 patients with CKD stage 5, reporting that itch was experienced by 74% of individuals.

Pathogenesis

Pathogenesis of ESRDCI is not fully understood, and various factors are described as contributing to the development of this symptom (**Box 1**). Renal failure leads to changes in blood urea nitrogen and creatinine, resulting in a certain "metabolic

Box 1
Important factors associated with the development of end-stage renal disease chronic itch

- Metabolic disequilibrium (increased levels of urea, creatinine)
- Xerosis (skin dryness)
- Vitamin A
- Low vitamin D
- Divalent ions (eg, calcium)
- PTH
- Phosphorus
- Mast cells
- Tryptase and chymase
- Histamine
- Serotonin
- Microinflammation (Th1/Th2 lymphocyte dysregulation, abundance of proinflammatory cytokines)
- HCV
- μ-Opioid overexpression and κ-opioid downregulation
- Neuropathy