Itch and Ache on Dialysis: New Approaches to Manage Uremic Pruritus and Restless Legs

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Keywords

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Abstract

Background: Uremic pruritus (UP) and restless legs syndrome (RLS) are highly prevalent complaints among patients with end-stage renal disease (ESRD) undergoing chronic dialysis. These chronic troublesome symptoms lead to a significant decrease in quality of life (QOL) and increase in mortality rate. Despite their distressing characteristics, these symptoms usually remain under-recognized by health-care providers. Therefore, careful history intake, and step-wise treatment are essential. Numerous pharmacological and non-pharmacological treatments have been demonstrated to help in controlling these 2 conditions. **Summary:** In this review, we discuss the latest findings regarding UP and RLS among ESRD patients on maintenance dialysis. We also examine different treatment options in this group of patients. The majority of these patients do not have the opportunity to receive a kidney transplant and need other treatments for these burdensome symptoms in order to improve their QOL and prognosis. **Key Messages:** UP and RLS are common but underdiagnosed conditions in ESRD patients on maintenance dialysis that are related to a decline in pa-

tients' QOL and poor prognosis. The pathophysiology of these conditions remains not well understood. Therefore, controversies still exist on treatment options. Treating these conditions provides an opportunity to improve the health-related QOL and outcomes of dialysis patients.

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Introduction

Patients with end-stage renal disease (ESRD) undergoing chronic maintenance dialysis frequently experience burdensome physical and psychiatric symptoms directly affecting their quality of life (QOL). Uremic pruritus (UP) and uremic restless legs syndrome (RLS) are frequent complaints of this group of patients compared to the complaints among the general population [1]. However, based on evidence, despite the overwhelming characteristics and high frequency, these symptoms remain under-recognized and under-treated by dialysis providers [2]. In the light of significant associations between uremic RLS and UP with poor QOL and increased risk for mortality [3–5], recognition and treatment of these disorders especially in individuals undergoing chronic dialysis is strongly indicated. In this mini-review, we discuss the latest findings regarding UP and RLS among

ESRD patients on maintenance dialysis. We also examine different treatment options in this group of patients. The majority of these patients do not have the opportunity to receive a kidney transplant and need other treatments for these burdensome symptoms in order to improve their QOL and prognosis.

Uremic Restless Leg Syndrome

RLS refers to complaints of an unpleasant sensation in the legs accompanied by an irresistible urge to move them. This syndrome's symptoms are circadian and usually begin in the evening. RLS symptoms worsen during periods of inactivity and rest and are transiently relieved by movement [6]. The estimated prevalence of RLS in the general population has been reported 3.9–15%. Among ESRD patients undergoing maintenance dialysis, the prevalence of RLS ranges from 6 to 60% [7, 8] with higher prevalence in females [9]. Moreover, uremic RLS has been shown to be associated with the duration of the dialysis session [8]. This increased incidence can be partly explained by the inactivity during dialysis exacerbating or triggering RLS symptoms.

As RLS can lead to insomnia, it is considered a separate sleep disorder. Evidence of muscle atrophy has also been observed in uremic RLS [10]. This syndrome is associated with decreased QOL and increased prevalence of anxiety and depression particularly among individuals undergoing hemodialysis (HD) [11]. Additionally, increased risk for cardio/cerebrovascular events and mortality has been demonstrated among these patients [3, 12]. Uremic RLS still remains an underdiagnosed clinical condition, and higher awareness of the physicians is required.

Pathophysiology

The pathophysiology of RLS in ESRD remains poorly understood. According to the most widely accepted hypotheses for RLS, abnormal iron metabolism in specific brain regions contributes to dopaminergic dysfunction, dysfunction of the central opiate system, damaged peripheral nerves and genetic predisposition [13]. Sub-clinical peripheral nerve abnormalities are observed in uremic RLS [14]. Uremic toxins may serve as contributors of uremic RLS, since this problem in the majority of cases improves after successful kidney transplantation [15].

Special attention has been placed on finding the genetic basis of RLS both in the general population and in ESRD patients. In a meta-analysis, Schormair et al. [16] identified potential molecular targets in RLS in European individuals. They reported that MEIS1 (as a transcriptional regulator, as well as, a transcriptional activator, located on 2p14), was confirmed as the strongest genetic risk factor RLS (OR 1.92, 95% CI 1.85–1.99). Previously, Schormair et al. [16] demonstrated that the BTBD9 gene (is known to be involved in protein-protein interactions, located on 6p21.2), correlates with uremic RLS in ESRD patients from Germany and Greece, hence, contributing to the genetic susceptibility to RLS in this group of patients [16].

Another study suggested possible pathological roles for homocysteine and high parathyroid hormone (PTH) levels, which results in calcium-phosphate product imbalance in patients on HD [17]. Recently, a correlation between C-reactive protein (CRP)/albumin ratio—a biomarker of peripheral inflammation and oxidative stress—and RLS has been suggested [18].

Management of Uremic Restless Leg Syndrome

Management of RLS in ESRD patients on maintenance dialysis is still challenging. Improved understanding of the pathophysiology in uremic RLS would enhance treatment strategies. Nonetheless, treatment can be divided into 2 general approaches; pharmacological and non-pharmacological. This condition may ameliorate by using either pharmacological or non-pharmacological treatments, or by a combination of these 2 approaches.

Non-pharmacological approaches for uremic RLS may effectively mitigate symptoms. In the general population, the approaches to mitigate RLS include maintaining good sleep hygiene, decreasing tobacco, alcohol, and caffeine use, increasing exercise, and discontinuing any medications that may exacerbate RLS. In addition, transcranial stimulation, pneumatic compression, vibrating pads, and acupuncture are emerging as interventions to study RLS. Participation in aerobic exercise training programs not only improves QOL and ameliorates the uremic RLS severity in HD patients, but also decreases the mortality rate [3]. Additionally, a combination of low dose dopamine agonist with exercise would be an alternative to high-dose dopamine agonists in these patients [3]. A multicenter, prospective, cohort study of short home HD with a planned 12-month follow-up by Jaber et al.

[19] showed that short HD sessions (6 sessions per week) after 12 months resulted both in significant improvement in RLS symptoms' severity score and reductions of sleep disturbances.

The pharmacological management of uremic RLS has been under-studied. Most commonly prescribed medications with the highest levels of evidence with this regard are gabapentin and non-ergot dopamine agonists such as ropinirole, rotigotine, and pramipexole. These agents have been approved by both the U.S. Food and Drug Administration and by the European Medicines Agency [3, 20]. Other studies have suggested that vitamin C supplement can play a role in controlling RLS by different mechanisms; as an antioxidant by decreasing inflammation and by increasing iron absorption from the gastrointestinal tract, iron bioavailability and metabolism. However, the beneficial effect of iron or erythropoietin supplementation on uremic RLS remains controversial [15]. Likewise, both vitamins E and C can increase dopamine synthesis [3]. Folate substitution may ameliorate uremic RLS as well [17].

In addition to all other benefits, kidney transplantation reduces symptoms of uremic RLS [15, 21]. There is evidence that parathyroidectomy improves RLS in HD patients [22]. However, this observation was drawn from a single-center, small unblinded study that should be tested in other settings and more rigorous designs.

Uremic Pruritus

UP is another common unpleasant symptom among patients with advanced kidney failure including individuals on chronic maintenance dialysis. UP does not present with a distinguished dermatomal pattern and can vary from localized itch to a generalized itch over the whole body surface. More than 40% of patients undergoing HD [2, 23, 24] and >60% of patients on peritoneal dialysis (PD) [24] report this chronic condition. UP has been reported more frequently among men [4]. This intrusive symptom has been associated with decrements in health-related QOL and is associated with depression and increased risk of death [4, 5]. UP is also associated with 2-year cardiovascular mortality in patients on maintenance HD [25]. Despite its distressing characteristics, this symptom is under-recognized by dialysis providers.

Clinical manifestation of UP may vary significantly in different patients and over time. In general, UP is a bilateral discontinuous itch that is more intense at nights and

can interfere with normal sleep. UP usually persists for a long time (months to years).

This condition has been associated with lower dialysis adequacy [26], use of low-flux (vs. high flux dialyzers) [26], hepatitis C virus positivity [4], higher serum CRP levels [27], higher serum calcium and phosphorus levels [4], current or recent smoking [4], older age [4], underlying depression [4], and elevated ferritin levels [28].

Uremic Pruritus in Patients on Peritoneal Dialysis versus Hemodialysis

Considering different modalities of dialysis, determinants, prevalence, severity, and outcomes of UP may differ between these 2 groups of chronic dialysis patients. A study by Min et al. [24] demonstrated that prevalence and intensity of UP were higher in patients on PD compared with HD patients. However, their results did not show any significant correlation between UP and all-cause mortality neither in HD nor in PD. Also, they found that UP was independently related to serum albumin levels in HD and total Kt/V in PD [24]. Likewise, the Dialysis Outcomes and Practice Patterns Study reported similar results regarding the relationship between serum albumin levels and intensity of UP in HD patients [4]. Ko et al. [26] reported similar results regarding an association between lower Kt/V and exacerbation of UP in HD patients. A prospective cohort study by Badiie Aval et al. [29] reported that UP in patients on PD had several independent determinants such as higher protein intake, longer duration of dialysis, higher blood levels of intact PTH, and higher CRP [30]. Badiie Aval et al. [29] reported that serum aluminum levels can be associated with the development of UP in HD patients [31]. This study was limited by a cross-sectional design and also lacked data on aluminum intake in diet or water.

Pathophysiology

The exact pathogenesis of UP remains unknown. Various substances have been suspected as pruritogens. Likewise, microinflammation has been suggested as a reason for UP. Persistent UP improves following parathyroidectomy among patients with uncontrolled secondary hyperparathyroidism. This observation led to the hypothesis that PTH may play a role in the pathogenesis of UP [23].

Xerosis cutis (abnormally dry skin) is another suspected factor for UP [2, 23]. Increased tissue concentrations of Vitamin A and metastatic microcalcifications caused

by calcium and magnesium salts as pruritogens in UP have been implicated and this observation remains controversial as well [23]. Researchers at an HD center in Taiwan showed that increased concentration of serum lead and aluminum levels directly correlate to UP [31, 32]. The major source of aluminum in maintenance HD patients is water used for dialysate solution and aluminum containing phosphate binders [31].

Elevated levels of CRP and relatively increased T-Helper1-cells and interleukin-6 concentrations in serum of HD patients have been considered microinflammatory factors causing pruritus [33]. Badiie Aval et al. [29] showed a correlation between interleukin-31 and intensity of UP [34]. Due to unresponsiveness of UP to antihistamines as treatment agents, the role of histamine is questionable [23].

Proliferation of the pruritus-mediating nerves has been suggested as another pathogenic mechanism for UP. Uremic itch substantially ameliorates after the oral application of the μ -opioid receptor antagonist naltrexone. These clinical observations led to the hypothesis that more intense stimulation of the central μ -opioid receptors by increased endorphins and accumulated endogenous morphine level can be causes for UP [23]. A recent study evaluated serum levels of neurotrophin-4 in uremic patients with and without pruritus compared to control subjects. Their results showed significant correlation between serum neurotrophin-4 levels and severity of UP [35].

Management of Uremic Pruritus

Treatment of UP is still a frustrating endeavor and there is no consensus about its management. The lack of effective known therapies originates from inadequate knowledge and understanding regarding underlying pathophysiological mechanisms. Various empiric treatment modalities including pharmacological, non-pharmacological, or combined treatment modalities have been tested and novel agents are also under study.

Physicians recommend a stepwise management of UP beginning with optimizing the dialysis modality, skin rehydration therapy, and nutrition. Considering xerosis as a strong etiology of pruritus in ESRD patients, daily skin rehydration therapy using emollients should be considered baseline treatment modality [23]. HD prescription modification has been suggested as a reasonable approach for UP management. High-flux HD, hemodiafiltration with hemoperfusion and high-permeability HD are HD alternatives that may significantly relieve UP [36]. Lower-

ing PTH levels in patients with high PTH and therefore optimization of calcium and phosphorus levels have been reported as another alternative [5]. Ultraviolet B phototherapy has been reported as an effective add-on therapy among PD patients with refractory UP. However, the increased risk of skin malignancy over a long-term period should be considered another serious side effect [23]. A systematic review and meta-analysis by Badiie Aval et al. [29] confirmed the effectiveness of acupuncture and acupressure as alternative therapy in treatment of UP non responsive to other treatments.

Based on different studies, anticonvulsants gabapentin and pregabalin, by centrally acting on alpha2-delta protein, an auxiliary subunit of voltage-gated calcium channels, are 2 viable medications for managing UP [23, 37]. Based on a hypothesis considering an imbalance between the activities of the mostly antagonistic acting μ – and kappa-opioid receptors in favor of μ -receptor activation, application of the kappa-agonist Nalfurafine was recommended for the treatment of uremic itch. Results of a systematic review and meta-analysis showed the antipruritic effect of this medication on managing uremic itch. Nonetheless, insomnia is a side effect of this agent that hinders its application for treating uremic itch [38].

Taking inflammation into account as an etiology, the efficacy of Montelukast, a leukotriene receptor antagonist, on UP especially on refractory itch has been reported [39]. Additionally, the anti-depressant sertraline, by modulating inflammatory markers and cytokines, has been put forward as an option for managing uremic itch. The fact that there is no need to adjust the dosage in ESRD patients makes sertraline a choice for managing this problem [40]. Furthermore, topical immunosuppressant ointments with tacrolimus and pimecrolimus revealed intensity reduction of UP [37]. Cromolyn sodium, by stabilizing mast cells, has been shown as another option for reducing UP intensity [37]. Natural oils, capsaicin, turmeric, and herbal agents have been studied for controlling uremic itch [36, 37]. However, definite treatment for refractory UP would be kidney transplantation.

Conclusion

Patients with ESRD are frequently affected by chronic symptoms and problems that have negative impact on their health-related QOL and result in poor sleep. RLS and UP are 2 major complaints that frequently overlap and co-exist. Despite their high prevalence, these syndromes are often overlooked by health care providers. Thus, obtaining

careful history is crucial to recognizing and treating these conditions. Considering available resources, providers should approach treatment based on patient preference, potential interactions between medications and adverse drug reactions. Treatment methods as aforementioned in this review can be stepwise and can vary from encouraging behavior modifications, non-pharmacologic and pharmacologic approaches. The stepwise treatments approaches can begin with non-pharmacologic therapies. The next steps to pharmacologic therapies should factor in severity of symptoms, impact of symptoms, and side effects along with patient preference. New pharmacologic and non-pharmacologic approaches are emerging to address UP and RLS among patients on maintenance dialysis.

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Author Contributions

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