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Effect of chronic kidney diseases-associated pruritus on patients' sleep quality, well-being and its management

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Abstract: Chronic kidney diseases-associated pruritus **(**CKD-aP) affects the patients' mental and physical health, potentially resulting in fatigue, depression, and directly affecting quality of sleep. Hemodialysis patients were reported to experiencing moderate to extreme CKD-aP, thus exhibited higher possibilities of remaining awake at night while sleeping in the day. Therefore, CKD-aP is attributed toward nocturnal awakenings and difficulty falling asleep. This condition (CKD-aP) significantly impacts the quality of life (QOL), triggering sleep disturbance, mood changes, and uncontrollable scratching. CKD-aP patients have a compromised QOL that is generally linked to limited personal freedom and control due to lengthy treatment time. Overall, the loss of freedom has wider implications, such as altering marital, family, and social relationships. Thus, this writing highlights the vital effect of chronic kidney diseases-associated pruritus on patients' sleep quality, social and mental well-being and providing comprehensive management and treatment options to improve patients' quality of life.

Keywords: chronic kidney diseases-associated pruritus; Malaysia; Pakistan; sleep quality; well-being; management

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INTRODUCTION

Chronic kidney diseases-associated pruritus **(**CKD-aP) influences the patients' mental and physical capacity, resulting in fatigue, depression, and quality of sleep[1–6]. Hemodialysis patients, experiencing moderate to extreme CKD-aP, exhibit higher chances of being awake at night while sleeping in the day. Hence, CKD-aP is attributed toward nocturnal awakenings and difficulty to sleep[2,3,7,8]. Pruritus is an undesirable disorder that stimulates itching and could negatively affect sleep quality and affecting the quality of life[9]. CKD-aP significantly influences patients' quality of life, causing sleep disturbance, mood changes, and uncontrollable scratching[10]. CKD-aP could cause serious problems such as discomfort, anxiety, depression, sleep disorders, and an overall negative effect on one's physical and mental health. About 42% of chronic kidney disease patients on dialysis experienced CKD-aP with intensity from moderate to severe, and also correlated with other health-related complications such as poor sleeping quality and poor quality of life[1]. Sleep disorders account for chronic fatigue which is connected with disturbed day and night rhythm, causing a negative impact on physical and mental ability[11]. Furthermore, CKD-aP is associated to higher risk of mortality in dialysis patients[10].

Chronic inflammatory skin diseases such as pruritus, psoriasis, and atopic eczema have a considerable impact on CKD patients QOL, including psychological health, physical well-being, family relationships and social development[12]. Among all the psychological complications, depression is common and has a serious impact on the quality of life of CKD patient and their caregivers.

It has a negative impact on social, economic, and psychological well-being[13]. CKD-aP has a substantial effect on patients QOL as it may cause serious discomfort, depression, anxiety[11] Depression is more frequently seen in CKD patients mainly between the 3rd to 9th years of treatment, with mostly female patients being affected. Depression is exhibited mainly in the form of sadness, anxiety, depressed mood, poor self-esteem, pessimism about the future, decreased libido, sleeps disorders, and reduced appetite[14].

Quality of life of patients having CKD is adversely affected by rising intensity of CKD-aP; and is correlated with higher mortality risk[15]. CKD-aP patients have a compromised QOL that is mostly linked to limited personal freedom and control due to lengthy treatment time. Generally, the loss of freedom has wider implications, altering marital, family, and social relationships[16]. CKD-aP has a negative impact on the social well-being of female patients on hemodialysis as compared to male patients[17]. A strong association exist between QOL score and CKD-aP intensity; therefore treating CKD-aP may improve the QOL of CKD patients[15]. CKD-aP should be frequently assessed and effectively managed to reduce associated morbidity, mortality and to improve the overall quality of life.

GUIDELINES FOR THE MANAGEMENT OF CKD-AP

CKD-aP is graded as one of the most common dermatological complications among patients on hemodialysis. Due to the refractory nature of CKD-aP and its unknown pathophysiology, there is no definitive cure for its management. Even though a wide range of therapeutic agents has been utilized for its management, however no therapy has been established for proper management of CKD-aP. Based on the proposed hypothesis for the pathogenesis of CKD-aP, different treatment options shall be discussed in this writing.

Alteration in hemodialysis techniques

Studies have suggested the role of optimum dialysis rates along with the use of dialyzer membranes can play a role in CKD-aP. The increasing dose of dialysis may improve CKD-aP[18–20]. Shaldon (1993)[21] suggested that short dialysis sessions and underdialysis could lead to patient malnutrition and death. Indeed, dialysis time of fewer than three hours and 30 minutes has been associated with a doubled rate of patient mortality as compared to patients dialyzed for four hours and being dialyzed thrice weekly. Likewise, among dialysis patients, clearance was strongly correlated with an increased duration time of dialysis[22]. High-flux hemodialysis is one the most frequent blood purification method used worldwide, but in developing countries, low-flux dialysis is the main method of extracorporeal blood purification therapy due to poor economic conditions. This method is not effective in removing the middle-molecule uremic toxins that contributes toward CKD-aP[23]. Ko *et al.* (2013)[24] also supports the notion that use of low-flux dialyzer has significant association with the aggravation of CKD-aP. As the high flux dialyzers efficiently remove average-sized molecules[25]. The occurrence of CKD-aP can be reduced by use of high flux hemodialysis, as it significantly contributes toward better improvement in patients' CKD-aP intensity[26,27]. Chen *et al.* (2009)[28] reported the use of high permeability hemodialysis (ultrafiltrate coefficient, 40 mL/h/mm Hg) in having significant improvement in CKD-aP with high-permeability as compared to conventional hemodialysis (ultrafiltrate coefficient, 5.5 mL/h/mm Hg). The use of hemodiafiltration with hemoperfusion is also effective in relieving CKD-aP[29]. The intensity of CKD-aP is also reduced by the use of biocompatible dialysis membrane (polymethylmethacrylate [PMMA])[30,31].

Local pharmacological therapies (Topical treatments)

Emollients and topical analgesic agents

Emollients such as high-water-content emollient[32,33], glycerol and paraffin[34] are the favored topical treatment of CKD-aP if xerosis (dry skin) is present. Aqueous gels with higher water content (containing 80g of water and 20g of aloe vera extract, squalane, naturally-derived vitamin E, silk powder with no artificial and synthetic substances) can help to relief discomfort of CKD-aP[33]. Topical analgesic agents are also useful in the treatment of CKD-aP such as Pramoxine HCl 1% lotion is reported to be useful in relief of CKD-aP[35]. Multiple studies showed that Topical Capsaicin 0.025% cream were effective for localized CKD-aP[36–38]. Suzuki *et al.* (2015)[39] stated that capsaicin act by desensitization of nociceptive nerve endings depletion of substance P causing blocking of the conductor of pruritus.

Tacrolimus ointment

The effects of Tacrolimus ointment in relieving CKD-aP is uncertain. With some studies indicating that it is effective in relieving CKD-aP[40,41], nevertheless, in a randomized control trial, Tacrolimus 0.1% ointment showed no effect of among patients on hemodialysis over control group[42].

Topical cromolyn sodium

The use of topical cromolyn sodium 4% was reported as more effective in decreasing CKD-aP as compared to placebo[43].

Gamma linolenic acid (GLA) enriched Cream

Chen *et al.* (2006)[44] reported that Gamma linolenic acid enriched cream contributes significantly improvement in CKD-aP severity.

Sarna and Eurax Lotions

Both Sarna lotion (0.5% of each camphor, menthol, and phenol) and Eurax lotion (10% crotamiton) has been reported to be effective in improving CKD-aP[45].

Systemic therapies

Although local pharmacological therapies are effective for the management and treatment of localized CKD-aP, yet for the management of generalized CKD-aP, systemic

therapies are used and shall be discussed here:

Oral histamines

Antihistamines are a widely used to relieve itch. They are classified into 2 categories: "histamine receptor antagonists such as hydroxyzine, diphenhydramine, loratadine, or cetirizine and medications that prevent the release of histamine like the mast cell stabilizers cromolyn sodium and ketotifen"[46].

Researchers reported that the used of histamine receptor antagonist for the management of pruritus and antipruritic activity have been generally unsuccessful[47–49]. Furthermore oral antihistamnes cannot be recommended as first line option for treatment of pruritus due to dangerous side effect[46]. While mast cell stabilizers are reported to be effective in the management of pruritus. It is stated that CKD-aP severity is reduced by using Ketotifen therapy[50,51], Cromolyn sodium[52,53], Zinc sulfate[54,55] and Nicotinamide[56].

Gabapentin and pregabalin

The use of neuroleptic agents such as gabapentin and pregabalin to manage CKD-aP has increased. But patients should be monitored closely for potential side effects from these agents.

Many studies reported favorable effects of gabapentin in treating CKD-aP. Studies showed that intervention with Gabapentin 100mg[51,57]; gabapentin 300mg[58–60] and gabapentin 400mg[61] could significantly improve CKD-aP intensity. Kobrin (2017)[62] stated that Gabapentin 100mg is the preferred initiating dose after each dialysis session, and the dose may be gradually increased to 350mg daily. However, a dose greater than 350mg daily are not recommended in dialysis patients.

Pregabalin could be used in patients who are unable to tolerate Gabapentin[63]. Pregabalin 25mg daily is the preferred initiating dose and can be gradually increased to 75mg daily. Dose greater than 75mg daily are not recommended in dialysis patients[64]. While Pregabalin 50mg[65] and Pregabalin 75mg[66] were reported to improve CKD-aP intensity significantly.

Opioid imbalance treatment

The overstimulation of central mu-opioid receptors or antagonism of kappa-opioid receptors is a contributing factor in CKD-aP. Therapies treating the opioid imbalance are employed to improve CKD-aP among patients.

Studies showed that Mu-opioid receptor antagonists such as Naltrexone 50mg were effective in the relief of pruritus[67]. But a study by Pauli-Magnus *et al.* (2000)[68] indicated no effect of Naltrexone in the relief of pruritus [68]. Kappa opioid receptor agonists indicated good result in CKD-aP patients on hemodialysis, and the widely used kappa opioid receptor agonist is Nalfurafine[69]. Nalfurafine 2.5μg[70] and Nalfurafine 5μg[69,70] displayed effectiveness in management of CKD-aP. Furthermore Nalbuphine hydrochloride 60 mg and 120mg extended-release tablet (mu-opioid receptor antagonist and kappa opioid receptor agonist) were reported as effective in the management of CKD-aP[71,72].

Other Systemic Treatments

Thalidomide 100mg[73], Montelukast 10mg[74], Cholestyramine 5gm[75], sertraline (selective serotonin reuptake inhibitor)[76–78] were reported as effective in the management and reduction of CKD-aP.

PHOTOTHERAPY

Studies were conducted and indicated potential effects of phototherapy on CKD-aP. The narrowband ultraviolet B phototherapy[79,80] was reported to be effective in the management of CKD-aP. However, study by Ko *et al.* (2011) [81] indicated that narrowband ultraviolet B phototherapy showed no significant improvement in CKD-aP. Nevertheless the potential carcinogenic effect of ultraviolet radiation requires serious consideration[82]. While Hsu *et al.* (2009)[83] reported that thermal therapy with far-infrared rays could effectively improving CKD-aP intensity.

ALTERNATIVE TREATMENT

Alternative therapies such as acupressure, acupuncture and homeopathic verum medication were used for treatment and management of CKD-aP. Acupressure therapy at LI-L11 point[84] and auricular acupressure[85] were stated to be effective in the management of CKD-aP. Acupuncture therapy which block spinal cord release of opioid-like substances, if applied at Quchi (LI11) acupoint is an easy, safe and effective ways in relieving CKD-aP[86]. A systematic review on acupuncture for treatment of CKD-aP in end-stage renal disease patients reported the beneficial effect of acupuncture intervention but also reported the high risk of bias[87].

ASSESSMENT OF SLEEP QUALITY AND QUALITY OF LIFE

Several validated and self-designed questionnaires were used to assess the sleep quality and quality of life among patients having CKD-aP undergoing dialysis.

Validated questionnaires for sleep assessment

The Pittsburgh sleep quality index (PSQI)

Pittsburgh sleep quality index (PSQI) is one of the most commonly used questionnaires for assessment of sleep quality among CKD-aP patients[88–91]. It assess the self-rated sleep quality over the past one month. This questionnaire consists of "19 items and seven domains: subjective sleep quality, sleep duration, sleep latency, sleep disturbances, habitual sleep efficiency, use of sleep medication, and daytime dysfunction", and responses were rated on a 4-point Likert scale[92,93]. The overall score was calculated by totalling the scores of the seven domains (range: 0 to 21)[94]. PSQI score of 5 and ≥ 5 were classified as bad sleepers and PSQI < 5 classified were as good sleepers[94].

Epworth Sleepiness Scale

The Epworth Sleepiness Scale (ESS) is a simple and inexpensive measure for evaluation of daytime sleepiness, it is a questionnaire comprised of 8 items. The questionnaire rates

the responses of sleepiness in 8 daily situations ranging from 0 to 3, giving a total score of 0 (no daytime sleepiness) to 24 (the most excessive daytime sleepiness). The score equal to or greater than 10 is the cutoff point for excessive daytime[95,96].

Sleep and Health Questionnaire

The Sleep and Health Questionnaire (SHQ) comprised of 16 questions that were grouped into 5 factors "self-reported breathing disturbances, functional impact of sleepiness, roommate-observed breathing disturbances, driving impairment, and insomnia"[97]. Most of the responses to the questionnaire utilized either a 5-point frequency scale "never", "rarely", "sometimes", "frequently" and "always" ; or by the use of a 6-point Likert scale which graded the severity of the symptoms "1–2 points (not affected); 3–4 points (mild); 5 points (moderate); 6 points (severe)"[97].

Itch Medical outcome study (Itch MOS)

The Itch Medical outcome study (Itch MOS) was developed from the Medical Outcomes Study sleep questionnaire[98]. The itch MOS instrument contained 10 questions assessing the effect of itch on sleep disruption, sleep latency and daytime somnolence[46].

Validated questionnaires for quality of life and sleep assessment combine

Kidney Disease Quality of Life Short Form (KDQOL)

Kidney Disease Quality of Life Short Form (KDQOLSF) is one most valid and reliable questionnaire for assessment of the QOL of CKD patients. It encompassed 3 domains: "Kidney disease component score (KDCS) comprising of effect of kidney disease, symptoms, work status, burden of kidney disease, sleep, cognitive function, sexual function, social support, quality of social interaction, patient satisfaction and dialysis staff encouragement". The Physical Component Score (PCS) included "physical functioning, role functioning, general health perceptions and pain", while Mental Component Score (MCS) consist of "energy/fatigue, social function, role emotional and emotional well-being"[99].

Short-Form Health Survey (SF-12 and SF-36)

The Short-Form Health Survey (SF-12) is one of the most widely used tools for assessing health-related quality of life, it is originally developed from the Medical Outcomes Study (MOS) 36-item Short-Form Health Survey SF-36[100]. The SF-12 is a health-related quality of life questionnaire containing 12 questions measuring 8 health domains to assess physical and mental health. "Physical health-related domains include General Health (GH), Physical Functioning (PF), Body Pain (BP) and Role Physical (RP). Mental health-related scales include Vitality (VT), Social Functioning (SF), Role Emotional (RE), and Mental Health (MH)"[101].

WHO-Quality of life BREF (WHOQOL-BREF)

WHOQOL- BREF is a 26-item instrument with 4 domains: "psychological health (6 items), physical health (7 items), social relationships (3 items) and environmental health (8 items). It also encompasses QOL and general health items. Each individual response is scored from 1 to 5 and then transformed linearly to a 0–100-scale"[102].

MANAGEMENT OF SLEEP DISTURBANCE AMONG CKD-AP PATIENTS

As sleep disturbance in CKD patients was mainly caused by CKD-aP, therefore the primary objective is mainly to treat the CKD-aP and eventually improves sleep quality. However, due to the refractory nature of CKD-aP, no absolute treatment is available for its management. So far, no reports on improving sleep quality using pharmacological or non-pharmacological treatment among CKD-aP patients. Nevertheless, for dialysis patients the therapeutic treatment options for sleep disturbance is available, these options include pharmacotherapy with hypnotic agents[103], pharmacotherapy with wide range of the rapeutic agents for treatment and relief of CKD-aP[104] and improvement of sleep; cognitive behavioral therapy[105] e.g., relaxation[106] and sleep hygiene[107]. Non-benzodiazepine hypnotics are considered to be alternative hypnotic agents in dialysis centers due to no physical dependence, good effects, no active metabolites and no or least adverse effects of inducing sleep apnea[108–110]. For non-pharmacological interventions, acupressure is applied at specific meridians or acupoints in Traditional Chinese Medicine to improve sleep quality[111–114]. Unlike pharmacological and other interventions, acupressure is a non-invasive therapy that has low risk of side effect profile[115].

CONCLUSION

In conclusion, acupressure and zolpidem tablets were able to improve sleep quality among CKD-aP patients on hemodialysis. With an overall improvement in sleep quality among CKD-aP patients observed in both control and intervention group. Healthcare practitioners should consider acupressure therapy as an alternate method to improve the quality of sleep among CKD-aP patients on hemodialysis. However, more studies are needed to establish suitable data using specific tools to determine CKD-aP and sleep quality for quantitative analysis. CKD-aP should be treated with equal importance as other complications to improve patient's quality of life, and to avoid secondary infections due to persistent scratching for relieve of the itch.

Conflict of Interest

The authors declare that there is no conflict of interest in this work.

Authors Contributions

The literature review and manuscript writing were performed by I-UR and T-MK.

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