

Epidemiology of Chronic Kidney Diseases (CKD) in Malaysia and Pakistan, Pathophysiology of CKD-Associated Pruritus and Other CKD-Associated Dermatological Disorders

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Abstract: Almost 50–90% of chronic kidney disease patients undergoing haemodialysis have been reported to have Chronic kidney disease-associated pruritus (CKD-aP). The intensity of CKD-aP may vary from a mild itch to an unbearable pruritic sensation which interferes with the patient's quality of life. CKD-aP has become one of the upmost distressing cutaneous and most common symptom of chronic kidney disease which is often overlooked by nephrologists, primary care physicians, and other health-care professionals. Typically sleep disorders, mental and social well-being have been correlated with chronic kidney disease patients. With that this article presents vital comprehensive review which includes epidemiology of chronic kidney disease in Malaysia and Pakistan, CKD-associated pruritus and other dermatological disorders associated with chronic kidney diseases, pathophysiology of CKD-associated pruritus, clinical features of chronic kidney disease-associated pruritus, diagnosis of CKD-associated uremic pruritus, differential diagnosis of CKD-associated uremic pruritus, assessment and quantification of pruritus severity.

Keywords: Chronic Kidney Diseases (CKD); Malaysia; Pakistan; pathophysiology of CKD-associated pruritus

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INTRODUCTION

In Malaysia, the prevalence of CKD is on the rise from 13,479 per million populations in year 2004 to 20,589 per million populations in year 2008^[1]. In Malaysia the exact estimation of CKD is unknown, nevertheless the expected incidence of chronic kidney disease in West Malaysia is 9.07%^[2]. Additionally, its distribution stage-wise i.e. Stage 1, 2, 3, 4, and 5 are 4.16%, 2.05%, 2.26%, 0.24%, and 0.36%, respectively^[2]. According to the 21st report of Malaysian dialysis and transplant registry, the number of patients on dialysis increased from 13,356 in year 2004 to 34,767 in year 2014^[3].

In Pakistan, chronic kidney disease is progressing, and multiple factors are responsible for this epidemic such as

poor health care facility, deficient primary health care system, no proper health education, insufficient funding and higher prevalence of diabetes and hypertension^[4].

DEFINITION AND STAGES OF CHRONIC KIDNEY DISEASE (CKD)

Kidney Disease Outcome Quality Initiative (KDOQI) defines chronic kidney disease (CKD) as an immediate or continuing to decrease kidney function or efficiency for a duration exceeding three months^[5]. The standards for assessing the disease initiation are mainly urinary outcome, proteinuria and hematuria^[6,7]. In some cases, the initial presentations are temporary and can be solved by early initiation of drug therapy while in the majority

of conditions, the decrease in the creatinine clearance and accumulation of waste products like urea and uric acid occurs^[7]. Glomerular filtration rate (GFR) and creatinine clearance (CC) are two parameters used for estimation of kidney function^[5,8]. “Glomerular Filtration Rate (GFR) can be defined as the amount of blood that is filtered by Bowman’s capsule per unit of time (mL/min/1.73m²)”. For a healthy human being the GFR values should be range from 120-130 mL/min/1.73m²^[8]. Listed here are two most common equations used in practice for estimating GFR based on serum creatinine (Scr_t).

1. Cockcroft-Gault equation^[9]
2. Modification of Diet in Renal Disease (MDRD) equation^[10]

Cockcroft-Gault Equation

CC (mL/min) = $([140 - \text{Age} \times \text{weight}] / [72 \times \text{Scr}_t]) \times 0.85$ if female

MDRD Equation

eGFR (mL/min/1.73 m²) = $186 \times [\text{Scr}_t]^{-1.154} \times [\text{Age}]^{-0.203} \times [0.742$ if female]

Note: for African/ Black use the multiplication factor 1.21

Stages of kidney diseases:

On the basis of Creatinine Clearance (CC) or estimated Glomerular Filtration Rate (eGFR) kidney disease can be classified in five stages^[5,11]:

- i. Stage 1: Normal or increased GFR i.e. 90 or more mL/minute/1.73m²
- ii. Stage 2: Mild decrease in GFR i.e. 60–89 mL/minute/1.73m²
- iii. Stage 3: Moderate decrease in GFR i.e. 30–59 mL/minute/1.73m²
- iv. Stage 4: Severe decrease in GFR i.e. 15–29 mL/minute/1.73m²
- v. Stage 5: Kidney failure i.e. Less than 15 mL/minute/1.73m² or on dialysis

Creatinine is basically a by-product that forms from protein metabolism. When the kidney function starts deteriorating, clearance from kidney reduces which leads to an elevated serum creatinine, uric acid and urea^[9]. Majority of the patients at stage 4 and stage 5 of kidney diseases get frequent dialysis based on their renal reservoir. In general, most of the patients get dialysis three times a week. The main aim for performing dialysis is to eliminate the waste products from the blood such as urea, uric acid, nitrogen and excessive electrolytes.

Low GFR alone is not confirmatory for diagnosis of CKD, as it may be borderline normal or normal. In order to establish the diagnosis for CKD, the presence of one or more markers as listed is vital^[12].

- Histological abnormalities
- Urine sediment abnormalities
- Albuminuria (albumin excretion >30 mg/24 hr)
- Electrolyte and other abnormalities owing to tubular disorders
- Renal transplantation history
- Structural abnormalities detected by imaging

EPIDEMIOLOGY OF CKD

CKD is currently one of most serious health crises. Epidemiological data suggests that CKD is a big threat globally for both developing and developed countries^[13]. According to 2010 statistic of Global Burden of Disease (GBD), among the directory causes of global deaths, CKD was categorized 27th in 1990 but due to its higher prevalence, it climbed to 18th in 2010^[14]. The 2013 statistic by Global Burden of Disease (GBD), comparing the mortality rate of CKD patients between 1990 and 2013, indicates mortality rate is increased by 134.6% in 2013 compared to 1990^[15]. The prevalence of CKD is heterogeneous globally, with the incidence of CKD was higher in Indo-Asians population as compared to the European population. The statistics indicated CKD is more prevalent in Asian countries as compared to the rest of the world. Malaysia reported prevalence of 9.07%^[2], while China and Nepal reported prevalence of 10-19%^[16] and 10-20%^[17] respectively. Whereas Pakistan, Bangladesh, and India reported prevalence of 20%^[18-20]. One possible reasons for the increased in prevalence is the reduced access to preventative health care, which helps to reduce the progression of kidney diseases^[21]. Furthermore the global increase in CKD cases and its progression toward end-stage renal disease due to global increase of diabetes and hypertension pandemics^[22-24].

Chronic kidney diseases in Malaysia

In Malaysia, the prevalence of CKD is increasing from 13,479 per million populations in 2004 to 20,589 per million populations 2008^[1]. In Malaysia the exact estimation of CKD is unknown, still the expected incidence of chronic kidney disease in West Malaysia is 9.07%^[2]. Moreover, its distribution stage-wise i.e. stage 1, 2, 3, 4, and 5 are 4.16%, 2.05%, 2.26%, 0.24%, and 0.36%, respectively^[2]. The 21st report of Malaysian dialysis and transplant registry stated the number of patients on dialysis increased from 13,356 in 2004 to 34,767 in 2014^[3], as depicted in Figure 1. The acceptance rate and prevalence rate of dialysis are 210 and 1065 per million populations respectively^[1]. The report stated that overall acceptance and prevalence rate of dialysis is almost doubled during the span of 10 years^[1]. States in Malaysia which are economically advanced have a much higher rate of dialysis treatment compared to those states which are economically less advanced. Approximately 90% of new dialysis patients are accepted into haemodialysis center and the rest into the peritoneal dialysis program^[1]. In 2013, the annual death rate on dialysis was reported as 11.3%, out of which 10.9% were of haemodialysis and 15.8% were of peritoneal dialysis^[1]. Diabetes is considered to be the typical cause of CKD, with reported cases of CKD due

to diabetes at 53% in 2004 and 61% in 2013^[1]. End stage renal disease caused by diabetes has increased dramatically and is accountable for 50% incidents in dialysis patients. The Malaysian National Registry estimated the prevalence of end-stage renal disease in 2007 will be 680 per million population^[25]. According to National Renal

Registry Malaysia (2015)^[3], 32,026 patients were on dialysis; of whom 91% were on haemodialysis and 9% were on peritoneal dialysis. It has been estimated that by 2040, the number of patients with end stage renal disease would triple from existing 2014 cases^[26]. Ibrahim *et al.* (2011)^[27] reported the prevalence of CKD-aP in Malaysia by 64.2% and sleep disturbance with 61.7% in CKD patients.

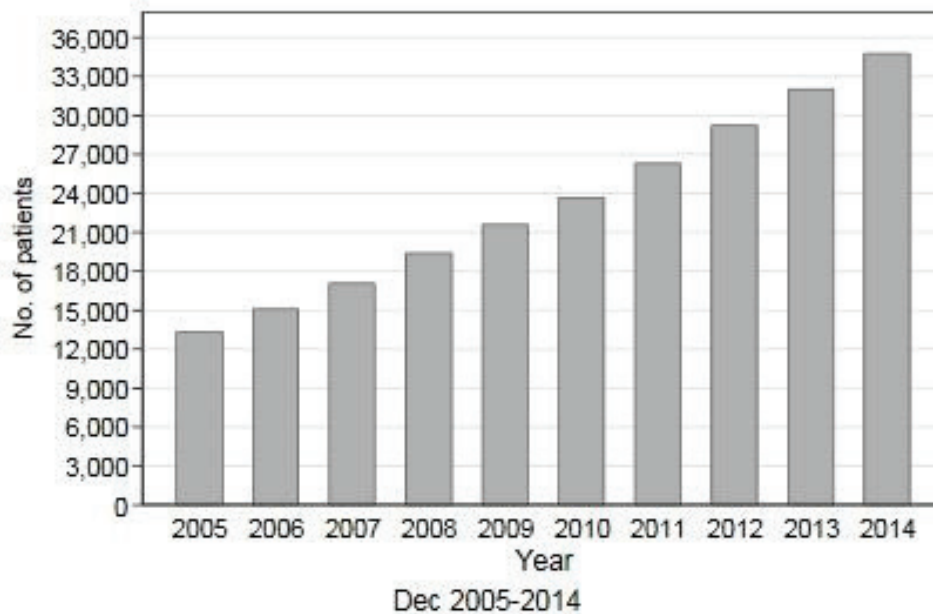


Figure 1. Statistic of increase in dialysis patients indicating an increase during December 2005- December 2014 in Malaysia.

Chronic kidney disease in Pakistan

In Pakistan, chronic kidney disease is progressing with multiple factors responsible for this epidemic such as poor health care facility due to deficient primary health care system, no proper health education, insufficient government funding and higher occurrence of diabetes and hypertension marked as a high-risk factor for CKD^[4]. In Pakistan, the absence of periodically maintained central registry kidney diseases on a national level about its epidemiological and burden makes it extremely difficult to assess the cases of CKD, dialysis, mortality, and allocation of the fund in Pakistan^[4]. Data from the Dialysis Registry of Pakistan 2007–2008 indicated the number of CKD patients increased from 4,393 in 2006–2007 to 6,127 in 2007–2008^[28]. While current data indicated 16,000 Pakistanis suffer from CKD annually and Pakistan is ranked the eighth in the world on basis of highest number of epidemiology and prevalent cases of CKD^[29]. Jessani *et al.* (2014)^[19] reported that CKD prevalence in Karachi is 12.5%. While Luqman *et al.* (2012)^[30] reported the prevalence of CKD in Pakistan as 64%.

CKD-ASSOCIATED PRURITUS (CKD-aP) AND OTHER DERMATOLOGICAL DISORDERS ASSOCIATED WITH CHRONIC KIDNEY DISEASES

Dermatological disorders are regularly observed in CKD patients. Skin-associated problems like CKD-aP, xerosis,

pallor, and hyperpigmentation are very common in CKD patients^[31]. Most often, in the case of renal failure, the skin becomes an excretory organ for the substances the kidney usually clears from the body. A study on dermatological problems associated with CKD indicated the prevalence of skin conditions observed were pallor 91.5%, xerosis 75.9%, pigmentary changes 65%, CKD-aP 60.2% and panniculitis 1.2%^[31]. CKD-aP is a commonly found complication reported by majority of chronic kidney disease patients^[32]. The prevalence of CKD-aP was found to be more in haemodialysis patients (68%) than in peritoneal dialysis patients (38%)^[33]. The occurrence of CKD-aP in CKD patients differ extensively from 22% to 90%^[34–38]. Normally, the whole body is affected while the back and forearms are most likely to get affected compared to other parts of the body. Severe CKD-aP has a major impact on the patient's life quality which leads to other disorders such as anxiety, disturbed sleep, and depression^[39–43]. Recently two studies (a Japanese study and the DOPPS) demonstrated a relationship between CKD-aP and an amplified threat of mortality^[34,38]. Several studies report a considerable prevalence of CKD-aP among dialysis patients, ranging from 10% to 70% in PD patients and 20% to 90% in HD patients^[44]. Almost 50% or greater chronic kidney disease patients are reported of having the dermatological problem like dry skin and itching^[45]. These associated dermatological problems have a significant impact on quality of life which negatively impacted on CKD patients' physical and mental health^[31].

Pruritus is linked with some other metabolic changes which

trigger and potentiate it, such as xerosis, decreased trans-epidermal elimination of pruritogenic factors, hyperparathyroidism, hypercalcemia and hypophosphatemia, higher levels of histamine and transdermal mast cell proliferation, and uremic sensory neuropathy^[46]. In parallel to internal factors, few external factors are also hypothesized to be related with pruritus, such as dehydration, excessive sweating, humid and hot weather, shower with cold/hot water and stress^[46]. Also CKD-aP patients could experience abnormal skin pigmentation and low platelet counts as a result of prolonged bleeding^[47]. Usually after a temporary relief from pruritus, the symptoms reappear within six months with much-intensified degree regardless of any demographic variables^[46]. CKD-aP occurs intermittently in some cases that may last for few minutes while some patients suffer from lengthy phases of severe CKD-aP that may be present during both day and night^[45]. CKD-aP onset, duration, and intensity can change over time and the itching is usually worsened at night time. Most normally affected body parts by CKD-aP are the back, limbs, chest, and head, however, approximately 20–50% of patients experience a generalized CKD-aP^[38].

PATHOPHYSIOLOGY OF CKD-ASSOCIATED PRURITUS (CKD-aP)

The exact mechanism associated with the pathophysiology of CKD-aP is poorly understood. Several hypotheses are discussed in this article for the pathophysiology of CKD-aP.

Immune-mediated hypothesis

CKD-aP is potentially due to dysregulated systemic inflammation^[48-50]. In CKD-aP patient's elevated levels of T-helper type-1 cells^[49], interleukin-6^[49], interleukin-2^[50] and C-reactive protein^[51] were observed. It is recommended that CKD-aP is associated with high white blood cell count, high ferritin level and low albumin level^[51]. The immune hypothesis refers CKD-aP as overproduction of pro-inflammatory substances such as histamine (by mast cells), interleukin 2, tumor necrosis factor α and interferon γ by T Helper 1 lymphocytes^[52,53]; elevated level of inflammatory markers such as C-reactive protein and interleukin 6^[50,54,55]. The elevated levels of serine protease and Proteinase-Activated Receptor-2 could also play vital roles in the pathogenesis of CKD-aP^[56].

Xerosis hypothesis

Xerosis (dry skin), is another common dermatological condition reported in patients with CKD^[57,58]. The reduction of the eccrine sweat glands size and the atrophy of the sebaceous glands are assumed as the main reasons for xerosis^[59]. Xerosis has been considered as a substantial contributor in CKD-aP severity^[60].

Histamine hypothesis

The increased of mast cells and histamine levels^[61-63], Serotonin level^[64], eosinophil's and tryptase have been witnessed in patients with CKD-aP^[61,62]. Nevertheless, Prasad et al. (2015) reported that despite increased mast cells and histamine levels there was no direct correlation between histamine level and CKD-aP.

Neuropathic hypothesis

The neuropathic hypothesis suggests that the somatic and autonomic neuropathy caused by lesion can result in neuropathic itch^[65,66]. It is recognized that neuropathic pain and pruritus shared the same neuronal pathway^[67]. The involvement of neuropathic mechanisms in the mediation of pruritus is further demonstrated with gabapentin and pregabalin that are effective in the improvement of the patient with pruritus^[68,69]. This also advocated that afferent C-terminal nerve fibers that are GABA-aminobutyric acid (GABA) dependent is involved in the CKD-aP^[70].

Opioid hypothesis

The opioid hypothesis suggests that the imbalance of endogenous opioidergic system plays an important role in the pathophysiological mechanism of pruritus by the ability of μ receptor antagonists and κ receptor agonists in relieving itchiness^[67,71,72]. The μ -opioid receptor activation is involved in the intervention of pruritus while κ -opioid receptor activation has an inhibitory effect on μ -opioid receptor both peripherally and centrally^[67,72-74].

Hyperparathyroidism hypothesis

The hyperparathyroidism is expected to play a role in pruritus through inducing mast cell secretion^[75]. Secondary parathyroidectomy trigger elevation of divalent ions such as magnesium, phosphate, and calcium, this could result in micro-precipitation that is known to have affect the modulation of mast cells degranulation^[76]. Low serum phosphorus level was recently found to be significantly lower in haemodialysis patients with severe and frequent CKD-aP as compared to those without CKD-aP^[77].

Other factors

Other factors associated with CKD-aP include the production of pruritogenic substances such as abnormal growth, cytokines, and sprouting of "itch fibers" in the skin, also neuropathy that leads to the decreased of the threshold for itch sensation^[78,79].

CLINICAL FEATURES OF CKD-aP

Clinical characteristic varies for each patient and over time among patients. As the CKD-aP onset, intensity and duration can change over time^[37], and the itch is typically worsened at night time^[45]. CKD-aP could be generalized or localized; however back, abdomen and forearms are most likely to be affected compared to other parts of the body^[38,45]. Other characteristics include:

- Worsen in itch intensity at night and cause sleep disturbance^[34,38,45,80,81].
- Xerosis (dry skin), skin scaling and epidermal cracking^[60].
- Elevated blood urea nitrogen (BUN), calcium, phosphate, and magnesium and parathyroid hormone (PTH), levels^[34].
- Fatigue and depression^[38,82].

DIAGNOSIS OF CKD-aP

CKD-aP is one of the most common complication reported by CKD patients on haemodialysis, so the diagnosis is easy unless there is other compelling evidence of other causes. The most common suggestive diagnosis characteristic of CKD-aP is its occurrence after the initiation of haemodialysis. Also, elevated calcium, magnesium, phosphate, blood urea nitrogen (BUN) and parathyroid hormone (PTH) levels^[34] were confirmed among CKD-aP patients on haemodialysis.

Differential diagnosis of CKD-aP

Several diseases could cause CKD-aP in patients with and without CKD. In order to confirm CKD-aP, a non-uremic cause of CKD-aP should be kept in thought among patients on haemodialysis with symptoms that are refractory to common treatments such as an oral antihistamines, gabapentin, analgesic agents and topical emollient^[83].

ASSESSMENT AND QUANTIFICATION OF CKD-aP SEVERITY

CKD-aP has become one of the most distressing cutaneous, and the most common symptom of CKD that is commonly overlooked by nephrologists, primary care physicians, and other health-care professionals^[46]. To assess the severity of CKD-aP, several instruments have been developed and these tools shall be illustrated in this review.

The literature showed that the rating scales are commonly used for assessment and quantification of CKD-aP. The rating scales/tools includes verbal rating scale (VRS), visual analogue scale (VAS), numerical rating scale (NRS), Eppendorf itch questionnaire (EIQ), Dermatology quality of life questionnaire (DLQI) and 5Ditch scale (5D-IS), Modified pruritus questionnaire for itch severity score, Skindex(Skindex-29 and Skindex-16)^[84-91].

Visual analogue scale (VAS)

Visual analogue scale is a unidimensional scale that is an easy and rapid tool commonly used for assessment of pruritus severity^[71]. The VAS consists of a 10 mm horizontal line indicating the severity of itch; “no itch” (0 points) and ending with “worst itching”^[92]. The evaluation of CKD-aP relying on a single measure is not sufficient, VAS is a useful tool for the assessment of pruritus intensity but it does not provide any further information on other aspects of CKD-aP^[93].

Verbal rating scale (VRS)

Verbal rating scale (VRS) is another unidimensional tool for assessment of pruritus that assists the patient to verbally describe the degree of pruritus. This is possibly the most convenient method for assessment of pruritus; with four-point scale “none, mild, moderate and severe pruritus”^[94] and five-item scale “none, mild, moderate, severe and very severe pruritus”^[95] are used for assessment of pruritus. The variability in different versions of VRS point scale contributes toward a major limitation of this scale, thus making the comparison of these results very diffi-

cult^[96]. However, VRS has the advantage as one of the most suitable tool for assessment of CKD-aP in certain populations such as elderly or patients with cognitive problems^[96].

Eppendorf itch questionnaire (EIQ)

The Eppendorf itch questionnaire was developed by Darsow *et al.* (2001)^[97], for the exact characteristic of pruritus using a comprehensive list of sensory and affective descriptors, and also collects evidence on the impact of pruritus on quality of life^[97].

Dermatology quality of life questionnaire (DLQI)

The Dermatology Life Quality Index, the first dermatology was by Finlay and Khan (1994)^[98], and contains 10 questions concerning “symptoms and feelings, daily activities, leisure, work, and school, personal relationships and treatment” over previous one week. The responses for this tool are ranged from 0 to 3 “not at all”, “a little”, “a lot” or “very much” respectively. Each response is scored from 0 to 3 and then summed up, score of 0 indicates no impairment of life quality while score of 30 indicates maximum impairment^[98].

5D-itch scale (5D-IS)

A 5D-itch scale is a multidimensional tool, that comprises of five domains, addressing the “duration, degree, direction, disability, and distribution of itching”^[87]. The duration, degree and direction domains each included one item, while the disability domain had four items. All items of the first four domains were measured on a five-point Likert scale (where 1 represented the lowest degree of pruritus, and 5 represented the highest degree). The 4th domain (disability) measured the effect of itching on daily activities, and its score was calculated by selecting the highest score. In the 5th domain, participants were asked to select which part of the body was most affected by CKD-aP, and participants could select as many body parts as they wished. If two body parts were affected, the score given was 1; 3–5 body parts affected was scored as 2, 6–10 body parts were scored as 3, 11–13 body parts were scored as 4, and 14–16 body parts were scored as 5. The overall score of the 5D-IS was calculated with all the five domains; 5 indicates no pruritus; whilst a score of 25 indicates severe pruritus^[87].

Modified pruritus questionnaire for itch severity score

The Itch severity scale developed by^[81] for evaluation of pruritus was modified by^[88], as the questionnaire by Yosipovitch *et al.* (2001)^[81] has no method of scoring for quantification of symptom severity. The modified questionnaire by Majeski *et al.* (2007)^[88] consists of 7 components: “frequency, itch description, affected body surface area, intensity, the effect on mood, an effect on sexual desire/function and effect on sleep”. The responses to a different component of the questionnaire were separately summed and divided by a maximum score for the respective question. All the seven values achieved were then added and multiplied by 3 to get a total out of 21 scores. The yielding total scores ranging from 0 to 21^[88].

Skindex questionnaire

Skindex is among the best dermatological instruments for the measurement of dermatological specific health related quality of life (QOL)^[89]. Skindex was originally comprised of 61 questions that were later on divided into two brief versions i.e. Skindex 16^[91] and Skindex 29^[90]. The Skindex-29 is instruments of choice in dermatology^[99], it is comprised of 7 items addressing the symptoms domain, 10 items for the emotional domain, and 12 items for the functioning domain. The responses of all domains were transformed to a linear scale of 100, varying from 0 (no effect) to 100 (effect experienced all the time)^[100]. Whereas Skindex-16 is a single page questionnaire, that is an accurate and sensitive measurement for patients experience and widely used for skin-related quality of life^[101,102]. The Skindex-16 comprised of 4 items related to symptoms, 7 items related to emotions and 5 items related to functioning scales and linear scale of 100, varying from 0 (no effect) to 100 (effect experienced all the time)^[91].

CONCLUSION

Researchers reported the prevalence of CKD-aP was slightly higher in Pakistani patients when compared to Malaysian patients. Prevalence studies in Pakistan reported rates of 64.0% to 77.7%^[30,103,104] while Malaysia studies reported rates of 58.6% to 64.2%^[27,105]. The pruritus median score was also significantly higher in Pakistani 10.0 [8.0–12.0] compared to Malaysian patients 8.0 [6.0–9.0]; $p < 0.001$. The possible reasons for the variation in the prevalence of CKD-associated pruritus between Malaysian and Pakistani because patients in Pakistan receive haemodialysis twice/week, whereas in Malaysia, it is three times/week. Moreover, low to medium flux dialyzers were used in Pakistan, whilst high flux dialyzer (which removes average-sized molecules more effectively — thus reducing the severity of uremic pruritus) was used in Malaysia. CKD-aP is believed to be caused by middle-molecule uremic toxins which are not dialyzed properly when using low flux dialyzer^[34]. Globally the high-flux haemodialysis is the most commonly used blood purification method. But in developing countries such as Pakistan, low-flux dialysis is the main method of extracorporeal blood purification therapy due to insufficient funds to purchase high flux dialyzers^[106]. Haemodialysis machines are also limited in Pakistan as in 2004 there were 140 dialysis centers although in 2009 these machines increased to 175^[107], alarmingly out of the available dialysis centers in Pakistan, 10–15% are non-functional and the patients have limited access to treatment^[107].

The Pakistani patients were significantly younger than Malaysian patients and had a shorter median duration of CKD and being on haemodialysis. This could be due to poorer management of chronic conditions (such as hypertension or diabetes mellitus) which predisposes an individual to renal damage at younger age. Additionally, Pakistani patients may have less knowledge of the complications of their chronic conditions and therefore may not take any preventive measures such as control of hypertension and dietary

modifications^[108]. Malaysian population was graded higher when their knowledge was tested against diabetes and hypertension^[109–112], these results were quite different for the Pakistani population^[113–116]. Furthermore, awareness and attitude also have a decisive role in the actions of diabetic and hypertension patients. In Pakistan, many factors may account for poorer outcomes during dialysis; such as malnutrition, late referral, anaemia and lack of qualified nephrologists at dialysis centers^[117–120].

In conclusion, this review provided vital insight on the epidemiology of chronic kidney diseases (CKD) in Malaysia and Pakistan, together with the pathophysiology of CKD-associated pruritus and other CKD-associated dermatological disorders. Both countries could improve the awareness of their populations and providing more support to the healthcare setting to increase the quality of life of CKD patients.

Authors Contributions

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

Conflict of interest

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

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