

Prevalence and Characterization of Chronic Kidney Disease Associated Pruritus in Patients Undergoing Maintenance Hemodialysis

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Abstract

Pruritus, a common complication of chronic kidney disease and end-stage renal disease (ESRD), is a uncomfortable, unpleasant symptom and apart from physical discomfort, affects social and psychological aspects of the life significantly. ESRD patients with CKD-aP have higher mortality rates, which have been reported to be as higher as 13% in DOPPS as compared to patients without pruritus. *Aim of the study:* The aim of this study was to provide a comprehensive description of the prevalence and clinical characteristics of pruritus affecting patients with end-stage renal disease on hemodialysis. *Material And Methods:* The study included 60 patients coming to the hemodialysis unit of Acharya Shri Chander College of Medical Sciences, for a period 18 months. Patients with active infection, recent hospitalization within three months, psychotic illness or other communication problems, primary skin disorders, cholestatic liver disease or acute hepatitis, and active malignancy were excluded from the study. *Results:* The 26 (43.3%) patients out of the sixty enrolled in study, were diagnosed with chronic kidney disease associated pruritus, 18 (69.2%) of the patients being male and females comprising remaining 8 patients (30.76%). *Conclusions:* The problem of pruritus in uremic dialysed patients remains unsolved. Our study underscores that uraemic pruritus is an important health problem among haemodialysis patients and its proper diagnosis and characterization is important to improve overall outcome of these patients.

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Introduction

Pruritus, defined as an unrestricted and uncomfortable sensation that elicits the desire to scratch, has been well recognized as a common complication in patients with chronic kidney disease (CKD) [1]. The term "chronic kidney disease-associated pruritus" (CKD-aP) has been proposed as an alternative term to uremic pruritus [2] as it is usually not seen in patients of acute kidney injury. The diagnosis of pruritus associated with kidney disease may be challenging because many patients are also suffering from other diseases, like diabetes

mellitus, chronic liver or hematological disorders, which may provoke itching either by itself or by medication given to treat these entities; nevertheless, because of the high prevalence of this condition in patients with advanced CKD and end-stage renal disease (ESRD), clinicians should consider any itching in these patients to be related to CKD-aP unless the presence of alternative condition is documented [3].

Aim of the Study

The aim of this study was to provide a comprehensive description of the prevalence and

clinical characteristics of pruritus affecting patients with end-stage renal disease who are undergoing hemodialysis.

Material and Methods

The study included 60 patients coming to the hemodialysis unit of Acharya Shri Chander College of Medical Sciences, for a period of 18 months. The study included all the patients who were on maintenance hemodialysis for at least 3 months, were over 18 years of age and who agreed to participate in the research by signing an informed consent. Case group patients were examined to rule out other causes of pruritus and patients with following conditions were excluded from this study—

(i) active infection, (ii) recent hospitalization within three months, (iii) psychotic illnesses or other communication problems, (iv) primary skin disorders, (v) cholestatic liver disease or acute hepatitis, or (vi) active malignancy

The demographic and clinical characteristics, including gender, age, presence of hypertension or diabetes, underlying renal disease, concurrent medications, as well as the regimens and vintage of

hemodialysis, of the participants were recorded. Venous blood was sampled in the morning, after an overnight fast exceeding 8 hours before the patient's mid-week dialysis. All laboratory tests were performed by the hospital's central laboratory.

The severity [4] of pruritus was assessed subjectively and scored as follows:

Mild: Episodic and localized pruritus without disturbance in usual work and sleep.

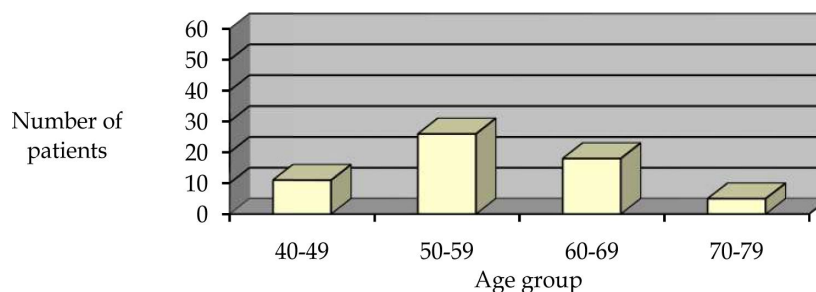
Moderate: Generalized and continuous pruritus without sleep disturbance.

Severe: Generalized and continuous pruritus spectrum interfering with all activities of daily living including sleep [4]. The study was approved by the ethical committee of the institution.

Results

The 60 patients coming for maintenance hemodialysis were selected for the study which included 40 males and 20 female patients. The mean age of males was 62.61 ± 7.43 and mean age of females was 60.25 ± 4.94 years.

Fig.1:

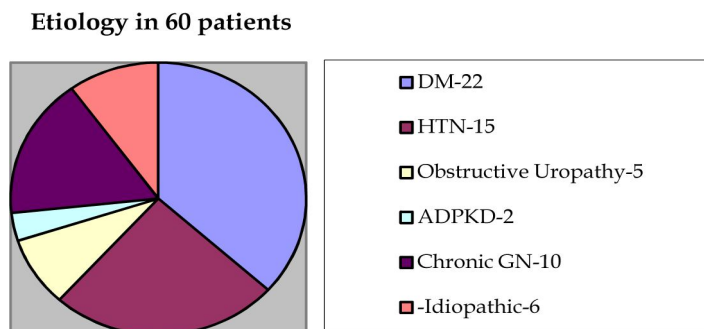


The common causes of CKD identified in these patients included diabetic nephropathy in 22 (36.66%), hypertensive nephrosclerosis in 15 (25%), chronic glomerulonephritis (CGN) in 10 (16.66%), obstructive uropathy in 05 (8.3%), Autosomal polycystic kidney disease in 2 (3.3%) and cause couldn't be ascertained

in the rest 6 (10%).

The 26 (43.3%) patients out of the sixty enrolled in study, were diagnosed with chronic kidney disease associated pruritus, 18 (69.2%) of the patients being male and females comprising remaining 8 patients (30.76%).

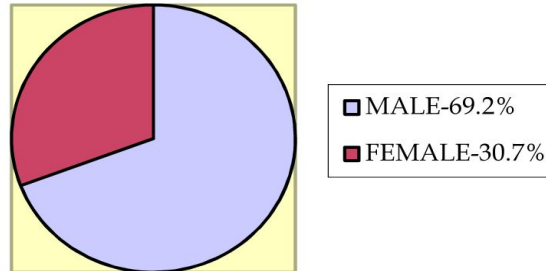
Fig.2:



When asked about the history of pruritus, 16 (61.53%) patients had onset of symptoms prior to the initiation of dialysis, the remaining 10 (38.46%) patients reported that their symptoms started after the initiation of the hemodialysis.

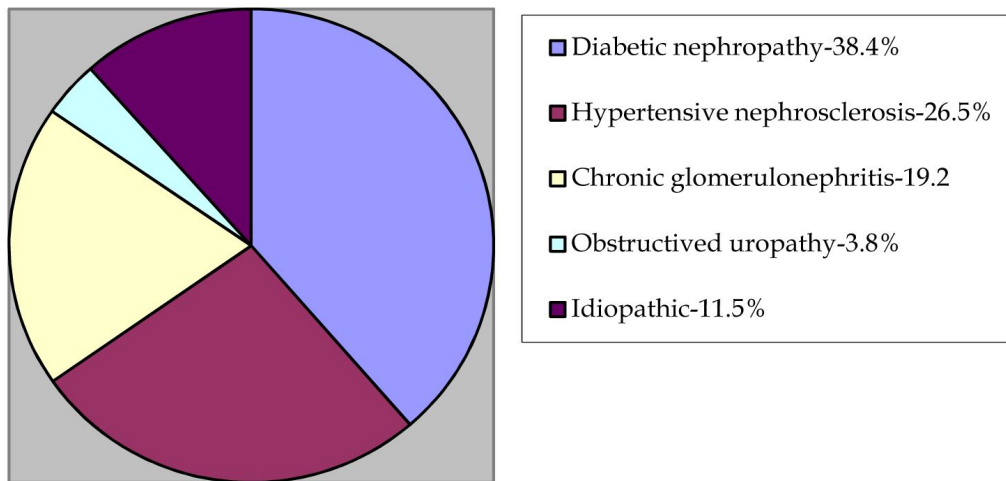
Percentage of pruritus in male and female patients

Fig. 3:



Etiology in CKD patients with pruritus(43.3%)

Fig. 4:



Etiology in Ckd patients without pruritus (56.6%)

Fig. 5:

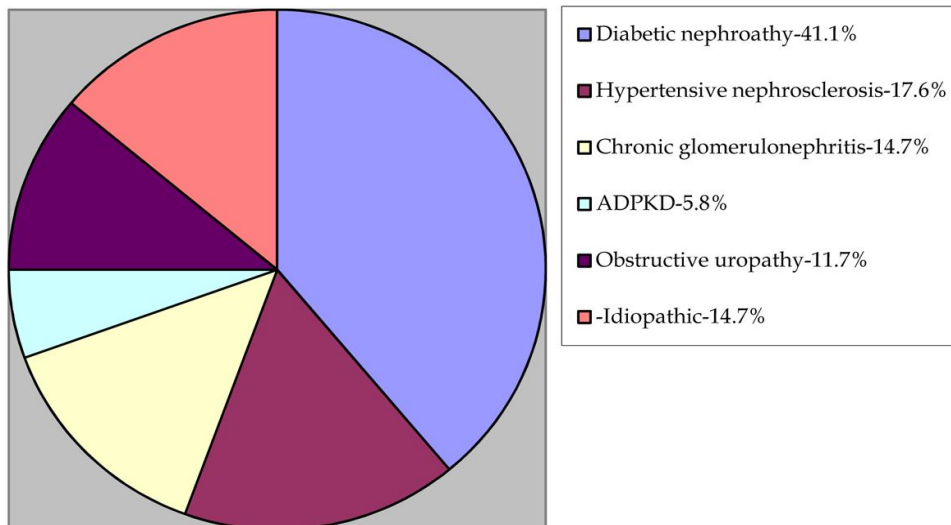


Table 1: Showing the basic demographic profile and biochemical parameters of the patients with pruritus

Sex	Age	Hemoglobin	S.Urea	S.Creatinine	S.Calcium	S.phosphorous
m	48	7	130	9	8.9	6
m	52	7	120	9.5	8.4	6.5
f	57	7.5	140	8	8.7	5.5
m	55	7.4	136	9	8.6	6
m	53	7.3	138	8.8	8	6.8
f	56	7	112	8.6	8.4	6.4
f	58	7.3	116	8	8.4	6
m	59	7	124	8.2	8.2	5.4
m	60	0.8	130	8.6	9.5	6.8
m	70	8	132	8.6	9.5	6.7
m	71	7.9	134	7.5	9.6	6
m	72	7.8	130	10	9.4	6.5
m	68	8	128	8.6	9.2	6.4
m	58	8.5	116	8.6	9.3	5.8
m	64	9	120	9	10	5.8
f	68	9.2	124	9.5	9.8	6.4
f	67	8	118	8.6	8.5	6.7
f	59	7.8	116	8.6	9.3	6.5
m	59	7.6	134	8.4	9.3	6
f	55	7.5	140	8.6	10	6
m	70	7	150	9.5	9.8	5.9
m	69	7.8	150	7	9.8	5.9
m	69	7.6	136	7.8	9	5.9
m	68	7.8	138	8.6	9	5.9
m	62	7.9	136	8	9	6
f	62	6.8	130	8.2	9	6.8

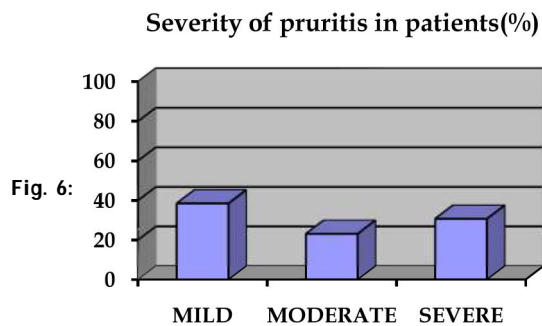
Table 2: Showing the basic demographic profile and biochemical parameters of the patients without pruritus.

Sex	Age	Hemoglobin	S.urea	S.creatine	S.calcium	S.phosphorous
m	40	8	80	8	8.5	5.5
m	45	7.5	90	8.5	8.6	5
m	48	8.5	70	9	8.4	5.4
m	65	8.6	100	9	8	6
f	60	8.7	80	8	8	6.5
f	68	8.5	60	7.5	8	6.8
f	45	9	100	7	8.6	7
m	48	9	112	8	9	7
m	49	9.5	100	9	9	6.8
m	57	9.5	92	9	9	6
f	56	9	80	8.5	9	5.8
m	48	9.5	100	8	8.6	5.8
m	67	8	120	9	9	5.9
f	68	9.5	90	8.5	9	6
f	70	9	90	9	9	7
f	70	8.5	98	8	8.5	6.5
f	56	8.5	80	9.5	9	6
f	55	8.5	85	8	9	6
m	62	7.5	90	7.5	9	5.6
f	66	10.5	80	8	8.5	5.6
f	72	10.5	100	9	9	5.4
m	60	11	120	9.3	9	5
m	59	9.5	116	9.2	10	6
m	58	9	118	9.4	8.5	6
f	57	9	120	8.5	9	5.4
f	58	9.5	98	8	9	5.6
f	49	9	100	8	8.5	5.4
m	50	8	120	8.5	8.5	5
f	52	7.5	130	8	8.5	6
f	58	9	120	8.5	8.6	6
m	48	9	90	9	9	5.8
f	70	10	70	9.5	9.5	5.8
m	68	9.8	84	9	9	6
f	64	10	72	9	9	6
m	50	11	72	8.5	8.6	4.5
f	58	8.9	90	8	7	4.5

Regarding distribution of itching, 15 (57.69%) patients had involvement of large, non-dermatomal areas with bilateral symmetry, where as in 10 (38.46%) patients, pruritus was localized, back being the most common site .

20 (76.92%) out of 26 patients reported worsening of itching during hot weather particularly in humid conditions.

About relationship with dialysis session,12 (46.15%) patients reported worsening symptoms prior to the dialysis and improvement in itching after the hemodialysis session, however 4 (15.38%)patients reported aggravation of pruritus immediately after the dialysis session The remaining 8 patients did not notice any relationship of itching with dialysis session. The examination to find out associated findings revealed that xerosis or excessive dryness of skin was the most common finding , reported by 14 (53.84%) patients followed by minor ulcerations in 8(30.76%) patients and papules in 5 (19.23%) patients.



Intensity of the pruritus was mild in nature in 10 (38.46%) patients, moderate in 6 (23.07%) and 8 (30.76%) patients reported severe itching. When asked about the impact of pruritus on emotional state of the patients like mood changes and depressive symptoms, 16 patients admitted being excessively bothered by the continuous itching they were experiencing without much relief with prescribed medicines.

Discussion

Pruritus is a common complication of end-stage renal disease (ESRD), affecting many patients. It is a chronic, unpleasant symptom and apart from physical discomfort, affects social and psychological aspects of the life significantly [5,6]. ESRD patients with CKD-aP have higher mortality rates , which have been reported to be as higher as 13% in DOPPS [7] as compared to patients without pruritus.

In our study, the results showed that the anaemia was more common in patients with pruritus than in those without pruritus and the difference was statistically significant. Similarly patients in pruritus group had higher mean values of blood urea, calcium and phosphorus and association was statistically significant. However, the difference in creatinine values between the two groups was not statistically significant.

The pathogenesis of CKD-aP remains incompletely understood leading to many hypothesis. The triggering factors may include uraemia-related abnormalities (particularly involving calcium, phosphorus and parathyroid hormone metabolism) [8] and accumulation of other uraemic toxins. The prominent role of secondary hyperparathyroidism and associated derangements of calcium and phosphorus metabolism in the pathogenesis of uremic pruritus was suggested nearly 50 years ago [9]. After that many studies concluded that pruritus in patients with end-stage renal disease likely results from uremia related toxins [10,11] as suggested by some other studies that more efficient hemodialysis with the target of Kt/V ≥ 1.5 , as well as the use of high-flux dialyzer, may play a role in reducing the severity of uremic pruritus [11]. In the DOPPS [7] patients with a calcium phosphorus product of >80 had a 1.5 times greater odds of pruritus compared with those having a product of 50–60. It has been further argued that improvement of CKD-aP prevalence rates over time is due to improvements in dialysis efficiency and better removal of toxins. Other studies, however, have not found a consistent association with serum calcium and phosphorus levels, Ca/P ratio, PTHi values and size of the dialyzer having a statistically significant association with pruritus [12].

Table 3:

Variable	Mean(Cases)	Mean(Control)	P value
Age	61.88±6.76	57.61±8.6	0.03 (S)
Hemoglobin	7.40±1.47	9.05±0.9	0.001 (H.S)
Urea	129.92±10.20	94.91±17.57	0.001 (H.S)
Calcium	9.1±0.57	8.73±0.50	0.008 (H.S)
Phosphorous	6.17±0.40	5.85±0.63	0.02 (S)
Creatinine	8.57±0.66	8.51±0.62	0.7 (N.S)

As the exact etiology of pruritus is still not known, other hypothesis have been proposed to explain the renal itch .The immune mediated hypothesis suggests that dysregulated systemic inflammation is the cause of CKD-aP ; marked by high white blood cell count, c - reactive protein, interleukin-6 and interleukin-2 levels and low albumin levels [13,14].

The over-stimulation of endogenous opioid receptors [15,16] as a cause of CKD-aP has been suggested, similar to its possible role in the pathogenesis of cholestatic pruritus. CKD-aP has also been postulated to result from an imbalance of mu and kappa-opioid receptor activity with mu-receptor over-activation and kappa receptor blockade resulting in increasing itching [17]. Increased levels of eosinophils, mast cells, histamine and tryptase have been observed in some of these patients and systemic inflammation is believed by many to play an important role in CKD-aP [18,19].

Some studies have suggested that dry skin is major contributor to CKD-aP as there is high co-occurrence of xerosis with pruritus in advanced CKD and ESRD patients [20].

The prevalence of pruritus in our study was 43.3%, and it has been reported to affect 20%-90% of patients of ESRD [1,2,3,4] in studies performed in last five decades. The wide range of prevalence rates of pruritus is likely related to varying characteristics of studied populations, the era when studies were performed and the diagnostic instruments used to define CKD-aP. Interestingly, the prevalence of CKD-aP may be improving over time, with rates declining from as high as 85% in the early 1970s, to between 20% and 40% in studies performed over the past 10 years [1,2,3].

Out of the 26 participants of this study, 18(69.2%) were males and females comprising remaining 8 patients (30.76%). Analysis of the gender have revealed mixed results that with one important study reported that it occurred statistically significantly more often in women [21], independent of method of renal replacement therapy whereas in other pruritus was significantly more common in men (DOPPS) The majority of studies have found no difference in gender preference.

In our study, 16(61.53%) patients had onset of symptoms prior to the initiation of dialysis, the remaining 10 (38.46%) patients had their symptoms started after the initiation of the hemodialysis. Regarding the prevalence in patients not initiated on dialysis yet, the pruritus was reported by 56% patients in stage 4 and 5 CKD and in 74% of patients with stage 5 CKD [22] (mean eGFR 11). In a cross-sectional study of stage 2-5 CKD, the prevalence of CKD-aP was 18.9% and pruritus was not affected by the stage of CKD in this study [23]. In a cross-sectional study of skin manifestations in 200 Indian CKD and ESRD patients (50 each in stages 3, 4, and 5 CKD and 50 patients with ESRD on dialysis), the prevalence of pruritus was 36% [24].

About relationship with dialysis session, 12 (46.15%) patients reported worsening symptoms prior to the dialysis and improvement in itching after the hemodialysis session, however 4 (15.38%) patients reported aggravation of pruritus immediately after the dialysis session and remaining 8 patients did not notice any relationship with dialysis. Contradictory reports have been published on the acute effect of dialysis on pruritus; itching can occur at any time in relation to dialysis i.e before, during, or after the dialysis session. Some studies have shown that the itch worsens during dialysis sessions while others have shown an immediate beneficial effect of dialysis on pruritus [25].

Some authors have reported that itching peaked at night after two days without dialysis, was relatively high during treatment and lowest during the day following dialysis. It has been suggested that the accumulation of pruritogens between dialysis sessions influences the intensity of itching. Similarly, pruritus may increase in intensity after hemodialysis as the patient may develop hypersensitivity to certain components used in hemodialysis like dialysis catheters, cellophane adhesives and nickel containing needle tips [26].

Regarding distribution of itching, 15 (57.69%) of our patients had involvement of large, non-dermatomal areas with bilateral symmetry, whereas in 10 (38.46%) patients, it was localized mostly to the back. The distribution of itching in CKD-AP has been described as generalized and symmetrical in about 20-50% patients in many studies but few studies have reported localized form which was more common in the back chest, scalp, face, and shunt arm [27].

Clinical characteristic varies over time and between patients. Itching can vary from a few minutes to continuous throughout the day [28,29]. The symptoms are more severe at night and disturbs sleep patterns, 20 (76.92%) out of 26 patients reported worsening of itching during hot weather particularly in humid conditions in our study. Many authors have studied the association of external heat, sweat and stress with pruritus and reported aggravation of symptoms with warmth, ambient temperature, sweat and stress [28,29].

The xerosis or excessive dryness of skin was most common finding, reported by 14 (53.84%) patients followed by minor ulcerations in 8(30.76%) patients and papules in 5(19.23%) in our study. Xerosis (dry skin) has been described in between 50% and 85% of patients [20]. Secondary skin lesions are superimposed complications of excoriation like impetigo, linear crusts, papules, ulcerations, and

prurigo nodularis, which are seen in some patients [30].

Intensity of the pruritus was mild in nature in 10 (38.46%) patients, moderate in 6 (23.07%) and 8(30.76%) patients reported severe itching in the present study. Severity of pruritus may vary over time, from barely noticeable to, itching that causes constant restlessness and these symptoms can be present intermittently or be persistent. The prevalence of moderate to severe itching was 42% in DOPPS II (2002–2004) compared to 45% in DOPPS I (1996–2001) and mild to moderate itching was 71% in DOPPS II and 74% in DOPPS I (The DOPPS is a prospective cohort study of hemodialysis practices based on the collection of observational longitudinal data for a random sample of patients from a representative and random sample of units in 12 countries (Australia, Belgium, Canada, France, Germany, Japan, Italy, New Zealand, Spain, Sweden, the United Kingdom, and the United States). Since 1996, data collection has yielded detailed information on more than 38,000 patients in over 900 dialysis facilities).

The 16 of our patients admitted being excessively troubled by the continuous itching as they were not getting good relief with prescribed medicines; although we didn't evaluate the quality of life by any standardized questionnaire. The affect of pruritus on the health related quality of life (HR-QOL) in terms of mood, social relations and sleep has been extensively investigated in many studies by SF-36 questionnaire and by other standard tools and about two-third patients of uremic pruritus reported skin related impaired quality of life [31].

Conclusion

The problem of pruritus in uremic dialysed patients remains unsolved. The etiology of pruritus has not been precisely explained, and sometimes no efficient treatment is available. Our study underscores that uraemic pruritus is an important health problem among haemodialysis patients and its proper diagnosis and characterization is important to improve overall outcome of these patients.

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