ORIGINAL RESEARCH

Spectrum of Skin Manifestations in CKD: A Tertiary Care Center Experience from North India

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ABSTRACT

Introduction: Dermal manifestations in chronic kidney disease (CKD) patients may range from mild ones, like xerosis, skin pallor, pruritus, coated tongue, superficial infections and hair and nail changes, to severe life-threatening ones, like nephrogenic systemic fibrosis, which is a rare entity in current times. The present study was done to evaluate the spectrum of mucocutaneous manifestations in patients with CKD and to look for an association between them and various biochemical parameters and inflammatory markers. **Material and methods:** This study was a 1 year prospective, observational study conducted on adult patients with CKD who presented to the Nephrology clinic in Pt. BD Sharma PGIMS, Rohtak. Patients between the ages of 17 and 75 years with CKD stages II or more with dermatological conditions were included in this study. Each participant was subjected to detailed clinical, biochemical, radiological and dermatological examination by same consultants in order to avoid interpersonal variations. Various skin, mucosal, nail and hair manifestations along with cutaneous infections were analyzed across the spectrum of CKD. **Results:** Among cutaneous infections, fungal infections predominated, amongst which, onychomycosis was the most common. Xerosis was the most common dermatological disease and the prevalence of xerosis, skin pallor and pruritus was found to increase significantly from Stage II to Stage V and V_D of CKD in a statistically significant manner. An association was found between xerosis and decreasing levels of hemoglobin and while ferritin was not different between patients with and without xerosis, high-sensitivity C-reactive protein (hs-CRP) was significantly higher in patients with xerosis. Similarly, hs-CRP levels were significantly elevated in patients with xerostomia and nail pallor as compared with those who did not have these conditions. Lastly, patients with nail pallor had significantly lower albumin. **Conclusion:** It was observed in our study that in CKD patients on hemodialysis and on conservative management, xerosis, pruritus, pigmentation, nail changes, oral mucosa changes and cutaneous infections were the predominant cutaneous manifestations. In patients with CKD, mucocutaneous manifestations progressively worsened as renal function deteriorated.

Keywords: Chronic kidney disease, xerosis, pruritus, pigmentation, nail changes

Chronic kidney disease (CKD) is characterized by progressive and irreversible loss of renal function over a period of months to years. This decline in renal function, as measured by glomerular filtration rate (GFR), is a function of nephron loss. The true community incidence and prevalence of CKD are difficult to determine as early CKD usually remains asymptomatic. The worldwide prevalence of CKD is estimated to be 13.4%[1]. In the 2015 Global Burden of Disease Study, CKD was the 12th major cause of death, accounting for 1.1 million deaths worldwide. In India, a 2013 study found the prevalence of CKD to be 17.2% with a distribution of 7% in Stage I, 4.3% in Stage II, 4.3% in Stage III, 0.8% in Stage IV and 0.8% in Stage V[2]. Patients with CKD constitute a significant social and economic burden, both in terms of resource utilization and indirectly through loss of productivity and impaired quality of life.

Impaired kidney function leads to disturbances in almost all systems of the body and skin is the most visible of them. Despite that, they are often overlooked by both the patients and the clinicians. Added to this is the fact

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that very little literature is available to describe these skin changes and their effect on the overall outcome for the patient. Dermal manifestations in CKD patients may range from mild ones, like xerosis, skin pallor, pruritus, coated tongue, bacterial and superficial infections, and hair and nail changes, to severe life-threatening ones, like nephrogenic systemic fibrosis, which is a rare entity in current times.

While many of these cutaneous disorders are caused by the underlying renal disease itself, a few are related to the severity and duration of uremia. This increase with increasing duration and severity of renal disease is in parallel with a graded increase in inflammation and oxidative stress. Numerous studies have reported an association between renal impairment and different markers of inflammation, including C-reactive protein (CRP) and serum ferritin. Altered calcium and phosphate homeostasis in CKD patients is also associated with higher prevalence of cutaneous manifestations. Lastly, various socioeconomic factors, such as low socioeconomic status, poor nutrition and poor social and personal hygiene also play an important role, especially in a developing countries like ours.

Skin diseases affect the morbidity, mortality and outcome in CKD patients. Length of hospital stay is significantly greater, and so are the reported treatment costs. Cutaneous findings in CKD patients may also be associated with psychological distress on account of cosmetic concerns. Despite better understanding of the pathophysiologic mechanisms of skin manifestations, optimal treatment still remains elusive for a large number of patients. Hence, it is necessary to search actively for signs of skin manifestation in renal disease because early diagnosis and treatment can improve the prognosis for CKD patients and reduce economic costs connected with treatment. The present study was done to evaluate the spectrum of mucocutaneous manifestations in patients with CKD and to look for an association between them and various biochemical parameters and inflammatory markers.

MATERIAL AND METHODS

This study was a 1 year prospective, observational study conducted on adult patients with CKD who presented to the Nephrology clinic in Pt. BD Sharma PGIMS, Rohtak. Patients between the ages of 17 and 75 years with CKD stages II or more with dermatological conditions were included in this study. A total of 125 patients were hence recruited over a period of 1 year between January and December, 2019.

Patients positive for human immunodeficiency virus (HIV), hepatitis B or hepatitis C as well as renal transplant recipients were excluded from the study. Similarly, those with a preceding dermatological disorder, connective tissue disease, comorbid hepatobiliary, pancreatic, thyroid disorder or malignancy were also excluded. After taking written and informed consent and a thorough history, each participant was subjected to detailed clinical, biochemical, radiological and dermatological examination by same consultants in order to avoid interpersonal variations. All patients underwent routine investigations along with high-sensitivity CRP (hs-CRP) measured by particle enhanced immune turbid metric assay and serum ferritin by enzyme immunoassay. hs-CRP >3 mg/L and serum ferritin >200 µg/L were considered significant and suggestive of active inflammatory stage of the patient.

Depending upon the stage of CKD, these 125 patients were classified into 5 groups – Group A through E: **Group A** consisted of 10 patients with eGFR between 60-89 mL/min/1.73 m^2 (CKD Stage II); **Group B** consisted of 15 patients with eGFR between 30-59 mL/min/1.73 m^2 (CKD Stage III); **Group C** consisted of 20 patients with eGFR between 15-29 mL/min/1.73 m^2 (CKD Stage IV); **Group D** consisted of 45 patients with eGFR <15 mL/min/1.73 m^2 not on hemodialysis (CKD Stage V); **Group E** consisted of 35 patients with eGFR <15 mL/min/1.73 m^2 on hemodialysis (CKD Stage V_D).

Statistical Analysis

Data were entered into Microsoft excel workbook 2019 and exported into SPSS. Categorical variables were expressed as frequency and percentage, and compared using Chi-square test. Normally distributed variables were compared between two group using Student *t*-test. One-way analysis of variance followed by Bonferroni post-hoc correction analysis was performed to compare quantitative variables between more than two groups. P value <0.05 was considered significant. Statistical analyses were performed using SPSS version 21.0 (IBM, USA).

RESULTS

Mean age of the patients was 43.1 ± 12.3 years with 5% of patients more than 60 years of age, and 60% of patients being male. The most common etiology of CKD was diabetes mellitus, accounting for 47% of cases, followed by hypertensive nephropathy (39%) and immunoglobulin A (IgA) nephropathy (33%). The least common etiologies of CKD were chronic glomerulonephritis (6%) and renal amyloidosis (5%).

Majority of the patients in our study were obese (67%), followed by normal (19%) and overweight (12%). Only 1.6% patients were underweight.

Various skin, mucosal, nail and hair manifestations along with cutaneous infections were analyzed across the spectrum of CKD. It was noted that xerosis was the most common dermatological disease and the prevalence of xerosis, skin pallor and pruritis was found to increase significantly from Stage II to Stage V and V_D of CKD in a statistically significant manner. Furthermore, xerostomia (the most prevalent mucosal manifestation) and nail pallor (the most common nail manifestation) were also found to have a significant rise in prevalence with increasing stage of CKD. Among hair changes, sparse scalp hair was the most common finding but none of the hair diseases were found to have a statistically significant increase from Group A to E. Among cutaneous infections, fungal infections predominated, amongst which, onychomycosis was the most common. The prevalence of dermatological manifestations and dermatological infections as a function of different stages of CKD is summarized in Table 1 and Table 2, respectively.

Patients were further divided into two groups – those managed conservatively and those on dialysis (Table 3). Perforating folliculitis was found in 4 patients

Table 1. Prevalence of Dermatological Manifestations as a Function of Different Stages of CKD

	Group A	Group B	Group C	Group D	Group E	Total (%)	P value
Skin manifestations							
Early wrinkling	0	1	1	5	3	10 (8%)	0.780
Perforating folliculitis	0	0	0	1	4	5 (4%)	0.122
Skin pallor	0	4	11	18	18	51 (41%)	<0.05
Diffuse hyperpigmentation	2	5	10	13	17	47 (37.6%)	0.199
Xerosis	0	2	7	31	25	65 (52%)	<0.05
Bullous lesions	0	0	1	3	3	7 (5.6%)	0.703
Pruritus	0	8	9	25	13	55 (44%)	<0.05
Mucosal manifestations							
Xerostomia	0	3	3	14	15	35 (28%)	<0.05
Angular cheilitis	1	2	3	7	7	20 (16%)	0.940
Fissured tongue	0	3	3	10	5	21 (17%)	0.512
Coated tongue	1	3	3	10	12	29 (23.2%)	0.372
Hair manifestations							
Lusterless hair	2	6	6	22	12	48 (38.4%)	0.356
Sparse body hair	1	5	5	18	14	43 (34.4%)	0.338
Sparse scalp hair	5	6	8	17	18	54 (43.2%)	0.765
Nail manifestations							
Dystrophic nails	0	1	2	10	5	18 (14.4%)	0.292
Nail discoloration	2	3	7	13	13	38 (30.4%)	0.685
Onycholysis	2	1	2	7	6	18 (14.4%)	0.816
Half and half nail disease	0	4	6	14	9	33 (26.4%)	0.374
Nail pallor	1	2	9	23	17	52 (41.6%)	<0.05

Data expressed in frequency and percentage; compared using Chi-square test.

Table 2. Prevalence of Dermatological Infections as a Function of Different Stages of CKD

	Group A	Group B	Group C	Group D	Group E	Total (%)	P value
Fungal infections (n = 43)							
Onychomycosis	0	4	3	10	9	26 (60.4%)	0.417
Tinea pedis	0	1	1	2	0	4 (9.3%)	0.644
Tinea curis and Tinea corporis	0	1	1	0	1	3 (6.9%)	0.537
Intertrigo	0	0	1	0	1	2 (4.6%)	0.565
Oral candidiasis	0	1	0	2	1	4 (9.3%)	0.770
Pityriasis	0	1	0	2	1	4 (9.3%)	0.747
Bacterial infections (n = 21)							
Folliculitis	0	1	2	4	5	12 (57.1%)	0.713
Furunculosis	0	0	0	2	1	3 (14.2%)	0.713
Ecthyma	0	0	1	1	2	4 (19%)	0.756
Carbuncle	0	0	1	0	1	2 (9.5%)	0.565
Viral infections (n = 8)							
Herpes simplex	0	1	2	2	1	6 (75%)	0.717
Herpes zoster	0	0	1	0	0	1 (12.5%)	0.259
Erythema multiforme	0	0	0	1	0	1 (12.5%)	0.774

All data expressed in frequency and percentage, compared with Chi-square test; total percentage of a specific infection has been calculated as a proportion of total number of infections caused by the particular category of organism.

Table 3. Prevalence of All Dermatological Manifestations in CKD Patients – Nondialysis vs. Dialysis Group

	CKD patients not on dialysis (n = 90)	CKD patients on dialysis (n = 35)	Total (n = 125)	P value
Skin manifestations				
Early wrinkling	7 (7.8%)	3 (8.6%)	10 (8%)	1.000
Perforating folliculitis	1 (1.1%)	4 (11.4%)	5 (4%)	<0.05
Skin pallor	33 (36.7%)	18 (51.4%)	51 (41%)	0.132
Diffuse hyperpigmentation	30 (33.3%)	17 (48.6%)	47 (37.6%)	0.114
Xerosis	40 (44.4%)	25 (71.4%)	65 (52%)	0.335
Bullous lesions	4 (4.4%)	3 (8.6%)	7 (5.6%)	0.640
Pruritus	42 (46.7%)	13 (37.1%)	55 (44%)	<0.05
Mucosal manifestations				
Xerostomia	20 (22.2%)	15 (42.9%)	35 (28%)	<0.05
Angular cheilitis	13 (14.4%)	7 (20.0%)	20 (16%)	0.625
Fissured tongue	16 (17.8%)	5 (14.3%)	21 (17%)	0.840
Coated tongue	17 (18.9%)	12 (34.3%)	29 (23.2%)	0.067

Table 3. Prevalence of All Dermatological Manifestations in CKD Patients – Nondialysis vs. Dialysis Group

	CKD patients not on dialysis (n = 90)	CKD patients on dialysis (n = 35)	Total (n = 125)	P value
Hair manifestations				
Sparse scalp hair	36 (40.0%)	18 (51.4%)	54 (43.2%)	0.247
Lusterless hair	36 (40.0%)	12 (34.3%)	48 (38.4%)	0.555
Sparse body hair	29 (32.2%)	14 (40.0%)	43 (34.4%)	0.411
Nail manifestations				
Nail pallor	35 (38.9%)	17 (48.6%)	52 (41.6%)	0.324
Half and half nail disease	24 (26.7%)	9 (25.7%)	33 (26.4%)	0.914
Dystrophic nails	13 (14.4%)	5 (14.3%)	18 (14.4%)	0.982
Nail discoloration	27 (30.0%)	13 (37.1%)	38 (30.4%)	0.861
Onycholysis	12 (13.3%)	6 (17.1%)	18 (14.4%)	0.794
Infections				
Bacterial infections	12 (13.3%)	9 (25.7%)	21 (16.8%)	0.096
Viral infections	7 (7.8%)	1 (2.9%)	8 (6.4%)	0.313
Fungal infections	30 (33.3%)	13 (37.1%)	43 (34.4%)	0.642

Data expressed in frequency and percentage; compared using Chi-square test.

on dialysis in comparison to 1 patient not on dialysis ($p < 0.05$). Xerostomia was also seen to be more common in patients on dialysis. Pruritus on the other hand, was significantly higher in nondialysis patients. Xerosis, early wrinkling, diffuses hyperpigmentation and bullous lesions were more common amongst conservatively managed patients, but this difference was not statistically significant.

We observed a decrease in serum ferritin levels with increasing CKD stage. Serum ferritin levels in the patients of CKD stage V_D were substantially lower in comparison to other stages ($p < 0.05$). There was no significant difference in serum ferritin levels amongst the other stages. It was also noted that hs-CRP levels increased with increasing CKD stage and patients with Stage V and Stage V_D disease had higher levels of CRP in comparison to other stages ($p < 0.05$); maximum values were noted in Stage V_D. Results of distribution of serum ferritin and hs-CRP among different stages of CKD are shown in Table 4 and Figure 1 a and b.

Table 4. Comparison of Inflammatory Markers among Different CKD Stages

	Serum ferritin	hs-CRP
Group A	202.50 ± 23.36	2.26 ± 0.90
Group B	197.76 ± 20.66	2.60 ± 0.47
Group C	197.65 ± 20.59	3.17 ± 0.51
Group D	193.91 ± 16.49	10.42 ± 6.96
Group E	173.86 ± 18.01	15.55 ± 5.82
P value	<0.05	<0.05
Pair-wise comparison	Group A vs. Group E <0.05 Group B vs. Group E <0.05 Group C vs. Group E <0.05 Group D vs. Group E <0.05 Others = nonsignificant	Group A vs. Group E <0.05 Group B vs. Group E <0.05 Group C vs. Group E <0.05 Group D vs. Group E = 0.05 Group A vs. Group D <0.05 Group B vs. Group D <0.05 Group C vs. Group D <0.05 Others = nonsignificant

Data expressed in mean ± SD; Kruskal-Wallis test used followed by pair-wise comparison.

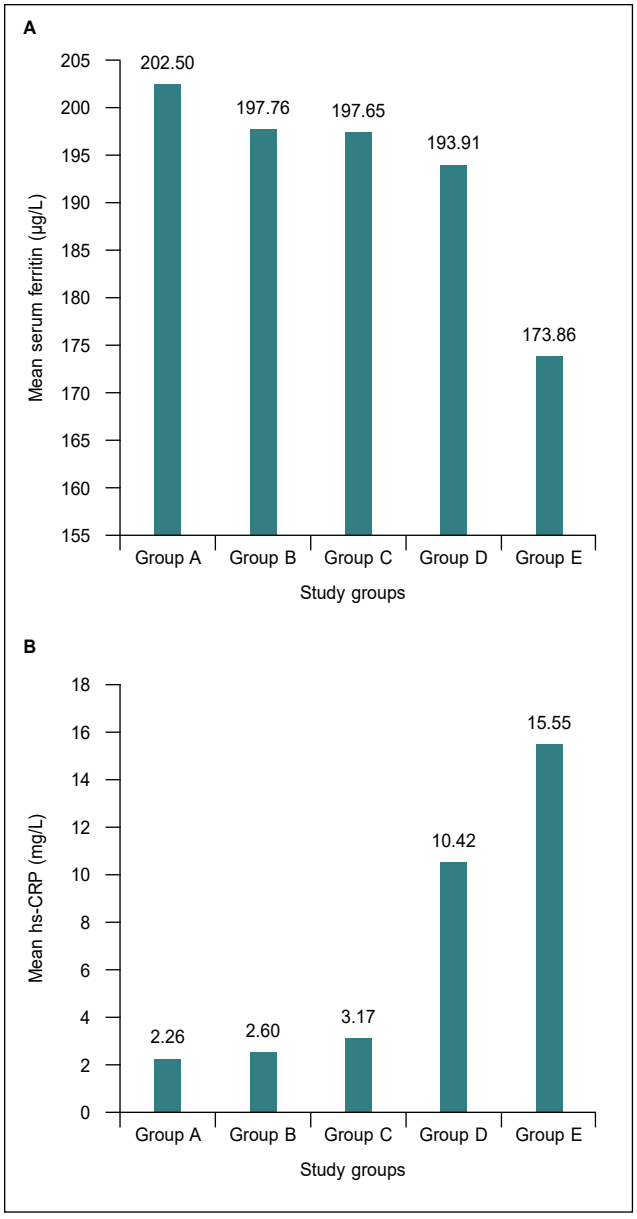

Figure 1 a and b. Association of inflammatory markers with different stages of CKD.

Other notable observations of our study include the fact that patients with skin pallor as well as nail pallor had comparable hemoglobin (9.3 ± 1.4 vs. 9.4 ± 1.3; p = 0.828), in comparison to the patients without these conditions. On the other hand, an association was found between xerosis and decreasing levels of hemoglobin and while ferritin was not different between patients with and without xerosis, hs-CRP was significantly higher in patients with xerosis. Similarly, hs-CRP levels were significantly elevated in patients with xerostomia and nail pallor as compared with those who did not have these conditions. Lastly, patients with nail pallor had a significantly lower albumin.

DISCUSSION

Xerosis was found to be the most common cutaneous manifestation in our study at a high prevalence of 52% with majority belonging to Stage V. The prevalence was reported to be quite high in studies on comparable populations, including Udayakumar et al and Khanna et al, who observed xerosis at a prevalence rate of 79% and 72%, respectively[3,4]. Xerosis was significantly associated with decreasing eGFR and hemoglobin levels and higher hs-CRP levels. Skin pallor was the second most common cutaneous manifestation, observed in 51 (40.8%) patients, out of which 36 patients had advanced CKD. It was significantly more prevalent in patients with lower eGFR ($p < 0.05$). Skin pallor in CKD patients can be explained by decreased renal erythropoietin levels, iron, folic acid or vitamin B12 deficiency, poor erythrocyte survival and blood loss during dialysis. Rashpa et al observed a 50% prevalence of skin pallor in their study of CKD patients, with it being the second most common skin manifestation[5]. Pruritus was recorded in 55 out of 125 patients (44%) in our study, with a majority of patients in CKD Stage V. Hajheydari et al observed that pruritus worsened after dialysis in 46.15% of patients in their study[6]. While it is commonly reported as the most troublesome dermatological symptom of renal disease, Hiroshige et al observed that aggressive dialysis led to significant reductions in pruritus severity[7].

Xerostomia was the most common mucosal manifestation observed in our study, present in 35 patients (28%). Out of 35 patients, 29 (83%) patients belonged to advanced CKD, out of which 15 patients were on hemodialysis. Hopcraft and Tan reported the association of xerostomia and CKD stages and found that the prevalence of xerostomia in the general population ranged from 10% to 46%[8]. Increase in frequency of xerostomia in patients with worsening renal function can be explained by restricted diets, malnutrition, poor oral hygiene, reduced dental visits, immunosuppression and the effects of medications and uremic toxins on the oral tissues. Xerostomia was also significantly associated with hs-CRP in our study. Patients with xerostomia having higher hs-CRP levels are at increased risk of lesions to the mucosa, gingiva and tongue. Many of these conditions are because of the chronic inflammation that is frequently present in patients on hemodialysis.

Hair changes observed in our study population included sparse scalp and body hair and lusterless hair. The most common finding was sparse scalp hair, seen in 43.2% of patients and its prevalence was higher in

predialysis patients than patients on dialysis. However, none of the hair diseases were associated with CKD stage or biochemical parameters. A study observed that the prevalence of hair findings across all stages of CKD may result from the higher mean age of the patients. Sparse scalp and body hair seen in 35.2% and 13.1% patients, respectively, and lusterless hair seen in 12.3% patients, could be attributed to anemia, stress of end-stage kidney disease/dialysis or neglect of hair care[5]. As for nail changes, nail pallor was found to be the most common nail manifestations seen in 52 out of 125 patients and was found to prevalence rose with increase in CKD stage. Amatya et al reported similar findings with nail pallor (white nail) being the most common nail manifestation in both dialysis and predialysis patients[9].

The CKD patients have increased susceptibility for skin infections due to reduced immunity. Cutaneous infections including fungal, bacterial and viral were seen in 34.4%, 16.8% and 6.4% of CKD patients, respectively. However, these skin infections were not consistently associated with different CKD stages. Hemodialysis patients get exposed to numerous infections during the course of treatment, and a large proportion of patients need to be hospitalized at least once every year for treatment of the same[10]. The type of vascular access in use plays an important role in the subsequent development of bloodstream infections. Central venous catheters tend to heighten the risk of bacteremia among dialysis patients[11]. Those with temporary catheters have been shown to have a 50% higher risk of septicemia compared to patients with a native fistula. Increasing the use of arteriovenous fistula as hemodialysis access can reduce the risk of infections.

While comparing skin manifestations between patients on dialysis and conservative management, we found a significant difference in terms of perforating folliculitis and xerostomia which were more common in the dialysis group, whereas pruritus had higher prevalence in the predialysis subset. This is in contrast to a study of 150 predialysis and 50 dialysis patients, in which the authors found that the prevalence of xerosis, pruritus and pigmentary changes was higher in dialysis patients, whereas nail changes showed no significant difference between the groups[4].

We found that serum ferritin level decreased with increasing CKD stage, and was significantly lower in CKD stage V_D. The levels of serum ferritin in a patient of CKD can be extremely variable. In addition to being an index of iron stores within the body, it is also a positive acute phase reactant. Hence, while severe iron deficiency anemia will be associated with low ferritin levels, prominent chronic inflammation associated with CKD would be associated with high levels. Studies have shown that ferritin levels below 200 ng/mL were associated with depleted iron stores, whereas levels in excess of 2,000 ng/mL were associated with iron overload[12,13]. Kalantar-Zadeh conducted a study on 72 hemodialysis patients with serum ferritin levels between 200 and 2,000 ng/mL. They found that increasing ferritin levels within this range was significantly associated with both malnutrition and inflammation as evidenced by SGA (subjective global assessment) and MIS (malnutrition-inflammation score) scores[14]. In our study, most of the patients had serum ferritin levels below 200 ng/mL indicating the high burden of iron deficiency anemia in the study population.

The mean value of serum hs-CRP was found to have an increasing trend from Group A to E and hs-CRP levels were high in 36% of our study population. In addition, most, if not all inflammatory markers, were elevated in CKD Stage V patients on hemodialysis, indicating high prevalence of inflammation in this subset. Chen et al conducted a study on the association of uremic pruritus with inflammation and hepatitis infection on 321 CKD patients on hemodialysis. They concluded that higher hs-CRP levels were associated with more severe pruritus and in turn poorer survival when adjusted for other mortality causing factors[15]. In our analysis; however, we did not find a substantial difference in hs-CRP levels between patients with and without pruritus. Patients with xerosis, on the other hand, had statistically significant hs-CRP levels.

Our study had a few limitations which include the fact that this is a cross-sectional study from which causal relationships cannot be drawn. Furthermore, only clinical examination of the skin lesions was performed and no diagnostic instrumentation or skin biopsy was done. The limited sample size may act as a deterrent to accurate justification of the results in our study.

CONCLUSION

In our study, CKD patients showed at least one cutaneous change. It was observed that in CKD patients on hemodialysis and on conservative management, xerosis, pruritus, pigmentation, nail changes, oral mucosa changes and cutaneous infections were the predominant cutaneous manifestations. Mucocutaneous manifestations progressively worsened as renal function deteriorated. The dermatological manifestations and presence of inflammation in CKD is a complex multifactorial problem which commences early and

progresses with the stage of the disease. Assessment of key components of dermatological manifestations and inflammation early in disease course will help identify high-risk subjects in whom modifying these predictors will assist in providing an active and healthy life to CKD patients.

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