Mucocutaneous Manifestations in Patients with Chronic Kidney Disease: A Cross-sectional Study

Abstract

**Background:** Chronic kidney disease (CKD)-associated mucocutaneous manifestations significantly impair the quality of life but often remain understudied. They may also vary across regions, socioeconomic and nutritional status, and racial differences. **Objectives:** To study the patterns of mucocutaneous disorders and their prevalence in CKD patients irrespective of clinical stage or dialysis status. **Materials and Methods:** 122 (M:F = 77:45) patients aged 21–85 (Mean ± SD = 57.5 ± 14.0) years having CKD for 3 month to 5 years were studied for mucocutaneous manifestations. Fifty (41%) patients were on hemodialysis for 1–42 months. Detailed medical history, clinical and mucocutaneous examination, and lab investigations were performed. KOH mounts, skin biopsy, Gram’s and Giemsa staining, bacterial or fungal cultures were performed as required. **Results:** Xerosis in 93 (76.2%), skin pallor in 61 (50%), pruritus in 57 (46.7%), pigmentation in 47 (38.5%), and purpura in 18 (14.8%) patients were the major dermatoses. Bullous lesions and perforating folliculitis occurred in 3 (2.5%) patients each. Major nail abnormalities were pallor (in 35.2%), absent lunula (in 23.8%), nail discoloration (in 18%), and “half-and-half nails” in 16.4% patients, respectively. Hair abnormalities included sparse scalp and body hairs (in 35.2% and 13.1%, respectively) and lusterless hair in 12.3% patients. Coated tongue (in 14.8%), xerostomia (in 12.3%), and macroglossia with teeth indentation (in 7.4%) patients were the mucosal manifestations. **Conclusions:** Xerosis, pruritus, skin pallor/pigmentary changes, nail pallor, absent lunula, nail discoloration, sparse hairs, coated tongue, xerostomia, macroglossia, and infections were the most common mucocutaneous manifestations in the studied patients irrespective of hemodialysis status. Cold and dry climates might be additional aggravators for xerosis/pruritus. Lifelong follow-up may be needed to reduce the morbidity associated with CKD/hemodialysis specific dermatoses appearing over a period.

**Keywords:** Cutaneous manifestations, end-stage renal disease, skin diseases

Introduction

Chronic kidney disease (CKD) is an irreversible deterioration in renal function classically developing over years and is defined as kidney damage or glomerular filtration rate <60 ml/min/1.73 m² for 3 months or more irrespective of the cause. Most patients with severe CKD progress to end-stage renal disease (ESRD) with significant morbidity and mortality. It is a worldwide problem and accounts for approximately 850,000 deaths every year and 15 million disability adjusted lives; ESRD is the 12th cause of death and 17th cause of disability globally. Cutaneous manifestations are common in all stages of CKD particularly towards ESRD with a prevalence of 50–100%. With the advent of hemodialysis as a therapeutic modality for ESRD, some skin manifestations such as uremic frost and erythema papulatum uremicum have become rare, however, many other abnormalities of skin and appendages have emerged. Skin manifestations specific to dialysis patients include acquired perforating dermatosis, calcific uremic arteriolopathy (calciphylaxis), bullous lesions, and nephrogenic fibrosing dermopathy. On the other hand, pruritus, xerosis, nail disorders, hair disorders, pigmentary changes, purpura, mucosal changes, pallor, and uremic frost, though not specific to hemodialysis, are more frequent. However, it may be difficult to implicate either CKD or hemodialysis alone for any particular cutaneous manifestation as many of them are associated with both. These manifestations may also vary across regions, with individual dietary habits, socioeconomic and nutritional status, and

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racial differences. Because there are no data on the pattern of mucocutaneous manifestations in CKD patients from this part of the country, this study was carried out.

**Patients and Methods**

This study included 122 consecutive CKD patients aged ≥18 years recruited from the renal unit under internal medicine during April 2015 to March 2016. The study was approved by the Institutional Scientific Protocol Review Committee and Institutional Ethics Committee. All enrolled patients participated after providing informed written consent. Human immunodeficiency (HIV)-affected persons, renal transplant recipients, and patients with acute renal failure, hepatobiliary, pancreatic, or thyroid disorders, cutaneous, or systemic malignancies were excluded. Details of medical history, clinical and mucocutaneous findings, and investigations were recorded. KOH mounts, skin biopsy, Gram's and Giemsa staining, and bacterial or fungal cultures were performed when needed. The diagnosis and clinical staging of CKD was as per the National Kidney Foundation severity assessment criteria, and the severity of pruritus and xerosis was graded as mild, moderate, and severe [Table 1]. The data was analyzed using Pearson’s Chi Square and Fischer’s exact nonparametric test was used for other variables that were not distributed normally. P < 0.05, calculated at the 5% level (95% confidence limit) was considered statistically significant.

**Results**

Table 2 depicts the baseline characteristics of patients comprising 77 men and 45 women (M:F = 1.7:1) aged between 21 and 85 (mean ± SD = 57.5 ± 14.0) years having CKD for 3 months to 5 years. Fifty (41%) patients were on hemodialysis for 1–42 (mean ± SD = 9.3 ± 9.0) months. The blood urea levels ranged from 100 to 280 mg/dl in 92 (75.4%) patients. Hemoglobin was between 4.5 and 12 g/dl in 120 (98.4%) patients. One or more mucocutaneous disorders occurred in 120 (98.3%) patients [Tables 3 and 4].

Xerosis in 93 (76.2%) patients, severe and ichthyotic in 10 (8.2%) patients, and pruritus of mild to severe intensity in 57 (46.7%) patients were the most common manifestations. The pruritus intensity was mild to moderate in 52 (55.9%) patients with xerosis. Photodistributed hyperpigmentation in 47 (38.5%), skin pallor in 61 (50%), yellow-tinted skin in 7 (5.7%), and purpura/eczymosis in 18 (14.8%) patients were present. Tense bullae over toes [Figure 1] and perforating folliculitis [Figure 2] were noted in 3 (2.5%) patients each who were also diabetic. Four (3.3%) patients aged 36–43 years had facial wrinkling. One patient, a diabetic and on hemodialysis for 3 months, had a nonhealing ulcer on the right foot. Mucosal abnormalities occurred in 48 (39.3%) patients and in the order of frequency were coated tongue in 18 (14.8%), xerostomia in 15 (12.3%), macrognlossia with teeth markings [Figure 3], and fissured tongue in 9 (7.4%) patients each, angular cheilitis in 5 (4.1%), and aphthous stomatitis and black pigmented tongue [Figure 4] in 2 (1.6%) patients each. Hair abnormalities in 55 (45.1%) patients included sparse scalp and body hairs and lusterless hairs in 45 (35.2%), 16 (13.1%), and 15 (12.3%) patients, respectively. Nail changes in 91 (74.6%) patients comprised nail pallor in 43 (35.2%), absent lunula in 29 (23.8%), nail

| Table 1: Staging of chronic kidney disease and severity grading of pruritus and xerosis |
|-----------------------------------------|------------------------------------------|
| Staging of CKD[^1,7]                  | Definition                                |
| Stage 1                                | normal estimated glomerular filtration rate (eGFR)* ≥90 mL/min per 1.73 m² and persistent albuminuria |
| Stage 2                                | eGFR between 60 and 89 mL/min per 1.73 m² |
| Stage 3                                | eGFR between 30 and 59 mL/min per 1.73 m² |
| Stage 4                                | eGFR between 15 and 29 mL/min per 1.73 m² |
| Stage 5                                | eGFR <15 mL/min per 1.73 m² or end-stage renal disease |
| Severity of pruritus[^8]               | Pruritus is episodic and localized without disturbance in routine work and sleep |
| Mild                                   | Pruritus is generalized and continuous without sleep disturbance |
| Moderate                               | Pruritus is generalized and continuous disturbing sleep |
| Severe                                 | Xerosis localized over legs only           |
| Severity of xerosis[^8]                | Xerosis localized over all the extremities |
| Absent (grade-0)                       | Xerosis generalized and ichthyosis-like |
| Mild (grade-1)                         |                                          |
| Moderate (grade-2)                     |                                          |
| Severe (grade-3)                       |                                          |

CKD, Chronic kidney disease; *eGFR, estimated calculated creatinine clearance (eCcr) is used as a correlate of GFR and calculated as: eCcr = (140–age) × (weight in kilograms) × (0.85 if female)/72 × Serum Creatinine in mg/dl.

Figure 1: Large tense bullae over toes in a patient with diabetic nephropathy
discoloration in 22 (18%), and Lindsay’s “half-and-half nails” [Figure 5] in 20 (16.4%) patients. Other nail changes included longitudinal ridging in 13 (10.7%), subungual hyperkeratosis in 11 (9%), onycholysis in 10 (8.2%), dystrophic nails in 7 (5.7%), Beau’s lines in 6 (4.9%), and koilonychia in 5 (4.1%) patients, respectively. Statistically, patients on hemodialysis were older, had longer duration of CKD, skin and nail pallor, elevated blood urea levels, and low hemoglobin (mean ± SD = 7.2 ± 0.8 g/dl) than patients without hemodialysis, and the difference was statistically significant (P < 0.05). Table 5 lists various bacterial, fungal, and viral infections noted in 59 (48.4%) patients.
Discussion

Clinicodemographic profile of our patients is similar to previous reports. Xerosis of variable severity is well known in 23–90% patients irrespective of dialysis status. Skin dehydration, diuretics, hypervitaminosis A, reduced sebum/sweat excretion, altered skin barrier, and low emollient usage have been primarily implicated for severity of xerosis whereas marked irritancy to external factors (sun, dust, detergents) is aggravating. However, prevailing dry and cold climate in this region was an additional aggravating factor in our patients. In addition to pruritus, associated with xerosis is elastosis and premature skin wrinkling in 33–40% patients. Only 4 (3.3%) patients showed early skin wrinkling in this study. Generalized or localized, episodic or continuous pruritus of variable intensity is frequent in CKD. It may or may not improve from hemodialysis and occurs in 15–49% during predialysis and in 19–90% hemodialysis patients. The pruritus was mild to severe in our 57 (46.7%) patients. However, there was no significant difference among patients with or without hemodialysis. The pathogenesis of uremic pruritus is poorly understood but its intensity is directly proportional to the severity of xerosis. The pruritus of mild to moderate intensity correlated to xerosis severity in our 52 (55.9%) patients. Sun-exposed skin hyperpigmentation observed in 47 (38.5%) CKD and 48% of the hemodialysis patients corroborated the reported prevalence of 22–54% patients correlating to the duration of dialysis as well. It is mostly attributed to excessive melanin in basal layer.

Figure 2: Perforating folliculitis with keratotic papules over (a) leg (b) abdomen. Note severe ichthyotic skin over trunk.

Figure 3: White coated tongue and Macroglossia with prominent teeth markings, the characteristic “tongue sign of uremia”.

Figure 4: Black pigmentation of tongue.

Figure 5: Lindsay’s “half and half nails” - a characteristic colored band over distal nail plate and pale proximal nail plate.
Table 3: Cutaneous and mucosal manifestations in patient with chronic renal disease

| Skin changes                        | Total n=122 (100%) | CKD Stage III n=6 (4.9%) | CKD Stage IV n=31 (25.4%) | CKD Stage V n=85 (69.7%) | On Hemo-dialysis n=50 (41%) | In pre-dialysis n=72 (59%) | P       |
|-------------------------------------|--------------------|--------------------------|---------------------------|--------------------------|-----------------------------|-----------------------------|---------|
| **Cutaneous manifestations**        |                    |                          |                           |                          |                             |                             |         |
| Xerosis                             | 93 (76.2)          | 4 (66.7)                 | 24 (77.4)                 | 65 (76.5)                | 38 (76.0)                   | 55 (76.4)                   | 0.9595  |
| Skin pallor                         | 61 (50.0)          | 0 (0.0)                  | 8 (25.8)                  | 53 (62.4)                | 32 (64.0)                   | 29 (40.3)                   | **0.0103** |
| Pruritus                            | 57 (46.7)          | 3 (50.0)                 | 12 (38.7)                 | 42 (49.4)                | 26 (52.0)                   | 31 (43.0)                   | 0.3291  |
| Diffuse hyperpigmentation           | 47 (38.5)          | 2 (33.3)                 | 7 (22.6)                  | 38 (44.7)                | 24 (48.0)                   | 23 (31.9)                   | 0.0735  |
| Purpura/ecchymosis                  | 18 (14.8)          | 0 (0.0)                  | 5 (16.1)                  | 13 (15.3)                | 9 (18.0)                    | 9 (12.5)                    | 0.4015  |
| Ichthyosis                          | 10 (8.2)           | 0 (0.0)                  | 5 (16.1)                  | 5 (5.9)                  | 4 (8.0)                     | 6 (8.3)                     | 0.9528  |
| Yellowish tinge                     | 7 (5.7)            | 0 (0.0)                  | 3 (9.7)                   | 4 (4.7)                  | 4 (8.0)                     | 3 (4.2)                     | 0.3775  |
| Early wrinkling                     | 4 (3.3)            | 1 (16.7)                 | 1 (3.2)                   | 2 (2.4)                  | 2 (4.0)                     | 2 (2.8)                     | 0.7160  |
| Bullous lesions                     | 3 (2.5)            | 0 (0.0)                  | 1 (3.2)                   | 2 (2.4)                  | 1 (2.0)                     | 2 (2.8)                     | 0.7805  |
| Perforating folliculitis            | 3 (2.5)            | 0 (0.0)                  | 0 (0.0)                   | 3 (3.5)                  | 2 (4.0)                     | 1 (1.4)                     | 0.3644  |
| Foot ulcers                         | 1 (0.8)            | 0 (0.0)                  | 0 (0.0)                   | 1 (1.2)                  | 1 (2.0)                     | 0 (0.0)                     | 0.2301  |
| **Mucosal manifestations**          |                    |                          |                           |                          |                             |                             |         |
| Coated tongue                       | 18 (14.8)          | 1 (16.7)                 | 6 (19.4)                  | 11 (12.9)                | 8 (16.0)                    | 10 (13.9)                   | 0.7488  |
| Xerostomia                          | 15 (12.3)          | 2 (33.3)                 | 0 (0.0)                   | 13 (15.3)                | 7 (14.0)                    | 8 (11.1)                    | 0.6327  |
| Macroglossia with teeth markings    | 9 (7.4)            | 0 (0.0)                  | 2 (6.5)                   | 7 (8.2)                  | 5 (10.0)                    | 4 (5.6)                     | 0.3633  |
| Fissured tongue (lingua plicata)    | 9 (7.4)            | 1 (16.7)                 | 3 (9.7)                   | 5 (5.9)                  | 2 (4.0)                     | 7 (9.7)                     | 0.2377  |
| Angular cheilitis                   | 5 (4.1)            | 0 (0.0)                  | 0 (0.0)                   | 5 (5.9)                  | 3 (6.0)                     | 2 (2.8)                     | 0.3833  |
| Aphthous stomatitis                 | 2 (1.6)            | 0 (0.0)                  | 0 (0.0)                   | 2 (2.4)                  | 0 (0.0)                     | 2 (2.8)                     | 0.2347  |
| Pigmented tongue                    | 2 (1.6)            | 1 (16.7)                 | 1 (3.2)                   | 0 (0.0)                  | 0 (0.0)                     | 2 (2.8)                     | 0.2347  |

CKD: Chronic kidney disease, A P<0.05 was considered statistically significant. Bold Value: Significant

Table 4: Hair and nail disorders in chronic renal disease patients

| Hair changes                        | Total n=122 (%) | CKD Stage III n=6 (4.9%) | CKD Stage IV n=31 (25.4%) | CKD Stage V n=85 (69.7%) | On Hemo-dialysis n=50 (41%) | In pre-dialysis n=72 (59%) | P       |
|-------------------------------------|-----------------|--------------------------|---------------------------|--------------------------|-----------------------------|-----------------------------|---------|
| Sparse scalp hair                   | 43 (35.2)       | 2 (33.3)                 | 11 (35.5)                 | 30 (35.3)                | 17 (34.0)                   | 26 (36.1)                   | 0.8120  |
| Sparse body hair                    | 16 (13.1)       | 0 (0.0)                  | 4 (12.9)                  | 12 (14.1)                | 6 (12.0)                    | 10 (13.9)                   | 0.7608  |
| Lusterless hair                     | 15 (12.3)       | 2 (33.3)                 | 2 (6.5)                   | 11 (12.9)                | 3 (6.0)                     | 12 (16.7)                   | 0.0781  |
| Nail changes                        |                 |                          |                           |                          |                             |                             |         |
| Nail pallor                         | 43 (35.2)       | 0 (0.0)                  | 8 (25.8)                  | 35 (41.2)                | 24 (48.0)                   | 19 (26.4)                   | **0.0145** |
| Absent lunula                       | 29 (23.8)       | 1 (16.7)                 | 6 (19.4)                  | 22 (25.9)                | 12 (24.0)                   | 17 (23.6)                   | 0.9595  |
| Half and half nails                 | 20 (16.4)       | 0 (0.0)                  | 3 (9.7)                   | 17 (20.0)                | 12 (24.0)                   | 8 (11.1)                    | 0.0594  |
| Nail discoloration                  | 22 (18.0)       | 2 (33.3)                 | 5 (16.1)                  | 15 (17.6)                | 7 (14.0)                    | 15 (20.8)                   | 0.3384  |
| Longitudinal Ridging                | 13 (10.7)       | 2 (33.3)                 | 3 (9.7)                   | 8 (9.4)                  | 5 (10.0)                    | 8 (11.1)                    | 0.8470  |
| Subungual hyperkeratosis            | 11 (9.0)        | 0 (0.0)                  | 4 (12.9)                  | 7 (8.2)                  | 5 (10.0)                    | 6 (8.3)                     | 0.7479  |
| Onycholysis                         | 10 (8.2)        | 0 (0.0)                  | 1 (3.2)                   | 9 (10.6)                 | 3 (6)                       | 7 (9.7)                     | 0.4653  |
| Dystrophic nails                    | 7 (5.7)         | 2 (33.3)                 | 2 (6.5)                   | 3 (3.5)                  | 1 (2.0)                     | 6 (8.3)                     | 0.1421  |
| Beau's lines                        | 6 (4.9)         | 0 (0.0)                  | 3 (9.7)                   | 3 (3.5)                  | 3 (6.0)                     | 3 (4.2)                     | 0.6531  |
| Koilonychia                         | 5 (4.1)         | 0 (0.0)                  | 0 (0.0)                   | 5 (5.9)                  | 3 (6.0)                     | 2 (2.8)                     | 0.3833  |

CKD: Chronic kidney disease, A P<0.05 was considered statistically significant. Bold Value: Significant

and superficial dermis from increased poorly dialyzable β-melanocyte-stimulating hormone. Yellow-tinged skin in 40% CKD patients is attributed to retained lipid soluble pigments in dermis/subcutis. However, it was noticed in our 7 (5.7%) patients only possibly due to poor appreciation of this subtle color against our dark-skin (type-V) patients. Anemia occurs in 34–94.3% CKD patients mainly from decreased renal erythropoietin, iron, folic acid, or vitamin B12 deficiency, poor erythrocyte survival, and blood loss during dialysis. Skin pallor in 61 (50%) patients was apparently from anemia and was significantly more common among patients on hemodialysis (P < 0.05). Purpura, ecchymosis, and petechiae reportedly occurred in 9–20%, 27%, and 19% CKD patients on
Comparatively, we noted “half and half nails” in 20 (16.4%) patients including among those on hemodialysis. Sparse scalp and body hairs in 45 (35.2%) and 16 (13.1%), and lusterless hairs in 15 (12.3%) patients, respectively, seen in our patients corroborates their reported prevalence of 30–70%.[10,16,22] Apparently, reduced sebum production and parathormone levels, anemia, stress of ESRD/dialysis, or neglecting hair care could be implicated.[11,13,14,22] The 28–70% CKD patients also have increased susceptibility for bacterial, fungal, and viral cutaneous infections due to reduced immunity.[4,13,23] In this study, 59 (48.4%) patients with or without hemodialysis also suffered these infections. More CKD/hemodialysis-specific dermatoses probably appear over a period.

**Conclusion**

Xerosis, pruritus, skin pallor/pigmentary changes, nail pallor, absent lunula, nail discolaration, sparse hairs, coated tongue, xerostomia and macroglossia, and infections were the most common mucocutaneous manifestations in majority of studied patients irrespective of their hemodialysis status. Cold and dry climates might be additional aggravators for xerosis/pruritus. Lifelong follow-up is needed to reduce the morbidity from dermatoses considered CKD/hemodialysis specific that may appear over time. Short duration and the cross-sectional nature of the study are some of the limitations of this study.

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Nil.

### Table 5: Cutaneous infections in patient with chronic renal disease

| Skin infections | Total n=122 | CKD Stage III (n=6 (4.9%)) | CKD Stage IV (n=31 (25.4%)) | CKD Stage V (n=85 (69.7%)) | On Hemo-dialysis (n=50 (41%)) | In Pre-dialysis (n=72 (59%)) | P |
|----------------|----------------|---------------------------|---------------------------|---------------------------|---------------------------|---------------------------|---|
| **Bacterial infections** | | | | | | | |
| Folliculitis | 15 (12.3) | 0 (0.0) | 7 (22.6) | 8 (9.4) | 3 (6.0) | 12 (16.7) | 0.0781 |
| Furunculosis | 8 | 0 | 3 | 5 | 2 | 6 |  |
| Ecthyma | 2 | 0 | 2 | 0 | 0 | 2 |  |
| Carbuncle | 2 | 0 | 0 | 2 | 1 | 1 |  |
| **Viral infections** | | | | | | | |
| Herpes simplex | 7 (5.7) | 1 (16.7) | 1 (3.2) | 5 (5.9) | 3 (6.0) | 4 (5.6) | 0.9260 |
| Herpes zoster | 5 | 1 | 0 | 4 | 3 | 2 |  |
| Erythema multiforme | 1 | 0 | 1 | 0 | 0 | 1 |  |
| **Fungal infections** | | | | | | | |
| Onychomycoses | 47 (38.5) | 5 (83.3) | 13 (41.9) | 29 (34.1) | 16 (32.0) | 31 (43.0) | 0.2213 |
| T. pedis | 28 | 3 | 8 | 17 | 9 | 19 |  |
| T. cruris and T. corporis | 4 | 0 | 0 | 4 | 3 | 1 |  |
| Intertrigo | 3 | 0 | 1 | 2 | 1 | 2 |  |
| Oral candidiasis | 2 | 1 | 0 | 1 | 1 | 1 |  |
| Pityriasis versicolor | 2 | 1 | 0 | 1 | 1 | 1 |  |

CKD: Chronic kidney disease, A P<0.05 was considered statistically significant.
Conflicts of interest

There are no conflicts of interest.

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