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Original Article

Mucocutaneous manifestations and nail changes in patients with end stage renal disease: A cross-sectional study

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Abstract

Background Mucocutaneous manifestations and nail changes are commonly seen in renal failure, more so in end stage renal disease (ESRD). Duration and treatment for renal disease may influence the frequency and type of these manifestations. Our objectives were to find the prevalence and pattern of mucocutaneous manifestations, nail changes in patients with ESRD, and their relation to duration of disease and mode of treatment i.e. on hemodialysis or without hemodialysis.

Methods A total of 170 consecutive patients with ESRD on hemodialysis or without hemodialysis, were examined for mucocutaneous manifestations and nail findings. Relevant investigations were done. Data collected was tabulated using simple statistical methods and chi-square test, wherever applicable.

Results Among 170 patients, 130 were male and 40 were female patients (M:F 3.25:1). Pruritus was present in 59 (34.7%) patients and frequency was more in those not on hemodialysis. Further, pruritus was seen more frequently in patients with longer duration of renal disease and hemodialysis. All the patients had at least one dermatological manifestation. Xerosis /acquired icthyosis was the most common skin finding, observed in 132 (77.6%) patients, more frequently in patients with longer duration of disease and hemodialysis followed by diffuse pigmentation in 51(30%) patients . Acquired perforating dermatoses were seen in 4 (2.7%) patients and cutaneous infections in 30 (27.5%) patients. Oral pallor was seen in 149 (87.6%) patients. Absent lunula was the most common nail finding observed in 105 (61.7%), followed by half and half nails in 62 (36.6%) patients.

Conclusion Mucocutaneous manifestations and nail changes are commonly encountered in ESRD. Frequency and spectrum of these changes may be related to duration of disease and treatment modality used.

Key words
Mucocutaneous, nail changes, chronic kidney disease, skin, systemic diseases.

Introduction

Chronic kidney disease (CKD) is characterised by slow and progressive loss of renal function resulting in various metabolic disturbances.[1]End stage renal disease (ESRD) or stage five CKD refers to the stage, when the glomerular filtration rate falls less than 15ml/min.[2]

Characteristic dermatological manifestations are commonly seen in patients with chronic kidney

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disease. Most of the patients with ESRD will have at least one associated cutaneous change.[3] Most of the cutaneous manifestations are not life-threatening. However, conditions like uremic pruritus will be distressing and adversely affect quality of life. Certain conditions like calciphylaxis can result in sepsis and subsequent mortality. Cutaneous manifestations occur with renal disease, sometimes after the initiation of dialysis. Occasionally, these may be the presenting signs of renal failure.[4]

Further, the mucocutaneous manifestations may also vary with race, climate, nutritional status and other factors. Only a few studies are available in literature, particularly on end stage renal disease. Hence, we conducted this study, to find the prevalence and pattern of mucocutaneous manifestations and nail changes in end stage renal disease. We also tried to correlate these manifestations, in relation to the duration of renal disease, hemodialysis and serum creatinine levels. Since the staging of chronic renal failure is based on glomerular filtration rate which depends on serum creatinine levels, we tried to correlate mucocutaneous changes with serum creatinine levels.

Methods

This was a descriptive, cross-sectional study. After obtaining the institutional ethical committee clearance, 170 consecutive ESRD patients (based on Kidney Dialysis Outcome Quality Initiative guidelines), attending dermatology, nephrology, medicine OPD and those admitted in medicine and dialysis wards, in between January 2015 to December 2015 were included. All patients with ESRD on hemodialysis and those not on hemodialysis, willing to participate in study were included. Those with renal transplant or on peritoneal dialysis were excluded.

After taking informed consent, a detailed history about the duration of renal failure, type of treatment undertaken, duration of hemodialysis, were taken. Regarding dermatological complaints, detailed history about pruritus, onset and evolution of skin lesions were asked for. All the patients were subjected to a detailed general physical, mucocutaneous, hair, nails and systemic examination. Routine hematological, biochemical investigations and urine analysis were done. Gram's stain, potassium hydroxide mount, skin biopsy, etc., were done wherever necessary. Both groups received oral iron, folic acid, calcium and vitamin D supplements. Injection erythropoietin (6000 units per week), was also given for those patients with haemoglobin less than 10gm percent, in both the groups.

Data collected was entered in a specially-designed proforma and analysed using SPSS version twenty. Statistical tests for descriptive analysis, like mean, frequency, percentage, standard deviation were used. For inferential statistics, Chi-square test was applied, wherever necessary.

Results

Among 170 patients, 130 were males and 40 were females, with a M:F ratio 3.25:1.Their ages ranged from 14 to 85 years (mean 46.5years). Majority, 48 (28.2%) patients, belonged to 41-50 year age group. Hypertension was the most common [63 patients; 37.1%], cause of ESRD, followed by undetermined etiology [46; 27.1%]. Co-existent diabetes and hypertension [36; 21.2%] constituted important cause of ESRD in our study.

Majority of the patients i.e. 147 (86.5%) were undergoing hemodialysis and others (23; 13.5%) were not on hemodialysis. The duration of ESRD varied from less than six months to more

Table 1 Specific mucocutaneous manifestations and nail changes in patients with ESRD.

Manifestations	*Patients on maintainance hemodialysis*		*Patients not on maintainance hemodialysis*		*P Value*
	Frequency	*Percent*	*Frequency*	*Percent*	
Symptom					
Generalised itch	47	32.0	12	52.2	0.058
Skin					
Xerosis	57`	38.8	9	39.1	0.974
Aquired icthyosis	60	40.8	6	26.1	0.177
Diffuse Hyperpigmentation	47	32.0	4	17.4	0.156
APD	4	2.7	0	0.0	0.951
Purpura/ Ecchymosis	4	2.7	0	0.0	0.951
Prurigo	7	4.8	3	13.0	0.116
Cutaneous Infections	21	14.2	4	17.3	0.695
Mucosa					
Oral Pallor	132	89.8	17	73.9	0.031
Angular Chelitis	5	3.4	0	0.0	0.957
Fissured/bald tongue	12	8.2	1	4.3	0.901
Hair					
Diffuse Alopecia	2	1.4	0	0.0	>0.99
Nails					
Longitudnal melonychia	40	27.2	7	30.4	0.747
Half and half nail	57	38.8	5	21.7	0.114
Koilyonochia	2	1.4	0	0.0	>0.99
Absent lunula	97	66.0	8	34.8	0.004
Splinter Haemorrhage	12	8.2	1	4.3	0.901
Subungual hyperkeratosis	23	15.6	3	13.0	>0.99
Onycholysis	39	26.5	6	26.1	0.964
Infections					
Fungal	12	8.2	1	4.3	0.901*
Viral	10	6.8	1	4.3	0.912*
Bacterial	4	2.7	2	8.7	0.374*

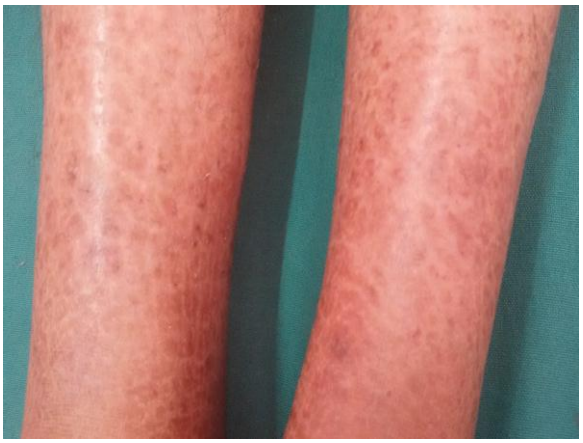

Figure 1 Acquired icthyosis involving lower limbs.

than 10 years with most, 92 (54.1%) having duration less than six months. The duration of hemodialysis ranged from less than a month to five years. Most, 59 (40.1%) were on dialysis for less than a month.

Various mucocutaneous manifestations and nail changes are shown in **Table1**. Generalised itching (pruritus) was a common complaint seen in many patients. It was more frequently seen in those not on hemodialysis. Among skin changes, xerosis/ acquired icthyosis **(Figure 1)**, was the most common finding, followed by diffuse pigmentation. Both were frequently seen in patients on hemodialysis. Pigmentation was seen mainly over the face, distal extremities and over sun exposed areas .Other findings like prurigo, purpura/ecchymosis and acquired perforating dermatoses (APD) **(Figure2)**, were seen in that

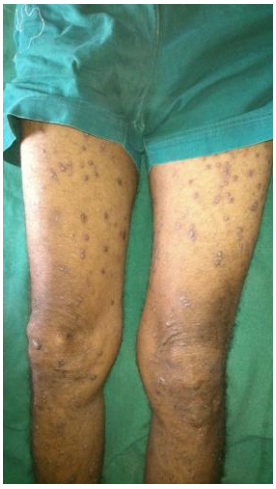

Figure 2 Perforating dermatoses over lower limbs.

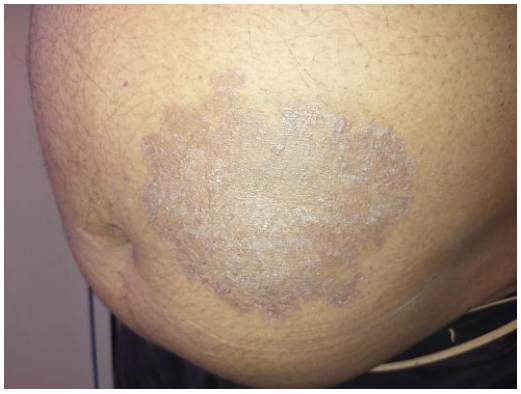

Figure 3 Tinea corporis.

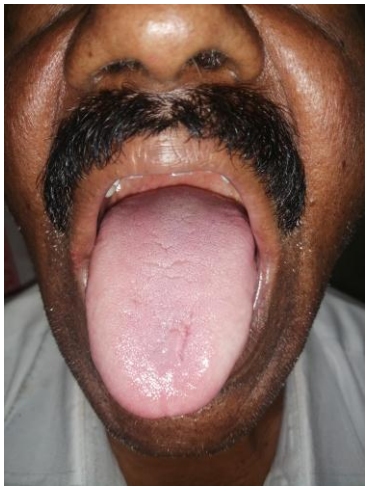

Figure 4 Oral pallor.

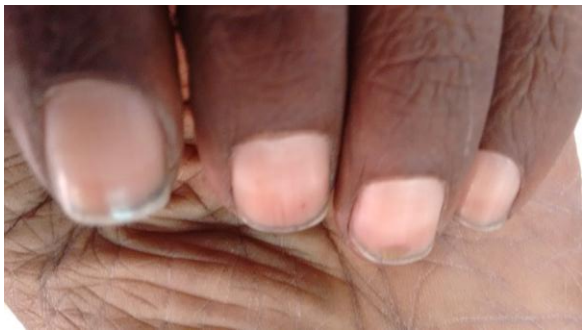

Figure 5 Absent lunula.

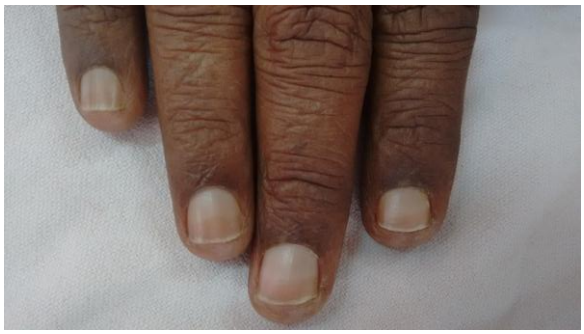

Figure 6 Half and half nails.

order. Cutaneous infections were observed in (30; 27.5%) patients commonest being fungal infections **(Figure3)**, and frequently found in patients on hemodialysis.

Most of the patients were having oral pallor **(Figure 4)**, more so in patients on hemodialysis and it was statistically significant (p-0.0031). Bald tongue, fissured tongue and angular cheilitis were the other mucosal findings.

Various nail changes were seen in our study **(Table 1)**. Absent lunula **(Figure 5)** was the commonest, frequently seen in patients on hemodialysis. This observation was statistically significant (p-0.004). Half and half nail **(Figure 6)** was the next common finding, followed by others.

Mucocutaneous manifestations and nail changes in relation to the duration of disease is shown in **Table 2**. Although, most of the findings were frequently observed with disease duration more than one year, certain conditions like purpura/ echymoses, prurigo, mucosal changes, splinter haemorrhages and bacterial infections were commonly seen in those with disease duration less than a year.

Table 3 represents comparison of dermatological manifestations in relation to duration of hemodialysis. Xerosis/ acquired icthyosis and diffuse pigmentation were observed more frequently in patients undergoing hemodialysis for more than a year and was statistically significant. Other findings were more frequent in patients undergoing hemodialysis for less than a year.

Table 2 Mucocutaneous manifestations and nail changes in patients with ESRD in relation to duration of disease.

Manifestations	*≤1 year (n=118)*		*>1 year (n=52)*		*P value*
	Frequency	*Percent*	*Frequency*	*Percent*	
Symptoms					
Generalised itch	36	30.5	23	44.2	0.083
Skin					
Xerosis	44	37.3	22	42.3	0.536
Acquired icthyosis	41	34.7	25	48.1	0.101
Diffuse hyperpigmentation	32	27.1	19	36.9	0.217
Acquierd Perforating	1	0.8	3	5.8	0.171
Dermatoses	4	3.4	0	0.0	0.457
Purpura/ecchymosis	7	5.9	3	5.8	0.966
Prurigo	16	13.5	9	17.3	0.524
Cutaneous infections					
Mucosa					
Oral pallor	107	90.7	42	80.8	0.07
Angular chelities	4	3.4	1	1.9	0.603
Fissured/bald tongue	11	9.3	2	3.8	0.358
Hairs					
Diffuse alopecia	1	0.8	1	1.9	>0.99
Nails					
Longitudnal melonychia	28	23.7	19	36.5	0.085
Half and half nails	38	32.2	24	46.2	0.081
Koilynochia	2	1.7	0	0.0	0.961
Absent lunula	68	57.6	37	71.2	0.094
Splinter hemmorhages	10	8.5	3	5.8	0.792
Subungual hyperkeratosis	18	15.3	8	15.4	0.982
Onycholysis	29	24.6	16	30.8	0.399
Infections					
Fungal	9	7.6	4	7.7	0.988
Viral	4	3.4	7	13.5	0.041
Bacterial	5	4.2	1	1.9	0.808

Dermatological manifestations in relation to serum creatinine levels are shown in **Table 4**. Among skin changes, APD, purpura/ ecchymosis were seen more frequently in patients with serum creatinine levels more than ten. Oral pallor was significantly associated with serum creatinine levels >10 (p-0.00060). Nail changes were more common, with serum creatinine levels more than 10, except subungual hyperkeratosis.

Discussion

Cutaneous manifestations of renal disease are not uncommon in patients with end stage renal disease. Earlier studies have shown that 50-100% of them will have at least one dermatological manifestation.[3] As very few studies are done on this subject, especially in ESRD or stage five CKD, we conducted this study, to find the dermatological manifestations in ESRD in our region. We found that almost all the patients had, at least one dermatological manifestation. This is possibly due to increased life expectancy and improvised health care facilities.

Most common age group in our study belonged to 41-50 years, which is consistent with the study by Udaykumar *et al*.[5] The mean age of patients in our study was 46.5 years similar to earlier studies.[6,7] As observed in previous studies, men were more commonly affected.[3,8,9] Hypertension was the most common cause of

Table 3 Mucocutaneous manifestations and nail changes in relation to duration of dialysis.

Manifestations	*< 1 year (n=116)*		*≥ 1 year (n=31)*		*P value*
	Frequency	*Percent*	*Frequency*	*Percent*	
Symptom					
Generalised itch	36	31.0	11	35.5	0.637
Skin					
Xerosis	39	33.6	18	58.1	0.013
Acquired icthyosis	51	44.0	9	29.0	0.133
Diffuse hyperpigmentation	30	25.9	17	54.8	0.002
APD	3	2.6	1	3.2	>0.99
Purpura/ ecchymosis	4	3.4	0	0.0	0.767
Prurigo	4	3.4	3	9.7	0.325
Cutaneous infections	18	15.5	3	9.7	0.614
Mucosa					
Oral pallor	107	92.2	25	80.6	0.058
Angular chelities	4	3.4	1	3.2	>0.99
Fissured tongue	11	9.5	1	3.2	0.466
Hairs					
Diffuse alopecia	1	0.9	1	3.2	0.756
Nails					
Longitudnal melonychia	29	25.0	11	35.5	0.244
Half and half nails	44	37.9	13	1.9	0.684
Koilynochia	1	0.9	1	3.2	0.756
Absent lunula	77	66.4	20	64.5	0.845
Splinter hemmorhages	12	10.3	0	0.0	0.102
Subungual hyperkeraosis	18	15.5	5	16.1	0.933
Onycholysis	30	25.9	9	29.0	0.722
Infections					
Fungal	10	8.6	2	6.5	>0.99
Viral	9	7.8	1	3.2	0.669
Bacterial	4	3.4	0	0.0	0.767

ESRD, in accordance with earlier studies.[3,8,10] However, Udaykumar *et al.*[5] found diabetes to be the most common cause.

Pruritus is the characteristic and distressing cutaneous symptom, which adds to the morbidity of the renal disease. In our study, 34.7% patients had generalized pruritus, similar to Hajyehdari *et al.*[10] and Khanna *et al*.[11] Among hemodialysis patients, pruritus was present in 32% of our patients, which is consistent with an earlier report of its prevalence of 19-90 percent.[12] Patients not on hemodialysis, had pruritus, more frequently than those undergoing hemodialysis. Further, we observed that pruritus was more in patients with longer duration of renal disease and hemodialysis, similar to other studies.[10,13] Also, more patients started experiencing itching after the onset of hemodialysis.

Uremic pruritus has been attributed to hypercalcemia, hyperphosphatemia, hyper-magnesemia and elevated concentrations of parathyroid hormone, with high calcium phosphate product. Also, the cytokines produced by the contact of blood with dialyser membrane, especially cuprophane and regenerated cellulose, will initiate an inflammation, inducing pruritus. The pruritogenic substances thus accumulated, which cannot be removed by dialysis, might exert effects on itch centers or receptors.[14] This indicates that dialysis has no role in alleviating pruritus. More prevalence of itching in our study may also be due to higher prevalence of patients with xerosis/ acquired icthyosis and associated malnutrition. Pruritus was commonly seen in our patients with serum creatinine levels less than

Table 4 Mucocutaneous manifestations and nail changes in patients with ESRD in relation to serum creatinine levels.

Manifestations	*Sr. creatinine<10 mg/dl (n=90)*		*Sr.creatinine ≥10 mg/dl (n=80)*		*P value*
	Frequency	*Percent*	*Frequency*	*Percent*	
Symptoms					
Generalised itch	35	38.9	24	30	0.224
Skin					
Xerosis	34	37.8	32	40.0	0.766
Acquired icthyosis	38	42.2	28	35.0	0.334
Diffuse pigmentation	28	31.1	23	28.8	0.737
APD	1	1.1	3	3.8	0.534
Purpural/ ecchymosis	1	1.1	3	3.8	0.534
Prurigo	7	7.8	3	3.8	0.434
Cutaneous infections	14	15.5	11	13.7	0.74
Mucosa					
Oral pallor	73	81.1	76	95.0	0.006
Angular cheilitis	4	4.4	1	1.3	0.445
Fissured/bald tongue	7	7.8	6	7.5	0.945
Hairs					
Alopecia	2	2.2	0	0.0	0.557
Nails					
Longitudnal melonychia	24	26.7	23	28.8	0.761
Half and Half nails	27	30.0	35	43.8	0.063
Koilyonochia	1	1.1	1	1.3	0.933
Absent lunula	54	60.0	51	63.8	0.615
Splinter haemorrhage	6	6.7	7	8.8	0.609
Subungual hyperkeratosis	15	16.7	11	13.8	0.597
Onycholysis	24	16.7	21	26.3	0.951
Infections					
Fungal	8	8.9	5	6.3	0.518
Viral	4	4.4	7	8.8	0.408
Bacterial	4	4.4	2	2.5	0.796

10mg/dl than with more than 10mg/dl, suggesting that, levels of serum creatinine has no role in itching in these patients, in contrast to Hu, *et al.* who found the levels of creatinine to be significantly higher in patients with itching, than without.[15]

Xerosis/ acquired icthyosis the most common cutaneous abnormality seen in these patients, predominantly over extensor surfaces of forearm, legs and thighs. A reduction in the size of eccrine gland and high dose diuretics, may contribute to its pathogenesis.[5] We found 77.6% patients to have xerosis/ acquired icthyosis, which is less compared to a study by Udaykumar *et al*.[5] However, studies by Hajyedari *et al.*[10] and Khan *et al*.[16] showed lower prevalence than our study. The difference could be due to the hot and dry climate, prevalent in our region. This finding was frequently observed with longer duration of disease. Xerosis was frequently observed in patients with higher creatinine levels (>10mg/dl) and also with longer duration of hemodialysis, and was statistically significant. This suggests that, dialysis has no beneficial effect in controlling xerosis. Chronicity of the disease, regional, racial differences and associated malnutrition may be the causative factors.

Renal failure leads to retention of chromogens and poorly dialyzable beta-melanocyte stimulating hormone, causing deposition of melanin in basal layer and superficial dermis.[17,18]

Diffuse pigmentation was observed in about one third of patients in our study which is in accordance with other studies.[1,19] Kolla *et al*.[20] have reported higher prevalence of pigmentation. Majority of our patients had shorter duration of disease and this might account for the lower prevalence of pigmentation in our study. Prevalence of pigmentation was high with longer duration of renal disease and was significantly associated with longer duration of hemodialysis, in our study. It has been shown in earlier studies that prevalence of hyperpigmentation increases with duration of dialysis.[21]

Acquired perforating dermatoses**,** are seen most commonly, in the context of patients with ESRD or Diabetes mellitus .The reported incidence is 4.5 to 17% of patients on hemodialysis.[5,22] In our study, APD were found to be quite low, consistent with Sultan *et al*.[8] Higher prevalence was found in a study by Sheikh *et al*.[1] The association between Diabetes Mellitus and APD has been established earlier. Lesser number of patients with diabetes in our series, may be the reason for low prevalence of acquired perforating dermatoses. Also there was no correlation with duration of disease and hemodialysis.

Purpura/ ecchymosis were relatively infrequent in our study similar to prior studies.[3,23] The reason could be that most of our patients were undergoing dialysis for a shorter duration. It may be possible that vascular fragility and other changes like defects in primary haemostasis develop late, during the course of dialysis.

Cutaneous infections were present in 27.5% of patients, which is consistent with earlier studies.[1,17] Our study had higher prevalence of fungal infections rather than viral and bacterial infections seen in other two studies.[1,17] This may be due to impaired cellular immunity and climatic variations like high temperature and sweating, prevalent most of the year, in our region.

Various mucosal changes were seen in our study. Most common change was oral pallor seen in 87.6% patients. It was seen frequently, in patients with hemodialysis and in those with serum creatinine levels more than 10, and both were statistically significant. Blood loss during hemodialysis, relative erythropoietin deficiency, iron deficiency, reduced erythrocyte survival, infection, inflammation, hyperparathyroidism, hemolysis and progression of renal disease affecting haemoglobin production, may be the possible explanations.[24,25] Although we found a statistically significant p value for oral pallor in relation to hemodialysis, the results should be interpreted with caution as anemia in ESRD may be due to several causes and we had not planned for the removal of all confounding factors. Other mucosal changes like angular cheilitis, fissured/ bald tongue, nutritional cheilitis, candidal balanoposthitis and actinic cheilitis were also seen, similar to other studies.[5,8] Among them mucosal changes attributable to nutritional deficiency, could have resulted due to restrictive dietary prescription, poor appetite and uremia related anorexia.

Characteristic nail changes are seen in renal disease. The etiology of nail pathologies remains unclear: some of them are apparently direct relation to the renal conditions, while others may be due to complications of the disease or therapy. Most common specific nail change in our study was absent lunula followed by half and half nails. Similar findings were reported by Sanad *et al*.[3] However, Salem *et al.*[26] found half and half nails to be the commonest change followed by absent lunula. Absent lunula is likely to be related to the metabolic disturbances and anemia occurring in renal failure patients.[27]

Appearance of half and half nail is caused by deposition of melanin in the nail plate due to stimulation of matrix melanocytes, increase of capillaries and thickening of their walls while proximal half of the nail appears white because of edema of the nail bed.[28] A higher prevalence of absent lunula was seen in patients without hemodialysis and was statistically significant. Thomas *et al*.[15] found half and half nail in 36.36% which is in accordance with our study, but it was the most common finding in their study. Udaykumar *et al*.[5] reported half and half nail in only 21% of patients, while Khanna *et al*.[11] found absent lunula in 22% of patients. Higher prevalence of these changes in our study may be due to high levels of urea, anemia and poor hygiene in our patients.

Prevalence of onycholysis, subungual hyperkeratosis and koilonychias were similar to study by Peres *et al*.[9] Onychomycosis was seen in 6.5 % of patients which are in agreement with Sanad *et al*.[3] We found a higher prevalence of Muehrcke's lines in contrast to Udaykumar *et al*.[5] who reported in 5% of patients. End stage renal disease and associated malnutrition may be responsible for this discordance. Splinter haemorrhages were similar to the reports by Udaykumar *et al*.[5] Other nail findings such as Terry's nail, clubbing, apparent leukonychia and Beau's lines, were also observed in our study, which were infrequently reported in earlier studies.[17,20]

Dry, lustreless hair and diffuse alopecia were seen in 41.2% and 2.4% of our patients. This result is in concordance with Sultan *et al.*[8] and Sanad *et al.*[3] who reported a prevalence of dry lustreless hair of 47% and 39% respectively. Udaykumar *et al.*[5] found a lower prevalence of 16%. This could be due to reduced sebum secretion. Other findings such as androgenic alopecia, scalp psoriasis, alopecia totalis and pressure alopecia were also seen in our patients.

Most common non- specific findings were seborrheic keratosis followed by acrochordons, cherry angiomas , senile comedones and other changes. These changes were similar to the findings reported by Udaykumar *et al*.[5]

Our study also had a few limitations. Patients without hemodialysis were less in number. We had not planned for overcoming the effects of confounding factors for anemia.

Conclusion

Mucocutaneous manifestations and nail changes are common in patients with end stage renal disease. The prevalence of mucocutaneous manifestations is almost 100% in these patients. Mucocutaneous manifestations may increase in frequency with duration and stage of the disease. Both patients on hemodialysis and those not on hemodialysis are equally affected. Pruritus is the commonest presenting symptom while xerosis/ icthyosis followed by diffuse pigmentation are common signs. Xerosis, diffuse pigmentation and oral pallor may be more prevalent with longer duration of the disease. Hence, early diagnosis and treatment may reduce morbidity and improve the quality of life in these patients.

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