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Clinical Pattern of Dermatoses in Patients with Chronic Kidney Disease in Ile-Ife, Nigeria

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Authors' contributions

This work was carried out in collaboration between all authors. Author MMO designed the study, perform the data collection, analysed and wrote the first draft of the manuscript. Authors OO, Olayinka Abimbola Olasode and FAA managed the statistical analysis and literature searches of the study. Authors Olumayowa Abimbola Oninla, FOO, OIE and OOO developed the structure, critically reviewed the analysis and contributed to the writing up of the manuscript. All authors read and approved the final manuscript.

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ABSTRACT

Bacground: Dermatoses are common in patients with chronic kidney disease (CKD). These dermatoses vary from the more common xerosis, pruritus, hyperpigmentations, to the less common manifestations such as nephrogenic systemic fibrosis, bullous dermatosis of haemodialysis. They arise as a consequence of failure of excretory or endocrine functions. Iatrogenic causes may also contribute to the development of these dermatoses. These manifestations impact greatly on the quality of life of patients with CKD by increasing the morbidity

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and rarely the mortality.
Objective: The objective of this study was to determine the pattern of dermatoses among patients with CKD in Ile-Ife.
Materials and Methods: The study was a cross sectional study involving patients with CKD attending Obafemi Awolowo University Teaching Hospitals Complex, (OAUTHC) Ile-Ife. One hundred and twenty patients recruited for the study had relevant clinical evaluation to confirm the dermatoses and to determine the stage of CKD. Data were analysed using SPSS version 16.
Results: The subjects aged between 18 and 84 years with a mean age of 50.76 (±18.6) years. Seventy six (63.3%) males and forty four (36.7%) females participated in the study. The occurrence of dermatoses was observed in the study to be 57.5%. The observed dermatoses did not vary significantly with stage of CKD (p=0.780). Xerosis was the commonest dermatoses observed in 26.7% of patients. Other dermatoses observed in these patients included, pruritus(13.3%), hyperpigmentation(12.5%). Pallor together with 'half and half' nails accounted for 10.8% each.Fungal infections and icthyosis also constituted 6.7% each. Plantar hyperkeratosis, follicular hyperkeratosis, chronic leg ulcer,arteriolar shunt dermatitis, alopecia, bacterial infections and Mee's lines were also documented.
Conclusion: This study shows a high prevalence of dermatosis (57.5%) among CKD patients. The observed prevalence was comparatively lower than the previously reported prevalence for this environment presumably due to improving access to better care.

Keywords: Dermatoses; kidney; pattern; disease; cutaneous manifestations.

1. INTRODUCTION

There is scarcely any systemic disease that has no cutaneous manifestation. Diseases of the kidneys are no exception, as they present with cutaneous manifestations such as pruritus, calciphylaxis, nephrogenic fibrosing dermopathy, abnormal pigmentation and abnormal keratinization. [1-3] Cutaneous infections, precancerous disorders, nail and hair changes have all been described. [1-3] These cutaneous changes can form part of the basis for evaluation and management of chronic kidney disease (CKD). The pattern of cutaneous manifestations of chronic kidney disease has been documented in previous studies with prevalence of dermatoses ranging from 50-100% [1-4].

Chronic kidney disease is very common globally with the prevalence approaching epidemic proportion. In a family practice population in Ile-Ife, a prevalence of 12.4% was reported by Afolabi et al. [5]. In the United States and Europe, CKD is estimated to affect 10% to 13% of adults [6,7].

The cutaneous manifestations of CKD could result from failure of excretory function, failure of endocrine function or as a consequence of management of CKD. The failure of excretory function and the attendant accumulation of toxic waste in the body causes some dermatoses such as bullous disease following the retention of porphyrin [8]. Reduced production of erythropoietin, 1,25-di hydroxycholecalciferol and associated dysregulation of vitamin A are examples of impaired renal endocrine functions implicated in skin pallor, uremic pruritus, perforating dermatoses and several other dermatoses. [9-13] A number of dermatoses have also been described in the settings of haemodialysis and with the use of immunosuppressant in the management of CKD patients [14-16].

Morbidity related to cutaneous manifestations of chronic kidney disease could be considerable. [17] Uraemic pruritus is recognized as an indicator of increased risk of mortality in CKD. [18] Calciphylaxis is associated with high mortality, with 1 year survival rate of 45% and 5 year survival rate of 35% [19-22].

As the outcome and survival of kidney disease improves with advances in the management approach, a change in the trend as well as the pattern of dermatoses may be expected. This is particularly so in the developing countries where modern facilities such as dialysis and increase human resources in term of specialist nephrologist becomes more accessible.

The increase in the number of kidney transplant, occasional by increasing number of Nigerian hospitals with the capability to carry out renal transplant as well as increasing medical tourism to Indian and Thailand have significantly increase the subpopulation of CKD patients with transplanted kidneys in the last decade. There has also been attendant increase in the use of

immunosuppressive agents in this group of patients which ultimately will be expected to reflect in the cutaneous presentation. This change in trend of management of CKD may alter the pattern of skin changes reported previously in these setting (developing countries) and hence the need to carry out this study.

The management of CKD is focused on retarding the progression of the disease and improving the quality of life of affected patients. Since cutaneous changes in chronic kidney disease negatively impact on the patient's quality of life, This study may also facilitate the diagnosis and management of skin diseases in these patients with associated improvement in their quality of life.

2. MATERIALS AND METHODS

2.1 Study Location

The study is a cross sectional study conducted at the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC) Ile-Ife. It is a 650 beds hospital located in the South-West geopolitical zone of Nigeria. The geopolitical zone is one of the six zones in Nigeria and comprises of six states. Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC) Ile-Ife is a referrer center attending to patients population referred from various parts of the zone.

2.2 Study Population

Patients attending medical out-patient department (MOPD), at OAUTHC Ile-Ife who are diagnosed with CKD and have a GFR less than 60 ml/min/1.73m^2 for more than three months. The patients were recruited from November 2013 to November 2014. Selected patients with systemic lupus erythematosus and those below the age of 18 years were excluded.

2.3 Data Collection

With the aid of a proforma, relevant history of symptoms, aetiology and treatment which are related to kidney disease and skin changes were obtained. Detailed examination of the skin and its appendages was carried out by the authors who are specialist dermatologist. The examination of the skin and its appendages were aided by magnifying lens when required. Patients with suspected systemic lupus erythematosus were screened using the American college of rheumatology criteria and those diagnosed with systemic lupus erythematosus were subsequently excluded from the study. Examination of other systems was also done.

GFR was calculated using the Cockcroft-Gault equation stated as:

Creatinine clearance = {(140-age) x weight (kg) x (0.85 if female)}/ {0.813 x serum creatinine (umol/L)} [23].

Patients with GFR less than 60 ml/min/1.73 m^2 for more than three months were recruited for the study. Based on GFR they were also subdivided into stages 3, 4, and 5 as shown below;

- Stage 3 kidney damage with GFR 30-59 mls / min 1.73 m^2
- Stage 4 kidney damage with GFR 15-29 mls / min 1.73 m^2
- Stage 5 kidney damage with GFR <15 mls / min 1.73 m^2 or patients on maintenance dialysis [24].

An initial GFR was obtained from the patient's records while the second was done at time of data collection to ascertain the present stage of renal disease and ensure an interval of three months. Other relevant laboratory investigations require to validate clinical diagnosis such as Skin biopsy, skin scrapings and nail clippings for fungal studies were done as appropriate. Fasting blood glucose, HIV I and II screenings, renal and liver ultrasounds were done.

2.4 Study Design

This study was cross–sectional study and a convenience (purposive) sampling requiring the consecutive recruitment of patients was employed. The data collection was aided by the use of a proforma.

The sample size was calculated based on documented 89.1% prevalence of skin changes in patients with chronic kidney disease.[3]

Using confidence interval of 95% and marginal error of 3% (0.03) a sample size of 103 was obtained. With 10% (10) of the sample size added to make for passible data loss (attrition), the total sample size is 120.

2.5 Statistical Analysis

Data were analyzed using version 16.0 SPSS statistical software. The demographic

characteristics and the cutaneous manifestations were presented using descriptive statistics such as frequency, percentage, mean. The association between the stages of CKD and the cutaneous manifestations was evaluated and presented using inferential statistics like chi-square.

2.6 Ethical Consideration

Approval of Ethics and Research Committee of the Obafemi Awolowo University Teaching Hospitals Complex (OAUTHC) Ile-Ife, was sought and obtained before the study was carried out. Informed consent was also obtained from all patients that participated in the study. Information linking patients with the data was excluded to ensure confidentiality.

3. RESULTS

One hundred and twenty patients with CKD were recruited for the study, and their socio-demographic characteristics presented in Table 1. The age of the patients ranged from 18 years to 84 years. Patients in the age range of 21-40 years and 41-60 years constituted the highest proportions of 31.7% and 39.2% respectively. This put 70.9% of the patients in the age range of 21-60years. The mean age was 50.76 (±18.6) years old.

Seventy six (63.3%) males and forty four (36.7%) females participated in the study. The occupational status of the participants as reflected in Table 1 showed that 13.3% were students, 34.1% were traders, 11.7% were civil servants, 5.0% were professionals, and 2.5% were unemployed while the remaining 33.3% were farmers, artisans, retirees etc. and were grouped together as unspecified categories.

The highest levels of education attained by the patients were similarly shown in Table 1. Thirteen patients (10.8%) had no education, twenty five patients (20.8%) each had primary education and another twenty five (20.8%) had

Table 1. General characteristics of the patients

Characters	Frequency	Percentage
Age		
0-20	3	2.5
21-40	38	31.7
41-60	47	39.2
61-80	28	23.3
81-100	4	3.3
Total	120	100
Gender		
Male	76	63.3
Female	44	36.7
Total	120	100
Occupation		
Student	16	13.3
Trader	41	34.1
Civil servant	14	11.7
Professional	6	5.0
Unemployed	3	2.5
others	40	33.3
Total	120	100
Educational qualification		
None	13	10.8
Primary	25	20.8
Secondary	25	20.8
Tertiary	57	47.5
Total	120	100
Duration of illness		
3months-2years	76	63
2years-5years	30	25
>5years	14	12
Total	120	100

secondary education, while fifty seven patients (47.5%) had tertiary education. The duration of illness was also evaluated as shown in Table 1. The minimum duration was 3 months and maximum was 216 months. The mean duration of illness of the patients studied was 32.37(±36.48) months.

Cutaneous manifestations were found in sixty nine patients (57.5%). Although some patients had more than one cutaneous disease, sixty nine (57.5%) patients had at least one manifestation while fifty one (42.5%) patients had no cutaneous manifestation.

The spectrum of cutaneous manifestations seen in this study and their proportions are shown in Table 2. Xerosis was the commonest and was seen in thirty two patients (26.7%), pruritus was seen in sixteen patients (13.3%), hyperpigmentation in fifteen patients (12.5%), half and half nail in thirteen (10.8%) patients and pallor in thirteen (10.8%) patients. Others are icthyosis seen in eight (6.7%) patients, fungal infections in eight (6.7%) patients, and follicular hyperkeratosis in three (2.5%) patients. Two cases each of Mee's lines and alopecia were seen while a case of chronic leg ulcer, planter hyperkeratosis, arteriovenous shunt dermatitis, bacterial infection and uraemic frost were also seen.

Table 3 shows that the proportion of cutaneous manifestations increased progressively with worsening kidney function. In stage 3 CKD, 53.5% of the patients had cutaneous manifestations, while 58.3% of patients with stage 4 CKD had cutaneous manifestations. The highest proportion of 61.0% was seen in patients with stage 5 CKD. However, the progressive increase in the proportion of cutaneous manifestations with the stage of CKD did not reach statistical significance.

The association between specific cutaneous manifestations and the stage of CKD is shown in Table 4. Some of the specific cutaneous manifestations such as xerosis, hyperpigmentation, half and half nail, and pallor increase progressively with stage of CKD but did not reach statistical significance. The incidence of Pruritus did not increase with worsening of kidney function. Fungal infections and icthyosis, despite having 50% of their presentation in patients with stage 4 CKD, did not show a significant statistical association with the stage of CKD.

4. DISCUSSION

Young and middle aged patients constituted the largest proportion of patients who participated in the study, with 70% of the patients between the ages of 21 years and 60 years. In a similar study by Thomas et al, patients in the middle age category constituted the largest proportions. This is because CKD is common in young and middle aged patients as has been depicted in previous stidies. [5,6] Seventy six males (63.3%) participated in the study while the females constituted 36.7%. The ratio of females to male in this study was 1:1.7. This is also similar finding by Thomas et al. where fewer number of females participated in their study with female to male ratio of 1:3.7.

Table 2. The prevalence of cutaneous manifestations among patients with chronic kidney disease (n=120)

Cutaneous manifestations	Frequency	Percentage
Xerosis	32	26.7
Pruritus	16	13.3
Hyperpigmentation	15	12.5
Half and half	13	10.8
Pallor	13	10.8
Fungal infection	8	6.7
Icthyosis	8	6.7
Folicullar hyperkeratosis	3	2.5
Alopecia	2	1.7
Mee's line	2	1.7
Chronic leg ulcer	1	0.8
Plantar hyperkeratosis	1	0.8
Arteriolar shunt dermatitis	1	0.8
Bacterial infection	1	0.8
Uraemic frost	1	0.8

The prevalence of cutaneous manifestations among patients with CKD in this study was 57.5%. This is within the prevalence range of 50-100% reported in literatures. [1-4] Falodun et al. [3] reported 89.1% while Thomas E A et al. [1] reported 97.9%. These showed that cutaneous manifestations are common in patients with chronic kidney disease. The sub-categories of patients with CKD who were involved in the study are in stage 3, 4 and 5 of CKD. About 53.5% of stage 3 patients had cutaneous manifestations, 58.3% of stage 4 patients had cutaneous manifestations, while 61.0% of patients in stage 5 had cutaneous manifestations. The proportion of patients with cutaneous manifestations progressively increased with worsening kidney function from stage 3 to stage 5 but did not reach statistical significance. The increasing proportion of cutaneous manifestations with stage could be because of the increased duration of illness in later stages of illness thereby allowing sufficient time for changes in the skin to occur.

Xerosis remained the most commonly observed skin change in patients with CKD.[25] The commonest dermatoses observed In this study was xerosis which occurred in 26.7% of patients. The xerotic lessions were mainly on the extremities. This might be due to the effect of climate and environment since the extremities are often exposed. This could cause local effect of dehydration. Other factors responsible for xerosis include, reduced size of eccrine sweat glands and sebaceous glands, the use of diuretic treatment, and the increase in plasma and skin vitamin A and its carrier retinal binding protein.[4,26,27] Fluid is also thought to shift away from the dermis following fluid mobilization by dialysis.[28] Thomas et al[1] reported a prevalence of 66.7% while Falodun [3] reported

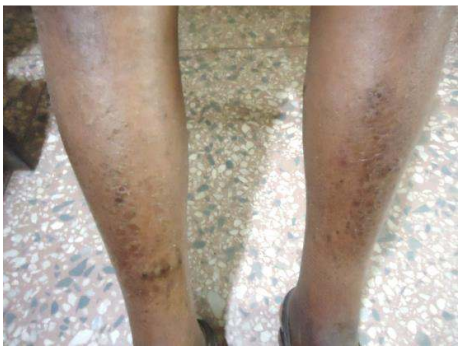
Table 3. Association between the stages of chronic kidney disease and the presence of cutaneous manifestations

Stages of chronic kidney disease	Cutaneous manifestations			
	Present		Absent	
	Frequency	Percentage	Frequency	Percentage
Stage 3	23	53.5	20	46.5
Stage 4	21	58.3	15	41.7
Stage 5	25	61.0	16	39.0
Total	69	57.5	51	42.5

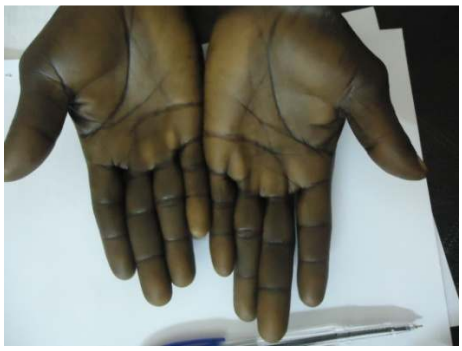
X^2 = 0.496; df=2; p-value= 0.780

Table 4. Association between the stages of chronic kidney disease and the presence of specific cutaneous manifestations

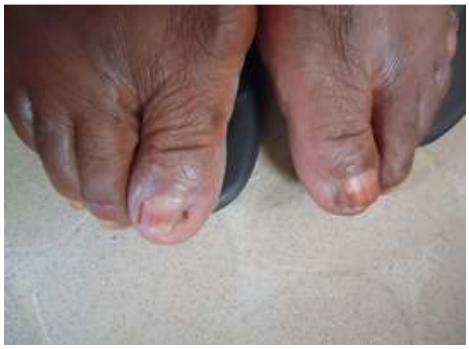
Cutaneous manifestations	Stage 3		Stage 4		Stage 5		p. value
	Frequency	%within disease	Frequency	%within disease	Frequency	%within disease	
Xerosis	8	25	11	34.4	13	40.6	0.671
Pruritus	8	50	5	31.3	3	18.8	0.426
Hyperpig-mentation	3	20	5	33.3	7	46.7	0.634
Half and half	3	23.1	4	30.8	6	46.2	0.518
Pallor	3	23.1	4	30.8	6	46.2	0.518
Fungal infection	3	37.5	4	50	1	12.5	0.312
Icthyosis	2	25	4	50	2	25	0.932
Folicullar Hyperkeratosis	_	_	_	_	3	100	0.060
Alopecia	2	100	_	_	_	_	0.252
Mee's line	2	100	_	_	_	_	0.252
Chronic leg ulcer	1	100	_	_	_	_	0.378
Plantar Hyperkeratosis	_	_	_	_	1	100	0.336
Arteriolar Shunt Dermatitis	_	_	_	_	1	100	0.336
Bacterial infection	_	_	1	100	_	_	0.504
Uraemic frost	_	_	_	_	1	100	0.336



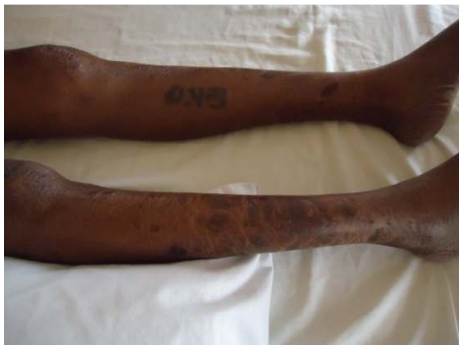
1a. xerosis



1b. hyperpigmentation



1c. half and half nail



1d. Icthyosis

Fig. 1(a-d). Dermatoses in CKD

that 60% of his patients presented with xerosis. The relatively low frequency obtained in this study may not be unconnected with the fact that the overall prevalence of dermatoses was lower though xerosis remained the commonest manifestation.

The proportion of patients with xerosis increases progressively with worsening of CKD. The proportions of xerosis observed in stages 3, 4, 5 were 25%, 34.4% and 40.6% respectively. The increasing proportion of xerosis may be a result of increased use of diuretic as renal function worsens and the added use of haemodialysis which can cause fluid shift away from the dermis. Despite the progressively increasing proportion of xerosis, the test of association did not show significant variation between the number of patients with xerosis and the stages of CKD.

Pruritus was the second commonest dermatoses in this study occurring in 13.3% of CKD patients. This was closely related to the frequency of pruritus reported in a review by Ponticell C et al. [29] where they reported 15-40% of patients with CKD presenting with pruritus. Thomas et al. [1] also reported a frequency of 43.4% while Falodun et al. [3] reported 26.7%. The patients presented with generalized pruritus of mild to moderate severity. There were no associated plaques or nodules. The frequent occurrence of xerosis (26.67%) noted in this study could have contributed to the observed prevalence of pruritus [30].

Diffuse hyperpigmentation was seen in 12.5% of patients in this study. This prevalence is within the documented range reported in previous studies. Prevalence of 7.5-43% had been reported in previous studies. [1,3,25] Mild diffuse hyperpigmentation may not be readily noticed in black skin as in the Caucasian skin. This may cause the observed frequency to be less than the actual frequency of diffuse hyperpigmentation. Self-reporting of hyperpigmentation by patients ‘‘since it has to be compared with usual level of pigmentation’’ may also alter the actual frequency of hyperpigmentation noted in this study.

Brown diffuse hyperpigmentation and yellow-grey discolourations were not seen in this study. This could be because they were either absent or because the study population was predominantly a Fitzpatrick skin type VI with high pigmentation, thereby altering the typical presentation. The inability of the kidney to excrete beta-melanocyte stimulating hormone (β - MSH) leading to accumulation of melanin and chromogens in basal layer and superficial dermis causes hyperpigmentation in patients with CKD [4,25,31].

A review of the variation in hyperpigmentary changes between stages 3, 4 and 5, shows 20% of the pigmentary changes in stage 3, 46.67% in state 4 and 33.3% in stage 5. The test of association between the stages of CKD and hyperpigmentary changes (p-value 0.634) was not significant. This shows that there is no significant relationship between hyperpigmentary changes and stage of CKD.

The prevalence of pallor seen in this study was 10.8% which is low compared with other studies. The cause of pallor in patients with CKD includes decrease production of erythropoietin by the kidneys, and increased haemolysis. [4,25] It was also observed that the patients on dialysis were given routine erythropoietin, as well as haematinics such as parenteral or oral iron and multivitamins. With increased likelihood of anaemia in stage 5 CKD patients compared to stages 3 and 4, the low prevalence of pallor may also be partly explained by the fact that stages 3 and 4 patients recruited for the study constituted two-third of participants.Other factor accounting for the reduced frequency of pallor is the correction of anaemia in these patients. Although pallor was also noted to increase with worsening kidney disease, the variations in its occurrence did not reach statistical significance.

Cutaneous infections arising from fungal infections affected 6.7% of the patients while 0.8% of patients had bacterial infections. The spectrum of fungal infections seen in this study included tinea unguium, tinea pedis, pityriasis versicolor which was similar to that reported by Udayakumar et al. [25]. However, this study recorded lower frequency of infections probably because the study population was not limited to haemodialysis population. Impair cellular and humoral immunity predisposes to cutaneous infections in patients with CKD. [32] The distribution of fungal infections between the stages showed that patients in stage 3 CKD had 37.5% of the burden of fungal infection. Stage 4 had 50% while the remaining 12.5% occurred in stage 5 CKD. The observed variation between fungal infection and the stages of chronic kidney disease was not statistically significant. Similarly, bacterial infections did not vary significantly with the stage of chronic kidney disease. Since bacterial and fungal infections have common pathogenic mechanism of defective humoral and cellular immunity in patients with CKD, similar pattern of association with stages of CKD may be expected. The observed associations were however not statistically significant.

Other abnormalities of keratinization that were seen in this study included icthyosis, follicular hyperkeratosis and plantar hyperkeratosis. Icthyosis was documented in 6.67% of the studied patients. Acquired icthyosis had been noted in patients with chronic kidney disease.[4] Acquired icthyosis being severe form of skin dryness had similar pathogenesis with xerosis as discussed above. A total of eight patients with icthyosis were seen in the study, with 25% in stage 3, 50% in stage 4 and remaining 25% in stage 5. Icthyosis also did not vary significantly with the stage of CKD.

A few patients with CKD have been reported to present with keratosis pilaris – like lesion.[25] This study similarly finds a small proportion of the patients (2.5%) with keratosis pilaris – like lesion(follicular hyperkeratosis). Increased plasma and skin content of vitamin A and its carrier, retinol-binding protein in uraemic patients have also been implicated in the pathogenesis of follicular hyperkeratosis as with other abnormalities of keratinization [4,26,27].

Hair changes in CKD include hair loss which could be due to telogen effluvium “following ill health”, xerosis, pruritus and drugs such as heparin, antihypertensives and antilipids [33,34]. Other hair changes include colour change and shaft abnormalities (such as twisting flattening, irregular diameter) which can be detected by election microscopy.[25,34,35,36] In this study, diffuse alopecia was found in 1.7% of patients with CKD. Hair changes have been reported in 10-30% of CKD patients who are on dialysis.[25] The relatively low frequency of hair changes seen in this study may be because of shorter duration on maintenance dialysis. The impact of drugs such as heparin will be more obvious as the duration on maintenance dialysis increases. This is less likely in this environment where dialysis though increasingly accessible but it is

still expensive and unaffordable by a large proportion of patients. The two cases of alopecia seen were among patients with stage 3 CKD.

Mee's lines were also observed in 1.7% of the patients. Udayakumar et al. [25] reported a higher prevalence of 7% among haemodialysis patients. Other nail changes due to infections observed were Tinea unguium, acute and chronic paronychia. The two cases of mee's lines seen were among patients with stage 3 CKD.

Arteriovenous shunt dermatitis occurs at the site of arteriovenous fistula. It arises due to irritant contact dermatitis from soaps or cleansing agents, disinfectant, and alcohol. Irritant dermatitis is dependent on both concentration of substance and duration or frequency of exposure to contact. Arteriovenous shunt dermatitis was seen in one patient. This gives a frequency of 0.8% among patients with CKD. The prevalence of 8% was reported in patients on chronic haemodialysis by Goh et al. [37]. The probable reasons for the low prevalence in this study could be the absence of arteriovenous shunts in most of the patients, and the low frequency of dialysis attributable to the high cost of the procedure and the low socio-economic status of affected patients. Arteriovenous shunt dermatitis usually occurs at the site of shunt in patients with CKD on haemodialysis. [37] Reports on shunt dermatitis have been limited to patients on chronic haemodialysis with shunts in place [37].

Uraemic frost occurs when the blood urea nitrogen level exceed 250-300mg/dl[4]. Urea concentration in sweat is increased and after evaporation, there is deposition of urea crystals on the skin surface. A patient with stage 5 CKD had uraemic frost in this study. The availability of dialysis, and the relatively high level of urea at which it occurs makes uraemic frost less common as observed in the study. Uraemic frost may be commoner in the later stages of CKD since urea is also higher in these stages. This may also explain why the only documented case in this study was in stage 5.

5. CONCLUSION

The occurrence of cutaneous manifestations is high among patients with chronic kidney disease with a prevalence of 57.5% observed in this study. As with several other studies, xerosis was the commonest skin changes observed in these patients. The patterns of cutaneous manifestations were not observed to vary with the stages of chronic kidney disease in this study. We recommend that the formulation of policy allowing increase access to improved care of kidney disease may further reduce the prevalence of dermatoses thereby enhancing patient's quality of life.

CONSENT

Patients consented to be part of the study, examination, diagnoses and agreed to have their pictures taken.

ETHICAL APPROVAL

Approval of Ethics and Research Committee of OAUTHC was sought and obtained before the study.

COMPETING INTERESTS

Authors have declared that no competing interests exist.

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