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Research Article

Cutaneous Abnormalities in Patients of Chronic Kidney Disease and In Dialysis Dependent End Stage Renal Disease

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Abstract

Background: Cutaneous manifestations occurring in patients with chronic kidney disease (CKD) are polymorphic and diverse. Comparison between cutaneous abnormalities of CKD patients with or without dialysis has never been explored in Bangladeshi population.

Objective: The aim of this study was to assess the prevalence and characteristics/patterns of different cutaneous manifestations in patients of CKD with or without dialysis.

Patients and methods: This cross-sectional observational study was done at the Department of Nephrology, Gonoshasthaya Somaj Vittik Medical College and Nagar Hospital, Dhaka, Bangladesh from April, 2019 to March, 2020. Total 150 Patients of CKD stage III – V with or without dialysis were included in the study. Detailed general and systemic examination was performed. e-GFR was calculated by Cockcoft-Gault (CG) formula. And according to the e-GFR, patients were grouped into different stages of CKD. Skin manifestations were evaluated by a qualified skin specialist in the department of Dermatology. Detailed biochemical parameters were assessed. Scraping for fungus and potassium hydroxide mount were done wherever clinically indicated. Data were expressed as mean ± SD, minimum-maximum, and number (percent), unpaired student's' test and Chi-square test. Statistical analysis was done by using Statistical Package for Social Science (SPSS) software for Windows Version-14.

Results: Among the 150 study subject 11 (8.73%) were in stage-3, 20(15.87%) in stage-4, 38(30.16%) in stage-5(stable) and 57(45.24%) in stage-5 on dialysis. 99 patients (66%) were male and 51(34%) female. 85 (67.5%) male and 41 (32.5%) female showed cutaneous abnormality. A total of 126 patients (84%) had at least one skin problem; pallor was the most common (72%), while xerosis (68.8%), pruritus (65.3%), pigmentation (33.3%) and half-and-half nail (38.7%) were other common problems. Purpura and fungal infection was 16.66% and 16% respectively. Half and half nails were the most common nail abnormality seen in this study. Pigmentation, purpura, ulcerative stomatitis, bacterial infections were significantly higher in dialysis group and found statistically significant. Pruritus was associated with higher serum calcium, phosphorous and calcium-phosphate product values. There was a significant association between pruritus and xerosis (p .001).

Conclusion: Dermatological manifestations are very common among CKD patients with or without dialysis. Most common manifestations were pallor, xerosis, and pruritus. Pigmentation, purpura, bacterial infections are the most frequent skin abnormalities observed in hemodialysis patients. Serum calcium-phosphate product has a direct relation with pruritus.

Keywords: adult polycystic kidney disease; hearing impairment; intestinal dialysis

Introduction

Chronic kidney disease (CKD) is growing as a global public health problem. There is a rising incidence and prevalence of kidney failure, with poor outcomes and high cost which is causing a burden to the nations.

Many studies showed high prevalence of cutaneous abnormalities are associated with chronic kidney disease (CKD) patients and range from the universal xerosis and pruritus to uncommon conditions like purpuric skin changes, acquired perforating dermatosis, and nail changes (1).

Skin manifestation may be the first important sign of CKD. Persistent cutaneous complaints such as xerosis and intractable pruritus may allow searching for underlying renal dysfunction.

The dermatological findings may even proceed any clinical or biochemical evidence of CKD and such cutaneous changes are overlooked during routine clinical practice.

Physician must be aware of such cutaneous manifestation to properly diagnose, reassure, & educate patients & to offer appropriate therapy. Some manifestation might require only simple treatment & dermatological consultation could offer great relief to these patients.

A prompt diagnosis & efficient treatment of these problems can help a lot in relieving patient's discomfort & improving the overall outcome of management and vastly reduce the morbidity and improve the quality of life. So patients with CKD should undergo regular examination for cutaneous manifestation, so that necessary treatment can be given to reduce the morbidity.

To the best of our knowledge, comparison between CKD patients with cutaneous abnormalities with or without dialysis has never been explored in Bangladeshi population. For this we have enrolled 150 CKD patients to find out the status and pattern of cutaneous abnormalities.

Patients and Methods:

This was a cross-sectional observational study was done at the Department of Nephrology, Gonoshasthaya Somaj Vittik Medical College and Nagar Hospital, Dhaka, Bangladesh. The study time was April, 2019 to March, 2020. Total 150 Patients of Chronic kidney disease (CKD) were included in the study. All patients were adult (>18 years) from both sexes and were suffering from CKD stage III-V, with or without dialysis. Patients with features of acute kidney injury, patients with renal transplant and patients with previous skin diseases were excluded.

Detailed general and systemic examination was performed. Demographic, clinical and medico legal data were collected from patient's case record format. e-GFR was calculated by Cockcoft-Gault (CG) formula. And according to the e-GFR, patients were grouped into different stages of CKD according to K/DOQI 2012 guidelines. Skin manifestations were evaluated by a qualified skin specialist in the department.

Complete blood count, routine urine examination, biochemical tests(serum glucose for fasting and 2hrs after breakfast, serum urea, serum creatinine, serum calcium, serum inorganic phosphate were done recorded in the data collection sheet. Urinary total protein (UTP) and serum fasting lipid profile were also estimate for these patients. Scraping for fungus and potassium hydroxide mount were done wherever clinically indicated.

Data were expressed mean ± SD, minimum-maximum, and number (percent) as appropriate. Unpaired Student's 't'. test, Chi-square test (with fisher exact modification) were perform to calculate statistical difference and/or association between groups where applicable. Statistical analysis was done by using Statistical Package for Social Science (SPSS) software for Windows Version-14.

Observation and Results:

Among the 150 study subject 11 (8.73%) were in stage-3, 20(15.87%) in stage-4, 38(30.16%) in stage-5(stable) and 57(45.24%) in stage-5 on dialysis. 126 (84%) patients (Group-A) had cutaneous abnormalities and 24 (16%) patients (Group-B) had no cutaneous abnormalities. 99 patients (66%) were male and 51(34%) female. 85 (67.5%) male and 41 (32.5%) female showed cutaneous abnormality. This distribution did not show any statistical significant association (p=0.387). Mean (±SD) age (yrs.) of the total study subject was 44.6 ± 12.3.

The mean (±SD)) haemoglobin of patient with Group-A were 7.82±1.42 g/dl and Group B 8.57±1.59g/dl. Mean haemoglobin between the two groups showed statistical significant difference (p=0.021).

The mean (±SD) UTP of patient with group-A were 2.02±1.03g/d and group B 1.53±1.08g/d. Proteinuria between the two groups showed statistical significant difference (p=0.038). The mean (±SD) serum creatinine and the mean (±SD) lipid profile of patient with group-A and group-B were evaluated and the two groups did not show statistical significant difference.

Among the study patients the main cause of CKD was glomerulonephritis 68 (45.33%) then diabetes 47(31.33%). The other causes were hypertension 16 (10.66%), Obstructive uropathy 10(6.66%), ADPKD 05 (3.3%), Chronic pyelonephritis 01(0.66%). In 3 patients, we could not found any cause of CKD.
The most prevalent skin manifestation was pallor, which was seen in 108 patients (72%).Other skin manifestations included xerosis 103(68.6%), pruritus 98(65.3%), hyperpigmentation 50(33.3%), purpura 25(16.6%) (Table I). Fungal infection was the leading cutaneous infection 24(16%) followed by bacterial 15(10%). Half and half nails were the most common nail abnormality seen in this study **(Table I).**

Types of Cutaneous abnormality present	Frequency	% among total patient
Pallor	108	72%
Pigmentation	50	33.33%
Xerosis	103	68.66%
Pruritus	98	65.33%
Purpura/Ecchymosis	25	16.66%
Dermatitis over the A-V fistula	01	0.66%
Bacterial infection	15	10%
Viral infection	08	5.33%
Fungal infection	24	16%
Parasitic infestation	04	2.66%
Xerostomia	10	6.66%
Ulcerative stomatitis	16	10.66%
Half-and- half nail	58	38.66%
Onycolysis	08	5.33%
Onycomycosis	11	7.33%
Mess line	04	2.66%
Koilonychia	11	7.33%
Clubbing	04	2.66%

Table-I: Cutaneous abnormalities present the study subjects (n=150)

**Some participants have more than one finding.

Among the 68 patients with dialysis, 57 (83.8%) had cutaneous manifestation and, 69 82.1%) in non-dialysis group (n=84). CKD with dialysis and without dialysis had hyperpigmentation 30 (52.6%) and 20(29%) (p-0.007) and purpura 20 (35.1%) and 5 (7.2%) (p=.0001), ulcerative stomatitis12 (21.1%) and 4 (5.8%) (p=0.015), bacterial infection11 (19.3%) and 4 (5.8%) (p=.027), respectively. Hyper pigmentation, purpura, ulcerative stomatitis and bacterial infection were statistically significant higher in dialysis group (Table II). Other cutaneous manifestation among the study groups did not show any significant difference.

Types of Cutaneous abnormality present	Frequency	Dialysis (n=57) No. (%)	Non-Dialysis (n=69) No. (%)	P value
Pallor	108	49(86.0)	59(85)	0.942
Pigmentation	50	30(52.6)	20(29.0)	0.007
Xerosis	103	46 (80.7)	57(82.6)	0.783
Pruritus	98	37 (64.9)	51 (73.9)	0.273
Purpura/Ecchymosis	25	20(35.1)	5(7.2)	0.001
Dermatitis over the A-V fistula	01	01 (1.75%)	-	0.452
Bacterial infection	15	11 (19.3)	4(5.8)	0.027
Viral infection	08	5(8.8)	3 (4.3)	0.466
Fungal infection	24	13(22.5)	11(15.9)	0.329
Parasitic infestation	04	2(3.5)	2(2.9)	1.000
Xerostomia	10	5(8.8)	5(7.2)	0.753
Ulcerative stomatitis	16	12(21.1)	4(5.8)	0.015
Half-and- half nail	58	31(54.4)	27 (39.1)	0.087
Onycolysis	08	4(7.0)	4 (5.8)	1.000
Onycomycosis	11	4(7.0)	7(5.8)	1.000
Mess line	04	2 (3.5)	2 (2.9)	1.000
Koilonychia	11	5 (8.8)	6 (817)	0.988
Clubbing	04	3(5.3)	1(1.4)	0.328

Table- II: Cutaneous abnormalities in pre-dialysis and dialysis patients

In group-A the mean (±SD) calcium was 1.87±024mmol/L and group B 1.77±0.20 mmol/L. Mean calcium between the two groups showed statistical significant difference (p=0017) (Table III). In the mean (±SD) inorganic Phosphate in group A was 1.74±0.29mmol/L and group-B 1.61±0.16mmol/L. Mean Phosphate between the two groups r showed statistical significant difference (p=0.002) (Table III). In group-A the mean (±SD) calcium phosphate product was 3.24±0.62 mmol/L and group B 2.84±0.37mmo1/L. Mean calcium phosphate product between the two groups showed statistical significant difference (p<0.001)

Parameters	Study group (n150)		P value
	Pruritus Group-A (n=98)	Non- pruritus Group-B (n=52)	
Calcium	1.87±0.24	1.77±0.20	0.017
Phosphate	1.74±0.29	1.61±0.16	0.002
Calcium phosphate product	3.24±0.62	2.84±0.37	<0.001

Table-III: Calcium, phosphate and Calcium phosphate product in subject with or without Pruritus

Out of 150 study subjects present with xerosis and 98 with pruritus. Among them 79 had both xerosis and pruritus. Only 19 study subjects had pruritus without xerosis. On the other hand, 24 had xerosis without pruritus and had no xerosis as well as pruritus. There was a significant association between pruritus and xerosis (p= <0.001).

Pruritus	Xerosis		Total	P value
	Present (n=103)	Absent (n=47)		
Present	79	19	98	<0.001
Absent	28	28	52	
Total	103	47	150	

Table- IV: Pruritus and xerosis in study subjects (n=150)

Discussion

Cutaneous manifestations are very common in patients with chronic kidney disease. [2, 3] Found prevalence of kidney disease in 100% and 79% patients respectively. [4, 5] also found prevalence of kidney disease in 100% and 88% patients respectively. [6] Has performed a study among patients receiving hemodialysis and cutaneous disorders were found in 82% patients. In our study population 84% had some form cutaneous complain while, only 16% was free from all skin disorder. These findings of the study accords with previous study.

Among those had cutaneous complains,8.73%(n=11)were in stage-3 CKD, 15.87%(n=20)were in stage-4 CKD, 30.16%(n=38)were in stage-5 CKD on medical treatment, 45.24%(n=57)were in stage-5 CKD on MHD.

In our study, 99 (66%) patients were male and 51 (34%) were female. Among the male patients, 85 (65.5%) and among the female 41 (32.5%) showed cutaneous abnormalities. So there is no significant statistical difference between male and female (p=0.387) in development of cutaneous abnormalities.

Patient with cutaneous abnormality had higher UTP and we found high proteinuria was associated with development of cutaneous abnormality in this study (p=0.038).

During evaluation of lipid profile among study groups, we did not find lipid level had no association with development of cutaneous abnormality.

In a study by (7) the main causes of CKD in 150 study patients were due to diabetes (54, 36%); then glomerulonephritis (38, 25%); hypertension/renovascular disease (26, 17%); reflux or other structural malformations (8, 5%); polycystic kidney disease (7, 5%); cancer, trauma, and nephrotoxic agents (9, 6%); or unknown causes (8, 5%).

In current study, the main cause was glomerulonephritis (45.33%, n =68), then diabetes (31.33%, n =47). The other causes are hypertension (10.66%, n =16), obstructive uropathy (6.66%, n=10), ADPKD (3.33%, n=5), chronic pyelonephritis (.66%, n =1). In 3 patients, we could not found any cause of CKD.

Among the cutaneous findings, Pallor of the skin was most common. [8] Observed pallor only 45.45%, but (4) observed pallor as high as 91.5% .In a previous study, (5) also observed pallor 82%. It was observed in 72% and was the most common skin manifestation among CKD patients in this study. Pallor is due to anemia. Mean hemoglobin was 7.82±1.42 in 91.5% of study patients. Anemia in CKD results from decreased erythropoiesis, reduced red cell life span and blood loss during dialysis and degree of anemia governs the quality of life [9]. In present study 85.5% CKD without MHD and 86% with MHD were pallor. Pallor was found slight increase in frequency in dialysis patients though statistically insignificant. Similar study done by (4) found 94.3% CKD without MHD and 89.6% with MHD were pallor. (8) Also found pallor more common in patients on MHD. Pallor more in MHD group, probably more blood loss during dialysis in these group.
Xerosis was a leading disorder reported in 46- 90% CKD [10, 11, 12]. Xerosis was the most common cutaneous abnormality (79%) in study done by [6] in dialysis patients. [8, 5] also observed xerosis 66.7% and 61% respectively. It was observed in 68.66% and was the second common skin manifestation among CKD patients in this study, predominantly over the lower back and extremities, which accord with previous finding. [4] Found 80% CKD without MHD and 72.9% with MHD had xerosis. In present study, we also found 82.6% CKD without MHD and 80.7% with MHD had xerosis.

A reduction in the size and functional abnormality of eccrine sweat glands, suggesting compromised eccrine secretion leading to epithelial dehydration [13] may contribute to the development of xerosis. Other factors considered in the pathogenesis of xerosis such as caloric and protein malnutrition are more prevalent in this subcontinent scenario as compared to the west [2].

In addition, the tropical climate with greater sun exposure and resultant chronic dehydration may be fenny contributory [14].

Pruritus is a frequent symptom of CKD and could be severe and intractable with decreased quality of life [15, 16]. It is not present in acute renal failure and does not necessarily subside with dialysis although it improves with kidney transplantation [17]. There is wide variation (15-90%) in its prevalence reported by various worker (18). In a study by [6] found the prevalence of pruritus to be 53%. [5] Also found 53% of patients complained of pruritus. In this study, 65.3% of patients complained of pruritus, a finding similar to previous studies. It was found in 46.7% CKD without MHD (19) and 41.9% to 67% with MHD (20, 21). In present study we also found pruritus in 73.9% CKD patients without MHD and 64.9% CKD patients with MHD respectively. In similar study by [4] found pruritus was present in 57.1% and 62.5% CKD without and with MHD respectively.

The cause of pruritus in CKD is multifactorial and may or may not improve with dialysis [22, 16]. There are a significant number of proposed etiologies for pruritus in CKD including: skin changes related to xerosis, urochrome deposition, uremic toxemia, calcium and phosphate dysregulation, mast cell proliferation with a concomitant increase in histamine levels, dialysis component allergic reactions, and hypovitaminosis D [23].

Parathyroid hormone and divalent ions (e.g. calcium phosphate and magnesium ions) have also been implicated in the pathogenesis of uremic pruritus, as itching frequently accompanies severe secondary hyperparathyroidism and an elevated calcium phosphate product (10). In the present study, those patients had pruritus, Calcium, Inorganic phosphate and calcium phosphate product were significantly higher than non-pruritus. There was a significant association between pruritus and xerosis(p .001).

Parathyroid hormone could not evaluated as costly and routinely not done.

Pigmentary changes can occasionally be conspicuous enough to point towards the diagnosis of kidney disease on first presentation [24].

Diffuse hyperpigmentation has been reported in 36.7%by Thomas et al and in 37% by [5].
Diffuse hyperpigmentation on sun-exposed areas were seen in 33.3% in this hemodialysis and consistent with previous studies.

[6] Observed, two types of pigmentary changes; hyperpigmentation (seen in 43% of patients) and a yellowish tinge to the skin (10%) with prominent hyperpigmentation over the sun exposed areas of CKD patients on MHD.

Diffuse hyperpigmentation has been reported in 36.7% CKD without MHD [19].

In this study hyperpigmentation was found in 29% CKD without MHD and 52.6% patients on MHD, which are significant higher in dialysis group and found statistically significant(p=.007). Such pigmentation is more marked in the sun exposed parts of the body in the subcontinent population could be due to tropical climate and excessive sun exposure in these patients [24].

The incidence is higher with longer duration of dialysis and attributed to the deposition of melanin in the basal layer and superficial dermis due to failure of kidney to excrete β melanocytic hormone that is poorly dialyzable [25].

Purpura and ecchymosis are spontaneous cutaneous bleeding affecting 9-20% of (26, 6). [8] Found purpura in 10(10.1%) patients, among whom 7 were on MHD. In this study, it was seen in 25 (16.6%) patients, among whom 20 (35.1%) were on maintenance hemodialysis and 5(7.2%) were without MHD which are significant higher in dialysis group and found statistically highly significant (p=.001). This is consistent with the previous report. Defects in primary haemostasis-like increased vascular

fragility, abnormal platelet function, and use of heparin during dialysis are the main causes of abnormal bleeding in these patients [2].

Mucosal changes in the oral cavity have been reported in up to 90% patients with CKD [28]. Xerostomia was seen in 6.66% of the patients, which could be attributed to mouth breathing and dehydration and similar to previous finding (5.05%) by [8] Ulcerative stomatitis, seen in 16(10.66%), significantly higher in dialysis group. [6] Reported ulcerative stomatitis 29% in dialysis group. This could be attributed to the poor oral hygiene [28] and reported to occur with high blood urea [28] as oral mucosal changes are predisposed by bad oral hygiene and superimposed bacterial infection, awareness of oral hygiene in CKD must be encourage.

[6] Found sixty-seven skin infections (13 bacterial, 42 fungal and 12 viral), distributed amongst 40 patients. Bacterial infections seen in 13 patients, were common in diabetics. The fungal infections were distributed among 30 patients (30%). Pityriasis versicolor was seen in 15 patients (15%). The viral infections included warts (8%), herpes simplex (3%) and herpes zoster (1%). (29) Have reported the incidence of fungal infection in patients undergoing hemodialysis to be 67%. In the present study bacterial infection, fungal infection and viral infection, parasitic infection were found in 15(10%), 24(16%) and 8 (5.3%), 4(2.66%) respectively. Bacterial infections seen in 15 patients, more marked in dialysis group and were common in diabetics. However among fungal infection pityriasis versicolor was seen in 18 patients; accords with that found in previous study. Patients with chronic kidney disease (CKD) have impaired cellular immunity due to a decreased T lymphocyte cell count; (30) this could explain the high prevalence of infection in these patients.

APD has been reported to occur in 4.5-17% of patients on hemodialysis. [31, 12]. These changes were significantly more prevalent in diabetic patients. In the previous study done by [5] kyrle disease was found in 3%. But it was not found in this study.

Arteriovenous shunt dermatitis may be seen in 8% of patients on long-term hemodialysis [32]. It was seen only 01 (0.66%) patient in this study. Dermatologic conditions such as uremic frost, erythema papulatum uremicum, uremic roseola, and uremic erysipeloid now seldom occur in patients with CKD.

Certain specific disorders associated with CKD such as calciphylaxis and nephrogenic fibrosing dermopathy resemble scleromyxedema [6] were not seen in this study, and this could be attributed to shorter duration of dialysis in our patients.

Previous studies have found a prevalence of half and half nails were 16-50.6%. [10, 2, 6]. Although half and half nails are not always seen in renal failure, they occur in as many as 40% of the patients on dialysis. [2] reported that the nail changes increased in prevalence with respect to time of dialysis and was significantly more pronounced in patients receiving haemodialysis Half and half nails were the most common nail abnormality seen in 58 (38.66%) of this study and more commonly seen in haemodialysis patients 31(54.4%). The pathogenesis of half and half nails has been attributed to increased levels of melanocyte stimulating hormone (MSH) [33].

Pathophysiology for this phenomenon is related to the proximal half of the nail appearing white because oedema associated with dilated capillary network and the other half of the nail bed appearing normal [21, 33].

Other nail changes observed included onycomycosis 11(7.33%), Onycolysis 8(5.33%), koilonychia 11(5.05%), Mee's line 4(2.66%), and Clubbing 4(2.66%) and no significant difference in dialysis and non-dialysis group.

Conclusions

The dermatological disorder was present in majority CKD patients without and with dialysis and pallor, xerosis and pigmentation were predominant changes. Pigmentation and purpura were significantly higher in MHD patients. There was a significant association between pruritus and xerosis. Dermatological evaluation prompt diagnosis and efficient treatment of these problems can help a lot in relieving patient's discomfort and improving the overall outcome of management and great relief could be offered to the patient if a dermatological consultation was sought.

Study limitations

This was a single center study with small sample size. A multicenter study with large sample can represent the overall cutaneous manifestations in CKD.

Ethical issue:

Approval to perform the study was taken from Institution Review Board (IRB), Gonoshasthaya Somaj Vittik Medical College and Nagar Hospital, Dhaka. All participating individual were thoroughly briefed about nature, purpose implications of the study as well as entire spectrum of benefit and risks. Informed written consent was taken from each study subjects.

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