ORIGINAL ARTICLE

Factors Affecting Dermatological Manifestations in Patients with End Stage Renal Disease

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Abstract

Objective: To determine skin changes in patients of End Stage Renal Disease (ESRD) on maintenance hemodialysis (MHD) and factors affecting these changes.

Study Design: Cross-sectional observational study.

Place and Duration of Study: Nephrology Department, Mayo Hospital, Lahore in collaboration with Dermatology Department, King Edward Medical University, Lahore, from October 2015 to January 2016.

Methodology: Two hundred patients who were undergoing MHD for more than three months were included in the study. Patients' demographic data, laboratory reports and dialysis records were noted in a predesigned questionnaire. Skin examination was carried out by consultant dermatologist after patient's permission.

Results: Among 200 patients included in study, 105 were males and rest of them were females. Major causes of ESRD were Diabetes Mellitus (n=83, 41.5%, followed by Hypertension (n=80, 40%), Nephrolithiasis (n=15, 7.5%) and Chronic glomerulonephritis (n=5, 2.5%). At least one cutaneous finding was present in every patient. Common skin findings observed were pigmentation (86%), xerosis (83%), pallor (79%), pruritus (69%), acquired ichthyosis (50.5%), and bacterial skin infections (18.5%). Among them, nail manifestations were half-and-half nails (52%), onychomycosis (30.5%), onycholysis (20.5%), subungual hyperkeratosis (23.5%), and Mee's lines (7.5). Among hair changes were sparse scalp hair (38.5%), brittle and lustreless hair (28%). The factors contributing to skin changes were patient's age, cause of ESRD, anti HCV positivity, high urea and creatinine levels, duration and frequency of hemodialysis, hemoglobin levels, calcium phosphate product and socioeconomic status. Some skin manifestations were interrelated with each other like xerosis with pruritus ($p<0.001$), pruritus with bacterial infection ($p<0.022$), acquired Ichthyosis ($p=0.008$) and hair changes ($p=0.035$).

Conclusion: ESRD patients on hemodialysis develop various skin changes during the course of disease process, which contribute to increased morbidity. Different factors affecting skin changes were the cause of ESRD, adequacy and duration of dialysis, employment, financial status, anti HCV positivity, and metabolic factors.

Key Words: *Chronic kidney disease. Hemodialysis. Skin manifestations. Pruritus. Xerosis. Pallor.*

INTRODUCTION

Chronic Kidney Disease (CKD) is defined when Glomerular Filtration Rate (GFR) is less than 60 ml/minute/1.73 m^2 for more than three months.[1,2] End Stage Renal Disease (ESRD) is the stage of CKD when life cannot be maintained without renal replacement therapy or renal transplant. Skin being the largest organ of the body shows manifestation of CKD very early. Skin changes can occur before dialysis and even after initiation of dialysis and transplantation they persist. As skin is the most easily accessible organ of the body, it can be used as diagnostic window to internal uremic milieu. Although these skin changes are benign but have negative impact on quality of life. CKD patients develop number of skin problems like xerosis, pruritus, hyperpigmentation, infections, ichthyosis, half-and-half nails, onychomycosis, onycholysis, subungual hyperkeratosis, brittle hair and sparse body hair.[2-4] In Pakistan, work has been done on the skin manifestations in these patients,[5-8] but there is paucity of the data on the factors affecting these skin problems. By identifying factors, we might be able to reduce skin changes in ESRD patients and improve their quality of life and disease outcome. So this study was conducted to determine the factors affecting skin changes in patients on hemodialysis.

METHODOLOGY

This observational cross-sectional study was conducted at the Department of Nephrology, Shalamar Hospital and Mayo Hospital in collaboration with Dermatology Department, Mayo Hospital, Lahore, from October 2015 to January 2016. All patients who were on MHD for more than three months were included in the study. The patients who were undergoing hemodialysis for less than three months and those with renal transplant dysfunction were excluded from the study. Approval was obtained from the Ethics Committee of King Edward Medical University, Lahore prior to initiating the study.

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The protocols used conformed to the ethical guidelines of the 1975 Helsinki Declaration. Patients' demographic and hemodialysis data were collected on a predesigned form.

Patients' blood samples were drawn and sent to laboratory for hemoglobin (Hb), biochemical (blood urea, serum creatinine, iron studies, serum albumin, serum calcium, phosphorus, intact parathyroid hormone, serum electrolytes) and viral markers (HbsAg and Anti HCV). Skin, nails and hair examinations were carried out by consultant dermatologist of Dermatology Department of the Mayo Hospital after patients' permission. All the skin manifestations were noted in a predesigned form. Necessary investigations like potassium hydroxide mount, Gram's stain, fungal culture, and culture and sensitivity for bacterial infections were done where indicated.

The data was entered using software SPSS version 21. The descriptive analysis was done using mean and standard deviation for continuous data and frequency was used for categorical data. Binary logistic regression analysis was done using Backward stepwise (likelihood ratio) to determine the significance of the variables affecting the skin manifestations. A p-value of less than or equal to 0.05 was considered as statistically significant value.

RESULTS

Almost half of the patients (n=105, 52.5%) were males and rest of them were females (n=95, 47.5%). The mean age of the patients was 48.15 ±13.74 years and most of the patients (n=107, 53.5%) were in the middle age (44-64 years) group. Major causes of ESRD were Diabetes Mellitus (n=83, 41.5%), followed by Hypertension (n=80, 40%), Nephrolithiasis (n=15, 7.5%), Chronic glomerulonephritis (n=5, 2.5%), Connective Tissue Disorders (n=5, 2.5%), Autosomal Dominant Polycystic Kidney Disease (ADPKD) (n=3, 1.5%) and unknown (n=9, 4.5%). Most of the patients were getting twice weekly hemodialysis sessions (n=155, 77.5%). Mean hemoglobin and serum albumin levels were 10.17 ±1.69 gm/dl and 3.59 ±0.42 g/dl, respectively. Majority of the patients were having low hemoglobin and serum albumin levels (n=137, 68.5%) and (n=161, 80.5%), respectively showing malnutrition. Serum calcium and calcium phosphorus product were normal in (n=186, 93%) and 175 (87.5%) patients, respectively. Half of the patients (55%) were having iPTH level >300 pg/ml. Patients were HbsAg and Anti HCV negative (n=169, 84.5%) and (n=122, 61%), respectively. At least one skin manifestation was present in every patient. Skin manifestations found among dialysis patients were pigmentation (n=172, 86%), xerosis (n=166, 83%), pallor (n=158, 79%), pruritus (n=138, 69%), and acquired ichthyosis (n=101, 50.5%). Among infections of the skin, bacterial infections were found to be most common (n=37, 18.5%). Among nail and hair manifestations were half-and-half nails (n=104, 52%), onychomycosis (n=61, 30.5%), onycholysis (n=41, 20.5%), Mees' lines (n=15, 7.5%), koilonychia (n=12, 6%), subungal hyperkeratosis (n=47, 23.5%), Beaus lines (n=3, 1.5%), sparse scalp hair (n=77, 38.5%), and brittle and lustreless hair (n=56, 28%). None of the patients had calciphylaxis. Different factors affecting skin manifestation are shown in Table I.

In this study, different skin factors were statistically correlated with each other. Xeosis is related with pruritus ($p<0.001$) and onychomyciosis ($p=0.05$). Pruritus is related with bacterial infection ($p=0.022$), acquired ichthyosis ($p=0.008$), sparse body and scalp hair ($p=0.035$), sparse scalp hair ($p=0.022$), and brittle and lusterless hair ($p<0.047$). Bacterial infections are not related with onychomycosis ($p=0.097$).

DISCUSSION

In this study, there is very high prevalence of dermatological manifestation as compared to studies conducted in the world like Tusinia, Egypt and India as shown in Table II.[9-11] There are different reasons of such a high prevalence in these patients. Due to under-development of the specialty and shortage of training institutes in Nephrology, there is severe shortage of nephrologists. This shortage of nephrologists causes unawareness of the kidney diseases not only among doctors,[12] but even the patients are not well aware of the early symptoms of kidney diseases. CKD patients have strong negative thoughts about the need of dialysis and 70% of the patients refuse dialysis when offered to them. These patients present for dialysis at a very late stage to nephrologist,[13] when they have already developed advanced complications including skin manifestations. Even the patients who are getting dialysis are not optimally managed.[14] As seen in this study, majority of the patients get inadequate dialysis (twice-weekly dialysis); whereas, international guidelines recommend thrice weekly dialysis.

Pigmentation is highly variable in different studies from 40% to 80%.[8-10] As evaluation of the skin color depends on the accuracy of the examiner's vision and the type and intensity of the environmental light, therefore, examination by a more accurate method such as a color meter reflectance is recommended.[15] Pigmentation was the most common skin lesion in this study. Moreover, in this study, cause of ESRD, low hemoglobin level and employment have statistically significant relationship with pigmentation. A brown-to-slate-gray discoloration may occur as a result of hemosiderin deposition in association with iron overload from excessive transfusions. In this study, most of the patients are anemic 137(68.5%) but iron is adequate in majority of the patients {(TSAT>20) in 85% and serum ferritin

Table I: Factors effecting dermatological manifestations.

Dermatological manifestations	Factors			P-value
Skin manifestations				
1. Pigmentation 172 (86%)	Cause of ESRD			
		DM	Non DM	
	Yes	15	13	0.017*
	No	68	104	
	Hb (Gm/dl)			
		<11	≥ 11	
	Yes	13	15	0.001*
	No	124	48	
	Employment			
		Yes	No	Housewife
	Yes	3	11	14
	No	56	45	71
2. Xerosis 166 (83%)	Duration of hemodialysis			0.059
		<18months	>18months	
	Yes	95	71	0.015*
	No	13	21	
	Blood Urea (mg/dl)			
		>200mg/dl	<200mg/dl	
	Yes	119	17	0.033*
	No	26	8	
3. Pallor 158 (79%)	Hemoglobin (Gm/dl)			
		≥11	<11	
	Yes	46	112	0.001*
	No	17	25	
	Frequency of hemodialysis			
		Twice/week	Thrice/week	
	Yes	127	31	0.049*
	No	28	14	
4. Pruritus 138 (69%)	Anti HCV			
		Negative	positive	
	Yes	75	63	0.003*
	No	47	15	
5. Bacterial infection 37 (18.7%)	Blood Urea (mg/dl)			
		>200mg/dl	<200mg/dl	0.025*
	Yes	32	5	
	No	143	20	
	Employment			
		Yes	No	Housewife
	Yes	16	9	12
	No	43	47	73
	Calcium Phosphorus Product			0.028*
		<55	>55	
	Yes	35	2	0.052
	No	140	23	
Nail manifestations				
1. Half-and-Half Nails 104 (52%)	Blood Creatinine (mg/dl)			
		>8	<8	
	Yes	45	59	0.09
	No	26	70	
2. Onychomycosis 61 (30.5%)	Anti HCV			
		Negative	Positive	
	Yes	28	33	0.016*
	No	94	45	
	Blood Urea (mg/dl)			
		>200mg/dl	<200mg/dl	
	Yes	59	2	0.01*
	No	116	23	
3. Onycholysis 41 (20.5%)	Anti HCV			
		Negative	Positive	
	Yes	18	23	0.013*
	No	104	55	
4. Koilonychia 12 (6%)	Corrected Calcium (mg/dl)			
		<8.5	8.5-9.5	>9.5
	Yes	4	6	2
	No	134	42	12
	Monthly Income in Rupees			0.004*
		<10,000	10,000-30,000	>30,000
	Yes	6	6	0
	No	60	106	22
				0.037*
Hair Manifestations				
1. Brittle and lusterless hair sparse scalp hair 56 (28%)	Age (years)			
		16-44	45-64	65-78
	Yes	18	32	6
	No	56	75	13
	Cause of ESRD			0.028*
		DM	Non DM	
	Yes	28	28	0.017*
	No	55	89	
	Frequency of HD			
		Twice/week	Thrice/week	
	Yes	51	5	0.001*
	No	104	40	

**Statistically significant value.*

>500ng/dl in 113 (60%) patients}. This iron and low hemoglobin may be the probable reason of the slate gray pigmentation. In this study, patients who were employed have more pigmentation on the sun exposed areas than unemployed patients. Basically, the employed patients have more sun exposure with sun causing an increase in deposition of melanin in the basal layer and superficial dermis and accumulation of poorly dialyzable beta-melanocyte stimulating hormone. In this study, cause of ESRD, like DM as compared to non-diabetics, also affected pigmentation as seen in another study.[4]

Xerosis was the second most common skin manifestation in dialysis patients in this study. Similar incidence was observed by other local and international studies.[16,17] Exact cause of the xerosis is not known. There are different probable mechanisms of xerosis like decreased water content in epidermis, decreased sweat gland, atrophy of the sebaceous glands and hypervitaminosis A. In this study, duration of dialysis and urea level in the serum affected xerosis. Similar observation was made by Beheshti *et al*.[4] The raised urea level is a sign of inadequate dialysis.

Pallor and pruritus was present in 79% and 69% patients, respectively. Similar prevalence of pruritus was observed by local,[4,6] and international studies.[9-11] In this

Table II: Showing comparison of dermatological manifestations in different studies.

Skin manifestations (sample size)	Present study (200)	Masmaudi *et al.* (Tunisia) (458)	Sultan *et al.* (Egypt) (100)	Pk. Kolla *et al.* (India) (143)
Pigmentation	86%	38.4%	54%	39.4%
Xerosis	83%	52.8%	54%	57%
Pallor	79%	60.7%	45%	-
Pruritus	69%	56.6%	55.%	56.6%
Acquired Ichthyosis	51%	-	-	-
Bacterial infection	18.5%	14.6%	5%	14.6%
Half-and-half nail	52%	46.3%	28%	9.09%
Koilonychias	6%		39%	18%
Onychomycosis	20.5%		6%	8.88%
Onycholysis	30.0%	20.9%	3%	2.19%
Subungual Hyperkeratosis	23.5%	-	10%	-
Brittle and lusterless hair	28%	-	46%	21.7%

study, majority of the patients were anemic, which was manifested in the form of pale color of the skin. Pallor of skin had statistically significant relationship with low hemoglobin and frequency of dialysis. There are different causes of anemia in patients with CKD like nutritional deficiencies, reduced RBCs life span, erythropoietin (EPO) deficiency, blood loss due to coagulation abnormalities. Instead of adequate iron store, this low hemoglobin is due to under-dose of the erythropoietin.[18] In this study, patients with twice weekly dialysis had pallor skin as compared to thrice weekly dialysis. Again, it supports that adequacy of dialysis may improve the anemia and decrease pale skin.

Pruritus was also common skin manifestation in patients with dialysis affecting 50-90%; about one-third of the patients prior to dialysis and two-thirds after dialysis experience itching.[19] Pruritus may be localized and generalized, episodic and constant, and mild to severe.

Exact mechanism of the uremia induced pruritus is not known, but it is assumed to be due to metabolic disequilibrium. In this study, pruritus was not related with age, gender, hypercalcemia, calcium phosphorus product, inadequate dialysis but it was associated with anti HCV positive patients. No study has highlighted this issue in ESRD patients but similar observation is made by another study in patients without CKD.[20] According to this study, patients with antibodies for HCV were having more pruritus either they were HCV PCR positive or negative. However, there is need to do more studies to explore this issue in HCV +ve patients with and without dialysis. In this study, xerosis and pruritus has statistically significant relationship (p=0.000). Similar observation was made by Onelmis *et al*.[21] It means some skin manifestations are interrelated with each other and further augment the skin problems.

In this study, bacterial infection was the most common skin infection. There was very low frequency (1%) of fungal infection in this study as compared to another local study where it was 52%.[9] The low incidence of fungal infection may be due to the season, because this study was conducted in winter with minimum humidity which prevents fungal infections. Hemodialysis procedure *per se* as well as disturbances in both innate and adaptive immunity make hemodialysis patients susceptible to infections.[22] In this study, high urea, employment and calcium phosphorus product were statistically related to bacterial skin infections. High urea level is one of the markers of the inadequate dialysis that favors uremic milieu in the body leading to impaired immunity. Employed patients are more exposed to environment containing dust, smoke and poor hygiene causing increased skin infections. Pruritus and bacterial infections had strong statistically significant association with each other. Actually pruritus leads to skin excoriations with repeated scratching causing break-down of skin.

Acquired Ichthyosis (AI) is a nonhereditary condition associated with internal disease. It is a marker of systemic disease and attributed to certain medications also.[3] Xerosis and acquired ichthyosis are common problems that can be associated with hyperpigmentation in the setting of kidney disease. In this study, almost 50% of the patients on haemodialysis were having acquired ichthyosis which has not been reported in previous studies.[4-7] In this study, AI is related with pruritus (p=0.008) and with xerosis. There is a need to find the probable cause of such a high prevalence of AI in our population.

Common hair changes in these patients are: diffuse hair loss of scalp, sparse and lusterless body hair, discoloration and dryness of the hair. These hair changes are related to xerosis, pruritis, severity of illness and due to medication like heparin, lipid lowering and anti-hypertensives used in these patients. In this study, hair changes were present in 28-30% of the patients. Similar frequency was noted in another local study.[6] In this study, age, cause of ESRD, and frequency of hemodialysis affect hair changes in these patients. In this study, hair change their texture like lusterless, sparse body and scalp hair, which may be the physiological change with advancing age. In this study, the frequency of dialysis, i.e. thrice weekly, affects hair changes. Frequency of dialysis is one of the parameters of adequate dialysis like twice weekly or thrice weekly. Inadequate dialysis affects not only morbidity and mortality of dialysis patients but it also affects quality of the hairs of the patients. This may be the probable reason for the high prevalence of hair problems in these patients as inadequate dialysis will lead to accumulation of uremic toxins in the body, causing hair changes.

Nail changes are much higher in CKD patients as observed in another study.[23] In half-and-half nail,

Lindsay's Nail, the proximal half of the nail becomes white while the distal portion becomes reddish-brown to brown due to nail bed edema associated with a dilated capillary. The exact etiology of this nail change remains unknown. In this study, serum creatinine level had a statistically significant association with Lindsay's Nail. It may be a sign of inadequate dialysis reverting on increasing adequacy of dialysis,[24] but it sometimes improves with renal transplantation.[25] In this study, patients who were anti-HCV positive had more nail changes as compared to patients who were anti-HCV negative. In this study, monthly income has statistically significant association with koilonychia and onychomycosis (p=0.004), (p=0.047), respectively. As already discussed, most of the patients belonged to low socioeconomic group which leads to malnutrition and poor hygiene, causing nail changes.

CONCLUSION

ESRD patients on hemodialysis develop various skin changes during the course of disease process, which contribute to increased morbidity. Different factors affecting skin changes were cause of ESRD, adequacy and duration of dialysis, employment, financial status of the patients, anti-HCV positive patients and metabolic factors. By reversing these factors, we can improve the quality of life of these patients.

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