

FREQUENCY OF CUTANEOUS MANIFESTATIONS IN PATIENTS OF END STAGE RENAL DISEASE ON HAEMODIALYSIS

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Abstract

Background: Chronic Kidney Disease (CKD) is a serious disease in which some type of replacement (renal transplant or dialysis) is required. End Stage Renal Disease (ESRD) is the name given to Stage 5 CKD. Various cutaneous manifestations are associated with it which may be due to the disease itself or caused by its treatment.

Objectives: This study was conducted to determine the frequency of cutaneous manifestations in patients

of end stage renal disease undergoing haemodialysis.

Material and Methods: One hundred patients undergoing maintenance haemodialysis in the Department of Nephrology, KEMU / Mayo Hospital, Lahore were examined from January to June, 2011, through specially designed proformas, to determine the presence of cutaneous manifestations in these patients.

Results: There were 58 males and 42 females with a mean age of 50 ± 4 years. Overall frequency of cutaneous manifestations was 82%. The commonest findings were xerosis 78% and pruritus 64%. Others were pallor 62%, hyperpigmentation 54%, nail changes 48%, infections 37%, hair changes 35% and mucosal changes 22%. Some rare manifestations seen were arteriovenous shunt dermatitis, acquired perforating disorders, calcification and nephrogenic fibrosing dermatopathy.

Conclusion: Cutaneous and mucosal findings are a common problem in patients of ESRD and those undergoing long-term haemodialysis. The commonest are xerosis and pruritus followed by involvement of hair, nails and mucous membranes.

Key Words: Chronic kidney disease, End stage renal disease, Haemodialysis, Xerosis.

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Introduction

Chronic Kidney Disease (CKD) or chronic renal disease is characterized by a progressive loss of kidney function over months to years through 5 stages.¹ Each

stage passes through a progression from an abnormally low to a deteriorating Glomerular Filtration Rate, which is indirectly determined by the creatinine level in blood. All those showing a GFR $< 60 \text{ ml / min / } 1.73\text{m}^2$ for 3 months are classified as suffering from chronic kidney disease, irrespective of the level of kidney damage.²

The incidence of chronic kidney disease is higher in South Asians than in the European population.^{3,4} In Pakistan, the number of CKD patients is on a rise with more than 100 new cases of End Stage Renal Disease (ESRD) per million population / year.⁵

The disease may be preceded by skin manifestations which can be the first important sign of CKD.⁶ In almost all patients with progressive kidney failure, at least one of the cutaneous features can be observed. There are several cutaneous manifestations in patients on haemodialysis like xerosis, pruritus, pallor, pigmentary changes, purpura, nail changes e.g. half and half nails, hair abnormalities, oral mucosal changes and cutaneous infections (bacterial, viral, fungal). Some rare manifestations are uraemic frost, perforating dermatoses, arteriovenous (AV) shunt dermatitis, nephrogenic fibrosing dermatopathy and calcification.

The present study was aimed at determining the frequency of cutaneous manifestations in patients of ESRD undergoing haemodialysis, changes which can either precede renal changes or occur as a consequence of underlying renal disease which can alert the physician about an underlying disease or provide insight about resistant cases due to renal toxicity.

Material and Methods

This was an observational study conducted in the Department of Nephrology and Dermatology, KEMU/ Mayo Hospital, Lahore from a period of January to June, 2011. The study protocol was approved by the Hospital Ethical Committee, Mayo Hospital, Lahore.

One hundred patients of all ages and both sexes, having end stage renal disease undergoing hemodialysis, were enrolled. Patients excluded from the study were those on haemodialysis following a renal transplant rejection or peritoneal dialysis and patients who had undergone renal transplantation. Patients with pre-existing skin disease, or systemic disorders like liver disease, connective tissue disease and malignancy were also excluded. Patients having End Stage Renal Disease of less than 3 months duration were also excluded.

Demographic data of patients such as age, sex, weight, primary and secondary diagnoses and a detailed history as regards to the onset of disease, duration of chronic kidney disease, duration of dialysis and duration of skin ailment, were recorded. In order to monitor the renal functions, routine investigations were carried out. The Glomerular Filtration Rate was noted. Cutaneous manifestations due to disease itself or hemodialysis were noted. Effects of medication given during that period were also noted.

Data was entered into SPSS version 15. Study variables were recorded. Quantitative variables, like age, were expressed as Mean \pm Standard Deviation. Qualitative variables, like sex and presence or absence of cutaneous manifestations, were calculated by chi square. Statistical analysis was done and a *p* value of ≤ 0.05 was considered statistically significant.

Results

A total of 100 patients (58 males and 42 females) were examined. The mean age was 50 ± 4 years with a range of 18 – 70 years. The duration of ESRD varied from 3 months to 5 years with a frequency of dialysis for 2 – 3 times per week. Eighty-two percent of patients developed some kind of skin problem. The most common cutaneous finding was xerosis (78%) with pruritus (64%), pallor (62%) and cutaneous hyperpigmentation (54%) to follow.

Nail changes were seen in 48% of the patients, out of which the most frequent was nail bed pallor (42%), followed by onychomycosis 22%, subungual hyperkeratosis 14%, koilonychias 12% and half and half nails 10%. Infections (37%) were common in diabetics, and these included fungal 52%, bacterial 30% and viral 18% (herpes simplex, herpes zoster). Hair changes were present in 35% with dry, lusterless hair. Diffuse hair loss, from whole body (including scalp) was seen in majority of the patients (60%) followed by hair loss on the body (mostly extensors) 24% and scalp 16%.

Mucosal changes comprised 22% of the total changes. Out of these, xerostomia was 60%, ulcerative stomatitis 24%, macroglossia 10% and angular cheilitis 6%. Purpura including bleeding disorders were observed in 8% of the patients. Acquired perforating disorders, calcification, nephrogenic fibrosing dermatopathy and AV shunt dermatitis were noted in 1 patient each.

Comparison between gender and cutaneous manifestations showed greater incidence of xerosis in fema-

les as compared to males (p value = 0.014) (Table 1), while comparison between age groups revealed a greater incidence of pigmentation with a p value of 0.003 (Table 2).

Table 1: Association between Gender and Cutaneous Manifestations Cross – Tabulation.

Gender	Hair Changes (%)	Pigmentation (%)	Xerosis
Male	44	47	44
Female	56	53	20
p value	0.114	0.748	0.014

Table 2: Association between Age Groups and Cutaneous Manifestations Cross – Tabulation.

Age Group	Hair Changes (%)	Pigmentation (%)
< 50 years	25	40
> 50 years	57	82
p value	0.016	0.003

Discussion

A broad spectrum of cutaneous disorders may be encountered in patients on haemodialysis. Sometimes, the clinical or biochemical evidence of ESRD may even be preceded by cutaneous findings.⁷

Of the total 100 studied patients on haemodialysis, 82% complained of some skin problem. There was a significant association of the number of cutaneous manifestations with age of the patient, but not with haemodialysis duration. Cutaneous manifestations in CKD may be related to 3 processes: primary renal disease, uremic state or the therapeutic processes used in their handling.⁸ Etiopathogenesis of skin manifestations in CKD patients is related to multiple processes namely reduction of the water content and imbalance of metabolites like calcium and phosphate due to the failure of kidneys to excrete various harmful substances.

Xerosis is the commonest cutaneous abnormality in ESRD.⁹ In the present study, it was noted in 78% of the cases, while similar prevalence has been seen in other studies as well (79%).⁶ It is mostly seen on the extensor surfaces of limbs.^{1,7} A similar trend was observed

in our patients. In serious cases, ichthyosiform scaling is reported.⁸ It is severe in diabetics.⁸ Possible causes may be a decrease in the size of eccrine glands and / or high – dose diuretic therapy.⁹ Uremic xerosis signifies changes underlying the epidermis like elastic fragmentation and atrophy of the sebaceous glands. Xerotic changes can also lead to changes like premature skin aging.⁹

Pruritus is the second commonest symptom seen in patients of ESRD. It is not a feature of acute renal failure and does not generally vanish after dialysis, however, it improves with kidney transplantation.¹⁰ Water content in the stratum corneum has been shown to be reduced in pruritic patients on hemodialysis.¹¹ Some studies have recorded it as the commonest prevailing symptom even upto 90%.¹²⁻¹⁴ The cause of pruritus in these patients is not known. Nevertheless, it has been linked with the severity of renal damage (urine output of < 500 ml), xerosis, secondary hyperparathyroidism, hypermagnesemia, hyperphosphatemia, increased serum levels of aluminium, proliferation of non-specific enolase – positive sensory nerves in the skin, increased levels of histamine, iron-deficiency anemia and hypervitaminosis A.^{7,15,16} In the present study, its incidence was 64%. Other studies show a varied prevalence, 60% in Nepal¹³, 55% in Egypt¹⁶ and 53% in the Indian population.⁶ Pruritus may be resistant to therapy, whereas xerosis may be alleviated by simple emollient therapy.¹¹

The likely causes are pruritogens of uncertain nature, that are slowly deposited over a period of months or years. Pruritus in ESRD is often thought harmless, but it has been seen that serious consequences can follow from ineffective therapy. Skin excoriations from scratching, sleep deprivation, depression and impaired quality of life are seen in these patients. Suicidal tendency has been a potential complication.¹⁷ Haemodialysis can be beneficial to relieve the symptoms.¹⁸

Cutaneous pallor caused by anemia has been labeled as the hallmark of CKD.¹⁶ It is one of the earliest findings and significantly contributes to the morbidity and mortality. It results from reduced erythropoiesis and increased haemolysis. Erythropoietin can reduce the pallor.¹ Its incidence in the present study was 62%. Other studies have shown a lower incidence of pallor, like 40% in Nepal¹³ and 45% in the Egyptian patients¹⁶ while the figure noted in the Indian patients is 60%.⁶ The high incidence of pallor could be due to pre-existing low Haemoglobin.

Pigmentation was observed in 54% of the patients while other studies have shown a varied incidence from 20 – 66.^{6,12,13,16,19} It is observed to be of two types in studies: hyperpigmentation and a yellowish tinge to the skin.¹⁶ Diffuse hyperpigmentation distributed on photo-exposed sites is related to an increased amount of melanin in the basal layer and superficial dermis due to failure of the kidney to excrete beta-melanocyte – stimulating hormone β -MSH.⁶ Yellowish discoloration of skin is thought to be induced by the accumulation of carotenoids and nitrogenous pigment urochrome in the dermis.¹⁶ Forty two percent of the patients had diffuse hyperpigmentation while yellowish discoloration was noted in 12%.

Acquired perforating cutaneous disorders like Kyrle's disease, perforating folliculitis and reactive perforating collagenosis have been seen in patients of CKD.⁶ The cause is usually thought to be the dermal connective tissue dysplasia and decay. There is a deposition of calcium in the microvascular environment which may lead to interruption of blood flow to the connective tissue, resulting in its death. In the diabetics, microvascular disease associated with scratching is thought to initiate dermal necrosis and this necrotic debris is extruded through the epidermis.²⁰ In this study, only the reactive perforating collagenosis was seen in one patient. In haemodialysis patients, keratotic pits of palms and soles have also been reported.^{21,22} These were not seen in our study.

Patients with ESRD may also exhibit purpura and ecchymoses which were seen in 8% in the present study while other studies have shown a different incidence from 9%⁶ to 18%.¹⁶ The main causes of abnormal bleeding are thought to be the defects in primary homeostasis like increased fragility of blood vessels, abnormal platelet function and use of heparin during dialysis.⁶ Dialysis partially corrects these changes.¹

Mucosal changes were seen in 22% of patients in our study. Oral changes usually consist of macroglossia with teeth markings, ulcerative stomatitis and xerostomia.⁶ Out of these, xerostomia was 60%, ulcerative stomatitis 25%, macroglossia 15% and angular cheilitis 10%. Xerostomia is attributed to mouth breathing and dehydration.⁵ Ulcerative stomatitis is usually seen in patients with blood urea > 150 mg / 100 ml.²³ Taste impairment in CKD patients is due to reduction in the number of fungiform papillae in addition to increased urea.²⁴ The study by Sultan *et al*¹⁶ shows macroglossia to be 42%, xerostomia 35%, angular cheilitis 15% and ulcerative stomatitis 9%. In the study by Udaykumar, *et al*,⁶ macroglossia constituted 35%, xerostomia 31%,

ulcerative stomatitis 29% and angular cheilitis 12%.

Nail changes were observed in 48% of patients. This figure differs from the one noted by Sultan, *et al*¹⁶ where the nail changes constituted 39% of the total manifestations. In the study carried out in Iran,¹⁹ nail changes have been reported in 40% of CKD patients on haemo peritoneal dialysis, which disappeared after transplantation. The most characteristic nail change²⁵ observed in ESRD patients is nail bed pallor which was seen in 20 (42% of nail changes) of our patients, similar to the results in studies from Brazil⁸ and Nepal.¹² It was associated with the generalized pallor already observed in our patients. Lindsay's nails²⁶ (half and half nails) were seen in 5 patients (10%) while the figure is higher (21%)⁶ in some studies and lower (4%) in the study by Amatya, *et al*.¹² It is due to the proximal half of the nail bed appearing white because of edema associated with a dilated capillary network and the other half appearing normal or pink. Other changes included onychomycosis 22%, diagnosed clinically, subungual hyperkeratosis 14% and koilonychias 12%. These numbers are small as compared to the study done in India by Udaykumar *et al*⁶ which revealed the figures to be 19%, 12% and 18% respectively. In the study by Sultan, *et al*,¹⁶ subungual hyperkeratosis was seen in 10% and onycholysis 3%.

Hair changes were observed in 35%, out of which brittle and lusterless hair were 60% (21 patients), followed by hair loss on the body 24% (8 patients) and scalp 16% (6 patients) respectively. The figures are less compared with studies in India⁶ where incidence of brittle and lusterless hair constituted 16%, sparse scalp hair 11% and sparse body hair in 30%. A higher trend is seen in the study by Sultan *et al*¹⁶ where brittle hair constitute 47%, and sparse scalp hair 46% and body hair 27%. Sparse body hair & diffuse alopecia with dry, lusterless hair have been reported due to decreased secretion of sebum.^{14,27} Generally, it has been seen that long-term chronic diseases result in hair loss.²¹ Nutritional supplements are required to prevent hair loss.¹

Cutaneous infections include bacterial, viral and fungal. Bacterial infections are common in diabetics.⁶ Infections were present in 37% of our patients, out of which fungal infections were 52%, bacterial 30% and viral 18%. Infections comprise different proportions in different studies, from 5 – 40%.^{10,12,16} Commonly seen viral infections in our patients were warts, herpes simplex and herpes zoster. Patients with ESRD have defective cell – mediated immunity due to a reduced T-cell count, explaining the increased prevalence of fungal

infections.⁹ Patients with renal disease on dialysis have impaired host defences which may be caused by the immunosuppressive effect of urea.²⁸ Several factors that may contribute to patient's susceptibility to infections are: Low albumin, elevated intracellular calcium, acidosis, iron overload, inhibition of chemotactic factors and repetitive vascular procedures.²⁸

Manifestations like nephrogenic fibrosing dermatopathy,²⁹ arteriovenous shunt dermatitis³⁰ and cannulation septicaemia¹⁰ have been reported. These were seen in a minority of the population (1% of each manifestation).

Comparison of the cutaneous manifestations on the basis of gender revealed that xerosis in males was significantly higher with a *p* value of 0.014 (Table 1). In our opinion, higher frequency of xerosis associated with renal disease in males could be due to greater emollient use in females due to an increased cosmetic awareness.

Comparison between age groups regarding cutaneous manifestations, patients who were more than 50 years revealed a much higher incidence of xerosis (*p* value = 0.03) and pigmentation (*p* value = 0.016) (Table 2). Pigmentation predominantly involving the sun – exposed sites could be due to prolonged sun – exposure in older patients as suggested in another study by Khanna, *et al.*³¹

Conclusion

Patients with CKD may present with an wide variety of cutaneous abnormalities. In many instances, these may not be directly linked to ESRD, but with secondary disorders that have an increased prevalence in these patients. Increased life expectancy of these patients due to haemodialysis results in newer and more chronic manifestations. Xerosis and pruritus are commonest, and an early recognition of cutaneous findings can relieve the suffering and decrease morbidity owing to prompt treatment. Some prophylactic and remedial measures can be employed to treat these conditions.

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