Journal of Pakistan Association of Dermatologists. 2021;**31(2)**:224-230.

Original Article

Prevalence and severity of cutaneous manifestations in patients of CRF on hemodialysis in relation to duration of replacement therapy

Sumara Rashid, Saleha Azeem*, Zaib, Usma Iftikhar†, Uzma Sarwar††, Aliya Akhtar‡**

Department of Dermatology, Fatima Memorial College of Medicine & Dentistry, Shadman, Lahore.
* 1st Year MBBS, King Edward Medical University, Lahore.
** Department of Dermatology, Sargodha Medical College, Sargodha.
† PhD. Scholar, King Edward Medical University, Lahore.
†† Department of Dermatology, Shalamar Medical and Dental College, Lahore.
‡ Department of Dermatology, Nishtar Medical University, Multan.

Abstract

Objective To determine the effect of duration of HD on the prevalence and severity of different cutaneous manifestations of ESRD.

Methods 100 patients of ESRD at Fatima Memorial Hospital, Shadman were randomly enrolled and analyzed for multiple cutaneous manifestations over a period of eight months. The severity of these manifestations as mild, moderate, severe or very severe and their prevalence along with other particulars and time duration of HD was recorded in addition to any co-morbidities these patients had. Data was organized into tables and graphs.

Results Out of 100 patients, 82% had xerosis, 69% had pruritus, 66% had pigmentary changes, 34% had nail changes, 15% had perforating dermatosis, 10% had bullous lesions, 30% had generalized hair loss and 7% had eczematization at the site of fistula. Out of 100 patients, 46% had severe xerosis, 19% had severe pruritus, 17% had severe pigmentary changes, 31% had severe nail changes, 14% had severe perforating dermatosis, no patients with bullous lesions fell in the category of severe disorder, 12% had severe hair loss and 4% had severe eczematization. The rest had mild and moderate forms of the disease.

Conclusion Cutaneous manifestations among HD patients are common and most of them increase with an increase in the duration of HD. Coordination between a patient's dermatologist and nephrologist can optimize their health experience.

Key words
Hemodialysis (HD), Cutaneous manifestations, End Stage Renal Disease (ESRD), Chronic Kidney Diseases (CKD).

Introduction

Chronic kidney diseases (CKD) is an irreversible deterioration of kidney function. It is named so when GFR is <60 ml/min/1.73m^2 for more than 3 months,[2,4] irrespective of its cause. Its further progression to end stage renal disease (ESRD) occurs when morbidity is up to an extent that threatens life and replacement therapy becomes essential. This disease has recently increased in prevalence worldwide, affecting more than 50 million people, more

Address for correspondence
Dr. Sumara Rashid, Associate Professor,
Department of Dermatology,
Fatima Memorial College of Medicine and Dentistry, Shadman, Lahore.
Ph: 03334275020
Email: dr.sumara@gmail.com

than 1 million of which are receiving replacement therapy.[6] It is estimated that the annual incidence of new cases of end-stage renal disease (ESRD) is >100 per million population in Pakistan.[4] Cutaneous manifestations are common in patients of ESRD either with or without hemodialysis (HD).[5] Pruritus, xerosis, nail and hair disorders, pallor, cutaneous infections and a number of other manifestations are believed to be independent of hemodialysis and acquired perforating dermatosis like calciphylaxis, nephrogenic fibrosing dermopathy, skin manifestations at fistula site and some bullous disorders are said to be present as complication of hemodialysis,[8] according to literature. It affects other organ systems but directly visible on skin either due to disease or its replacement HD therapy. Many factors affect the presence and the severity of these findings, amongst which length of duration of HD is significant.

This research was conducted to study these cutaneous manifestations in patients undergoing hemodialysis at Fatima Memorial Hospital, Lahore. An attempt was made to correlate these findings with duration of HD.

Methods

100 patients undergoing HD in Department of Nephrology, Fatima Memorial Hospital were enrolled for this cross-sectional study. The patients that were considered had at least one cutaneous manifestation and underwent regular sessions of HD at least twice a week for >6 months. This study was conducted in 8 months' time period from December 2018 to July 2019. After informed consent and brief history about CKD, duration of HD and other patients' particulars were noted. A detailed examination of cutaneous system was performed including skin and adnexa history. The severity of each cutaneous manifestation was classified as mild, moderate, severe or very severe and in certain manifestations these words corresponded to a specific number of lesions. Nail changes were considered mild if <2 nails were affected, 2-5 as moderate, 5-7 as severe and >7 as very severe. For perforating dermatosis and bullous lesions, mild meant <3 lesions, 4-8 lesions was moderate, 9-15 was severe and >15 was very severe. Generalized hair loss was taken as mild if it was localized, moderate if it was generalized, severe if generalized sparse hair were present and very severe in case of complete alopecia. Data was filled and recorded in proformas. KOH mounts were prepared. Photographs were taken only when necessary and biopsy of very few patients was done.

Among the 100 patients studied, 68 were males and 32 were females (the ratio between males and females being 17:8). Among the male patients, 52 were >60 years of age while 10 were between 50-60 years. 3 male patients were between 40-45 years of age and 3 more were <40 years old. In females, 28 out of 32 were >60 years of age and the remaining 4 were between 50-60 years old. These patients had different co-morbidities[7] **(Table 1)**.

Results

The prevalence of most of the cutaneous manifestations increased with the increase in duration of HD while some of them were not affected by it.

Table 1

Co-Morbidities	*Patients N (%)*
Diabetes	76(76)
Hypertension	88(88)
Analgesic Nephropathy	3(3)
Rheumatoid Disease (Rheumatoid Arthritis, Gout, SLE, sero –ve arthritis)	34(34)
IHD	64(64)
Others (Asthma, Pulmonary Tuberculosis, Vitiligo, Migraine)	12(12)

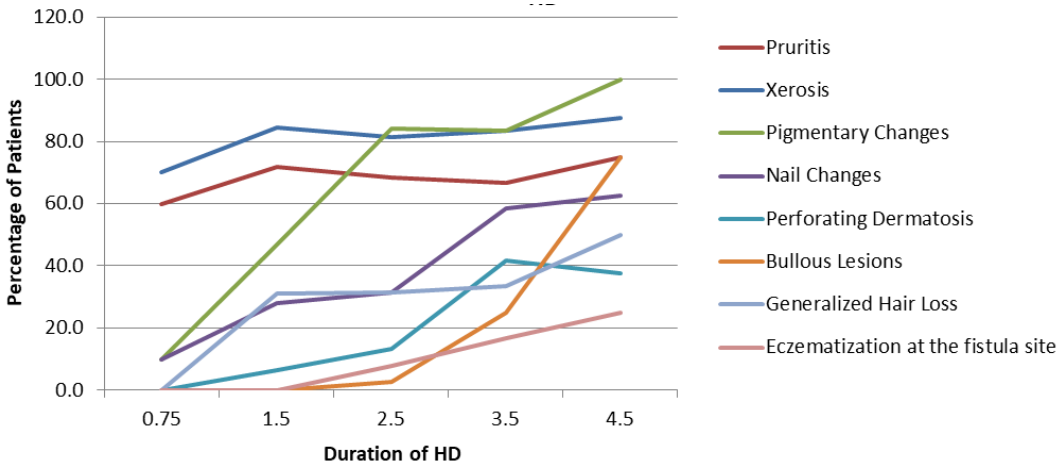

Figure 1 Relative prevalence of different cutaneous manifestations in relation to duration of HD.

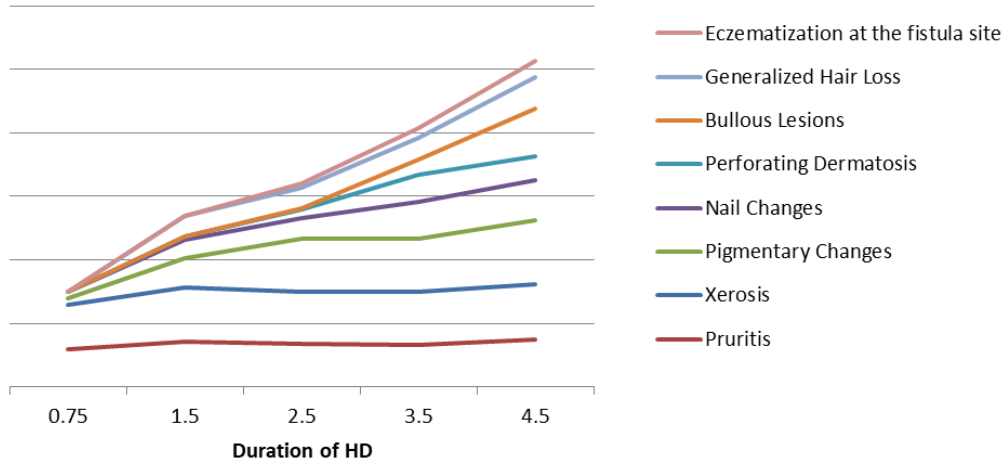

Figure 2 Trend in prevalence of different cutaneous manifestations in relation to duration of HD.

The relative prevalence of these manifestations in relation to the duration of HD and the trend of prevalence independent of the %age of patients affected can be seen in **Figure 1&2**.

In skin changes, xerosis was observed in 82% of patients, being the most common cutaneous abnormality, which was more marked on both lower limbs and back. Acquired ichthiosis like scaling on lower limbs was observed along with generalized xerosis in 4 patients.

Pruritus was present in 69% of patients. 28% of these showed severe pruritus while others ranged from mild to moderate in severity. 34 patients had it since before the start of HD while the rest of them developed it only after initiation of HD in their disease course. Only 3 were reported to have significant reduction after HD. The rest of them were persistent with complaints of increase in the severity of disease.

Yellow, greyish-black pigmentation was observed in 66% of patients. Greyish-black and slate grey color was more common in sun-exposed areas while pallor was evident throughout the skin.

Nail changes included pallor, half and half nails, onycholysis, discoloration, splinter hemorrhages, onychomycosis and koilonychias. These comprised 34% of the cases; out of these

cases, onychomycosis was present in 10 patients while the rest had other mixed changes. One of the patients had had their big toe amputated. In cutaneous infections other than onychomycosis, 12 patients had folliculitis, 10 had ecthyma while 2 had Herpes zoster at time of examination.

In perforating dermatosis, 15 patients had RPC like lesions. 3 were confirmed by biopsy. Out of these 15, 7 had >30 lesions on whole body showing extreme severity while 1 had its moderate form with <20 lesions.

Bullous lesions were present in 10 patients, most of them had >3 years duration of HD, with clear base on dorsum of hand and near fistula site as well as on lower legs. Biopsy could not be done in any patient because they were unstable, lethargic and unwell. These led to hemorrhagic crusting and atrophic lesions of patients. Calcifying lesions with white discharge were present in 3 patients. These were on extensor surface of forearm and were developed after HD started. In one patient, these ulcerative lesions were secondarily infected and needed systemic antibiotic therapy after C/S.

There were hair changes noted in 30% of patients, loss of body hair being the most common finding in 22 out of these 30 patients. There were, generally, opaque hair on body. Other changes include brownish hair discoloration, lusterless, rough scalp hair.

7 of our patients had yellow waxy hard skin with concomitant pain.

Patients with cutaneous manifestation in relation to the duration of HD, and %age of patients corresponding to each severity has been shown in **Table 2**.

Table 2

Xerosis (82%)					*Pruritus (69%)*				
Duration of HD	*Mild N(%)*	*Moderate N(%)*	*Severe N(%)*	*V.Severe N(%)*	*Duration of HD*	*Mild N(%)*	*Moderate N(%)*	*Severe N(%)*	*V.Severe N(%)*
6m-1yr.	3(43)	4(57)	0	0	6m-1yr.	1(17)	3(50)	2(33)	0
1-2 yrs.	5(19)	9(33)	12(44)	1(4)	1-2 yrs.	6(26)	16(70)	0	1(4)
2-3 yrs.	0	6(19)	23(74)	2(6)	2-3 yrs.	4(15)	10(38)	10(38)	2(8)
3-4 yrs.	1(10)	5(50)	3(30)	1(10)	3-4 yrs.	0	6(75)	1(12)	1(12)
4-5 yrs.	1(14)	2(29)	3(43)	1(14)	4-5 yrs.	0	4(67)	2(33)	0
Pigmentary Changes (66%)					*Nail Changes (34%)*				
Duration of HD	*Mild N(%)*	*Moderate N(%)*	*Severe N(%)*	*V.Severe N(%)*	*Duration of HD*	*Mild N(%)*	*Moderate N(%)*	*Severe N(%)*	*V.Severe N(%)*
6m-1yr.	1(100)	0	0	0	6m-1yr.	0	1(100)	0	0
1-2 yrs.	10(67)	5(33)	0	0	1-2 yrs.	0	2(22)	7(78)	0
2-3 yrs.	15(47)	14(44)	3(9)	0	2-3 yrs.	0	0	9(75)	3(25)
3-4 yrs.	0	2(20)	7(70)	1(10)	3-4 yrs.	0	0	5(71)	2(29)
4-5 yrs.	0	2(25)	4(50)	2(25)	4-5 yrs.	0	0	5(100)	0
Perforating Dermatosis (15%)					*Bullous Lesions (10%)*				
Duration of HD	*Mild N(%)*	*Moderate N(%)*	*Severe N(%)*	*V.Severe N(%)*	*Duration of HD*	*Mild N(%)*	*Moderate N(%)*	*Severe N(%)*	*V.Severe N(%)*
6m-1yr.	0	0	0	0	6m-1yr.	0	0	0	0
1-2 yrs.	0	1(50)	0	1(50)	1-2 yrs.	0	0	0	0
2-3 yrs.	0	0	3(60)	2(40)	2-3 yrs.	1(100)	0	0	0
3-4 yrs.	0	0	3(60)	2(40)	3-4 yrs.	2(67)	1(33)	0	0
4-5 yrs.	0	0	1(33)	2(67)	4-5 yrs.	4(67)	2(33)	0	0
Generalized Hair Loss (30%)					*Eczematization at the site of fistula (7%)*				
Duration of HD	*Mild N(%)*	*Moderate N(%)*	*Severe N(%)*	*V.Severe N(%)*	*Duration of HD*	*Mild N(%)*	*Moderate N(%)*	*Severe N(%)*	*V.Severe N(%)*
6m-1yr.	0	0	0	0	6m-1yr.	0	0	0	0
1-2 yrs.	5(50)	5(50)	0	0	1-2 yrs.	0	0	0	0
2-3 yrs.	0	8(67)	3(25)	1(8)	2-3 yrs.	0	3(100)	0	0

3-4 yrs.	0	0	4(100)	0	3-4 yrs.	0	0	2(100)	0
4-5 yrs.	0	0	2(50)	2(50)	4-5 yrs.	0	0	2(100)	0

Discussion

Clinical and demographic details of polymorphous lesions in our patients showed known trends with some variability. Most of them had direct relationship between their severity and the duration of HD while a few findings were independent.

It was common in accordance with other local and international studies[1,5] that xerosis is a known cutaneous finding, and arguably the most common one[3] in HD patients. Factors attributing to this are use of diuretics, miniaturization of sebaceous/sweat glands, co-morbidities and decreased use of emollients. Cold and dry weather was another contributing factor to the disease,[11] which of course is aggravated by sunbathing, soaps etc. Xerosis, in our patients, increased in severity after HD though it was reported to be present before that as well.

Pruritus, generalized or localized to the back, abdomen or head,[5] was present in 69% of our patients. Again, presence was irrespective of starting of HD, although the severity increased with its duration. It is unclear whether increased pruritus is related to prolongation of ESRD or associated with HD. Although pruritus is poorly understood in these patients, causes may include xerosis, metabolic disequilibrium,[10] secondary hyperparathyroidism and aluminium overload in HD. We could not relate it with age, gender or pre-existing diseases. Xerosis and pruritus are also related as evidenced by Shirazian's study.[9]

Cutaneous hyperpigmentation was observed in 66% of cases, a manifestation which has variable occurrence such as from 40% to 80% in different studies.[15-17] Prevalence increased with longer duration of dialysis. Pallor is also co-related to slate grey pigmentation. There is deposition of Hemosiderin and excessive transfusions leading to iron overload. As these patients are relatively less tolerant to cold, sunbathing led to increased pigmentation in sun-exposed areas because of increased melanin deposition in basal layer and superficial dermis. Increased MSH is present due to the failure of kidneys in excreting it.

Concerning nail changes, onychomycosis was present in 29% of cases involving one or multiple nails. Half and half (Lindsay's nails) is a fairly common finding. Here proximal nail is white while distal is reddish-brown and unaffected by pressure. Other nail findings are onychomycosis, onycolysis, onycoschizia, splinter hemorrhages, subungual hyperkeratosis and nail discoloration. Tercedor and Pico's studies also show a positive relation of increase in nail changes with duration of HD.[12,13]

Perforating cutaneous disorders (RPC-like lesions) were also present in 15% of cases. Herpes Zoster and bacterial infections were also present in 9 patients which is less as compared to other studies,[2] immuno-compromization due to disease treatment and HD being prominent causes.

Hair changes were noted in 30% of cases. Sparse, brittle and loss of hair were notable findings. Causes may be xerosis, pruritus and medication e.g. lipid lowering and anti HTN medication. There remains an increasing number of hair changes with chronicity of HD. Similar frequency was noted in another study [1] whereas a much higher frequency was noted in another one,[18] making its occurrence variable. Lusterless hair[3,14] and some loss can be a physiological change but more rapid in these patients. However, how much HD attributes to it remains to be studied. Uremic toxins in the body may lead to rapid hair changes. Increasing urea levels depict the inadequacy of HD as a probable

cause. Most of our patients had dialysis biweekly and increasing it is recommended to increase it to thrice a week.

Bullae (either diabetic bullae) or pseudoporphyria usually affects 2-18% of patients.[19,20] In our study, 10% of patients had these blisters. Calciphylaxis and nephrogenic fibrosing dermopathy remained in observation but biopsy could not be done as most of the patients did not consent to it, owing to the distress caused by HD. Most of these patients had >3 years duration of HD so it was assumed that it has a positive relationship with duration of HD.

Majority of cutaneous changes have a significant direct relation with length of duration of dialysis. Now, there is a further need to study whether the same pattern persists without HD as well but as the life expectancy is decreased in patients who refuse to have dialysis or cannot afford to due to poor economic condition, this remains a limitation for other studies as to how dialysis increases severity of cutaneous manifestations.

Conclusion

There are various diverse cutaneous manifestations in ESRD. Some of them may not have their relation with hemodialysis e.g. xerosis, pruritus etc. but majority of these findings increase in severity with time and HD as a replacement therapy. This significantly increases morbidity of these already sick patients. Our study limitations could be weather and climate and effects of other co-morbidities which influence these skin findings e.g. diabetes mellitus and drugs. Understanding of prevalence of these findings, adequacy of hemodialysis in terms of frequency and method used is important to know. There should be a better collaboration between the dermatologist and nephrologist for early detection and better management of these diseases to improve quality of life of these patients.

References

1. Bouhamidi A, El Amraoui M, Rafik H, Boui M, Hjira N. Dermatologic Manifestations in Patients on Chronic Hemodialysis. *J Dermatol Res Ther*. 2019;**5**:069. doi.org/10.23937/2469-5750/1510069
2. Anees M, Butt G, Gull S, *et al*. Factors Affecting Dermatological Manifestations in Patients with End Stage Renal Disease. *J Coll Physicians Surg Pak*. 2018;**28(2)**:98-102. DOI: 10.29271/jcpsp.2018.02.98
3. Udayakumar P, Balasubramanian S, Ramalingam K S, Lakshmi C, Srinivas C R, Mathew AC. Cutaneous manifestations in patients with chronic renal failure on hemodialysis. *Indian J Dermatol Venereol Leprol*. 2006;**72**:119-25
4. Ullah K, Butt G, Masroor I, Kanwal K, Kifayat F. Epidemiology of chronic kidney disease in a Pakistani population. *Saudi J Kidney Dis Transpl* 2015;**26**:1307-10
5. Markova, A., Lester, J., Wang, J., & Robinson-Bostom, L. (2012). Diagnosis of common dermopathies in dialysis patients: a review and update. *Seminars in Dialysis*. 2012;**25(4)**:408-18.
6. Kidney Disease Outcomes Quality Initiative (K/DOQI). K/DOQI clinical practice guidelines on hypertension and antihypertensive agents in chronic kidney disease. *Am J Kidney Dis*. 2004;**43(5)**:S1-290.
7. Fraser, S.D.S., Roderick, P.J., May, C.R. *et al*. The burden of comorbidity in people with chronic kidney disease stage 3: a cohort study. *BMC Nephrol*. 2015;**16**:193.
8. Galperin, Timur A *et al*. "Cutaneous manifestations of ESRD." *CJASN*, 2014; **9(1)**: 201-18. doi:10.2215/CJN.05900513
9. Shirazian S, Aina O, Park Y, Chowdhury N, Leger K, Hou L, Miyawaki N, Mathur VS. Chronic kidney disease-associated pruritus: impact on quality of life and current management challenges. *Int J Nephrol Renovasc Dis*. 2017;**10**:11-26. doi: 10.2147/IJNRD.S108045. PMID: 28176969; PMCID: PMC5271405.
10. Tapia L. Pruritus on hemodialysis. *Int J Dermatol*. 1979;**18**:217–8.

11. Szepietowski, Jacek & Reich, Adam & Schwartz, Robert. Uraemic xerosis. *Nephrology Dialysis Transplantation*. 2004;**19(11)**:2709-12.
12. Tercedor J, Hernandez BL, Rodenas JM. Nail diseases in hemodialysis patients: Case-control study. *Br J Dermatol*. 2001;**144**:415-48.
13. Pico MR, Lugo-Somolinos A, Sánchez JL, Burgos-Calderón R. Cutaneous alterations in patients with chronic renal failure. *Int J Dermatol*. 1992;**31**:860–3.
14. Morton CA, Lafferty M, Hau C, Henderson I, Jones M, Lowe JG. Pruritus and skin hydration during dialysis. *Nephrol Dial Transplant*. 1996;**11**:2031–6.
15. Mirza R, Wahid Z, Talat H. Dermatological manifestations in chronic renal failure patients on hemodialysis, *JLliaq Univ Hel Scic*. 2012;**11**:22-8.
16. Masmoudi A, Darouiche MH, Salah HB, Hmida MB, Turki H. Cutaneous abnormalities in patients with end stage renal failure on chronic hemodialysis. A study of 458 patients. *J Dermatol Case Rep*. 2014;**8**:86-94.
17. Sultan MM, Mansour HM, Wahby IM, Ali S Houddy. Cutaneous manifestations in Egyptian patients with chronic renal failure on regular haemodialysis. *J Egypt Women Dermtal Soc*. 2009;7-1.
18. Mourad B, Hegab D, Okasha K, Rizk S. Prospective study on prevalence of dermatological changes in patients under hemodialysis in hemodialysis units in Tanta University hospitals, Egypt. *Clin Cosmet Investig Dermatol*. 2014;**7**:313–9. Published 2014 Nov 11. doi:10.2147/CCID.S70842
19. Abdelbaqi‐Salhab M, Shalhub S, Morgan MB. A current review of the cutaneous manifestations of renal disease. *J Cutan Pathol* 2003;**30**:527‐38.
20. Lupi O, Rezende L, Zangrando M, Sessim M, Silveira CB, Sepulcri MA, *et al*. Cutaneous manifestations in end stage renal disease. *An Bras Dermatol*. 2011;**86**:319‐26.