ORIGINAL ARTICLE

Dermatological Manifestations in Patients with Chronic Renal Failurea: A Clinicopathological Study

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Abstract

The present study was planned to evaluate the spectrum of clinical profile and histopathological changes in skin of CRF patients and to elucidate their association with the severity of disease process. One hundred diagnosed cases of CRF were studied. The patients were examined for any dermatological manifestation of CRF. Histopathological evaluation of normal looking skin and from specific lesions was done. The dermatological and histopathological changes were then correlated with the severity of renal failure. All patients had, at least, one cutaneous manifestation. Pruritis was the most common complaint (58%). Xerosis was the most frequent skin change (55%). Pallor was the most prevalent pigmentary change (93%). The most commonly observed hair change was diffuse alopecia (26%) and among nail changes, onchodystrophy and absence of lunula were the most frequent findings (19% each). Infections were seen in 19% cases and decreased sweating in 27% cases. The most common histopathological change seen was hyperkeratosis (91%) followed by epidermal atrophy (89%). The most common dermal change was perivascular lymphocytic infiltrate (62%) and the most frequent adnexal change was sweat gland atrophy (36%).CRF is associated with number of dermatological manifestations, some of which are related with the severity of renal disease. Early recognition and management of some of these dermatological manifestations may reduce the associated morbidity and vastly improve the cutaneous outcome in these patients.

Key Words

Chronic Renal Failure, Dermatological Manifestation, Histopathology

Introduction

The skin is not an inert covering but a sensitive dynamic boundary. In addition to disorders that primarily affect the skin, most of the major systemic diseases have cutaneous manifestations (1). Skin is the most visible and easily accessible organ of the body. It is a mirror for many systemic diseases including renal diseases (2).

The protean cutaneous manifestations of renal disease are primarily encountered in patients with chronic renal failure (CRF) (3). About 50-100% of patients with end stage renal disease (ESRD) have at least one associated cutaneous change (4,). These cutaneous disorders can precede or follow the initiation of hemodialysis treatment and there are more chances of developing newer skin changes during the course of hemodialysis therapy (5). Some of these cutaneous disorders disappear following kidney transplantation, confirming that the metabolic milieu resulting from the malfunctioning kidney is responsible for some of these changes. Other lesions may be related to the cause of CRF (6).

The present study was planned to evaluate the spectrum of clinical profile and histopathological changes in the skin of CRF patients and to elucidate their association with the severity of disease process.

Material and Methods

This study was done on one hundred diagnosed cases of CRF taken from the outpatient department, medical wards and dialysis ward of the department of Medicine, Government Medical College, Jammu. Data of the patients on age, sex, underlying cause of CRF, duration and severity of CRF and duration of hemodialysis was collected. Attempt was made to establish the etiology of CRF by appropriate investigations in all cases. The patients were categorized into mild, moderate, severe CRF and end stage renal disease (ESRD) according to their creatinine clearance levels. They were examined thoroughly for any dermatological manifestation of CRF. Histopathological evaluation of biopsy specimen from normal looking skin of the left thigh and from any specific lesion was done to determine microscopic changes seen

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in the skin of these patients. Dermatological and histopathological changes were then correlated with the severity of renal failure. The Chi-square test was used to determine significant differences in proportions. Differences were considered significant when p value was less than 0.05.

Results

Of the 100 patients evaluated, 63 were males and 37 were females (*Fig 1*) with a mean age of 50.13 with a standard deviation of 14.81. (*Table 1*) The most common causes of CRF in the patients were hypertension (27% cases), diabetes mellitus (17% cases), diabetes mellitus with hypertension (24% cases) and chronic glomerulonephritis (20% cases). Less frequent causes were polycystic kidney disease (6% cases), analgesic nephropathy (4% cases) and medullary cystic kidney disease (2% cases) (*Fig 2*). Of the total 100 patients, 42 were undergoing maintenance hemodialysis with duration of hemodialysis ranging between 15 days and 14 months. The mean duration of CRF was 1.4 years with a standard deviation of 1.53 years. Of the 100 cases evaluated, 53 had moderate CRF and 36 had severe CRF. Mild CRF was found in only 4 patients and ESRD in 7 cases. For statistical analysis the mild and moderate CRF cases were grouped together and ESRD cases were combined with severe CRF cases. (*Table 2*) All the patients had at least one dermatological manifestation. Forty three patients had 2 or more manifestations. Pruritis was the most common complaint, seen in 58% cases. Among skin changes, xerosis was the most frequently observed (55% cases). Of the pigmentary changes, pallor was the most prevalent finding (93% cases). The most commonly observed hair change was diffuse alopecia (26% cases) and among the nail changes, onchodystrophy and absence of lunula were the most frequent findings (19% cases each). Infections were seen in 19% cases and decreased sweating in 27% cases (*Table 3*). Statistically significant difference in the 2 groups (i.e Group I & II) was observed in the prevalence of pallor, absence of lunula, Beau's line and decreased sweating (*Table 4*). On histopathological examination of normal looking skin of CRF patients, the most common finding seen was hyperkeratosis occurring in 91% cases followed by epidermal atrophy in 89% cases. The most common dermal change observed was perivascular lymphocytic infiltrate seen in 62% cases and the most frequent adnexal change was sweat gland atrophy seen in 36% cases (*Table 5*). Statistically significant difference in the 2 groups (i.e Group I & II) was observed in the prevalence of microangiopathy and adnexal changes (*Table 6*).

Discussion

It has commonly been remarked that dermatology is an outpatient speciality concerned with the diseases associated with low mortality (7). This notion could lead to less dermatological attention given to patients with systemic diseases by some of their attending physicians which may allow the skin diseases to run a chronic course with significant effects on the general health as well as the quality of life of the affected individual. Moreover, certain systemic disorders can be suspected through cutaneous symptoms and signs (8).

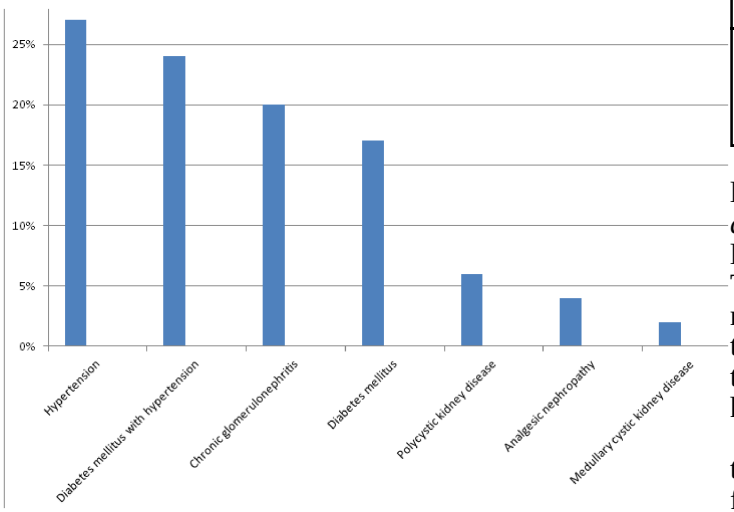
The mean age of the patients in the present study was 50.13 ± 14.81 years similar to that reported by Mirza *et al* who found the mean age of their patients to be 50.58 ± 14.84 years (9). Out of 100 patients, 63 were males and 37 were females. Similar male predominance in CRF has been reported by Sanad *et al* (10).

This study estimated that hypertension, diabetes mellitus followed by chronic glomerulonephritis were the most common causes of CRF. This is in agreement with Sheikh *et al* (11). The duration of CRF in our study ranged from 1 month to 6 years with a mean duration of 1.4 years. Duration of CRF was reported to be between 3 years and 2 years by Singh et al in their study (12). Majority of our patients had moderate CRF (53%) followed by severe CRF (36%), ESRD (7%) and mild CRF (4%). This is in concordance with earlier studies in which majority of patients presented with moderate and severe CRF. (12,13) The results of the present study showed that all patients with CRF had one or more cutaneous manifestations as has also been reported by Sultan *et al* (14) and Pico *et al* (15). When specific type of dermatological disorders were analysed, the most common was pruritis. Among skin changes, the most common was xerosis (55%), followed by purpura (15%). Among pigmentary changes, pallor was the most prevalent finding (93%). Among hair problems, the most common was diffuse alopecia (26%) followed by fine brittle hair (21%). Among nail problems, onychodystrophy and absence of lunula were the most frequent findings (19% each). Infections (19%) and decreased sweating (27%) were also observed. Pruritis, seen in 58% of our patients, is one of the most common cutaneous complaints in patients with CRF (16). Udayakumar *et al* also reported this finding in 53% of their patients although the most prevalent finding in their study was xerosis (5). Slowly accumulated pruritogens of uncertain nature are the likely cause of pruritis (5). It has also been associated with the degree of renal insufficiency (urine output < 500 ml), secondary hyperparathyroidism, xerosis, increased serum levels of magnesium, calcium, aluminium, phosphate and histamine, uremic sensory neuropathy, abnormal fatty acid metabolism, hypervitaminosis A and iron deficiency anemia (5, 17). Xerosis was observed in 55% cases in the present study. Similar results have been observed by Sultan *et al.* (14). The etiology of xerosis in CRF may be

Table 1. Age Distribution of Patients

Age Group (in years)	No. of Patients n = 100
10 – 20	4
21 – 30	6
31 – 40	16
41 - 50	25
51 - 60	28
61 – 70	18
70	3

Fig 2. Causes of Chronic Renal Failure



due to complication of diabetes; a reduction in the size of eccrine sweat glands may be contributory although high dose of diuretic regimens are also implicated (18). Purpura was seen in 15% of our cases. Mirza et al observed purpuric lesions in 13.6% of their patients which is close to that seen in our study (9). Defects in primary hemostasis like increased vascular fragility, abnormal platelet function and use of heparin during dialysis are the main causes of such lesions in these patients (5). Mild thrombocytopenia has also been stated as a possible cause (16). Pallor, the most common pigmentary change in our study (93% cases), had significant association with severity of CRF. It was seen in all cases of severe CRF and ESRD. Sanad et al reported pallor in 91.2% of their cases (10). Pallor is due to associated anemia seen in CRF. Anemia is primarily the result of inadequate erythropoietin production by the failing kidneys. Other contributory factors include iron deficiency, folic acid or vitamin B12 deficiency and decreased erythrocyte survival (16). Brown hyperpigmentation predominantly located on the sun exposed areas of the body was seen in 29% cases in our study. Abdelbaqi-Salhab reported that pigmentary alteration occurs in 25-70% of the dialysis patients and increases with the duration of renal disease (19). An interesting finding of hyperpigmented macules on palms and soles was seen in 18% cases in the present study. Similar

Fig 1. Sex Distribution of Patients

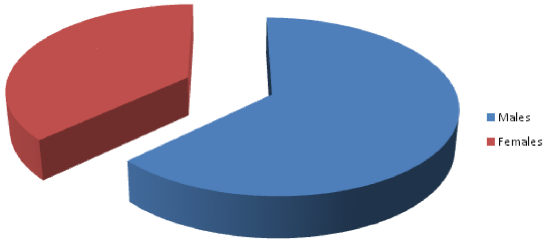


Table 2. Severity of CRF

Group	*Severity of CRF	No. of patients n = 100
Group I	Mild	4
	Moderate	53
Group II	Severe	36
	ESRD	7

Severity assessed by creatinine clearance

lesions were observed by Mirza *et al* (9) and Pico *et al* (15). There are some of the very few studies in literature to have documented these lesions in CRF. This diffuse hyperpigmentation can be attributed to retention of chromogens and deposition of melanin in the basal layer and superficial dermis due to failure of the kidneys to excrete beta-melanocyte-stimulating hormone (5, 16).

The most commonly observed hair changes in the present study were diffuse alopecia (26%) followed by fine brittle hairs (21%). Out of the 26 cases with alopecia 15 were observed in patients who had undergone hemodialysis. Loss of hair was seen mainly from the scalp; however few patients also complained of loss of body hair. Sultan et al in a study on Egyptian patients reported brittle hair in 47%, sparse scalp hair in 46% and sparse body hair in 27% of patients with CRF (14). The higher incidence of hair changes in their study could be attributed to racial variation. The alopecia in CRF patients may be related to tellugen effluvium associated with severity of illness, xerosis, pruritis or due to drugs (heparin, anti-hypertensives, lipid lowering) used in these patients (4). On the whole, nail changes were seen in 65% cases in our study which is comparable to that observed by Tercedor and coworkers (20). The most common nail changes observed were absence of lunula and onychodystrophy (19% each). Absence of lunula was more commonly seen in patients having severe CRF and ESRD. Singh and associates observed onychodystrophy in 20% of their cases which is comparable to that seen in our study (12). Dyachenko et al., in their exclusive study of nail changes in patients of CRF found absent lunulae in 13% of their cases (21). In our study there were 19 cases of skin infection. The commonest one was onychomycosis seen in 10%

Table 3. Dermatological Manifestations in CRF Patients

S.No	Dermatological Manifestations	No. of Patients
1.	**Pruritis**	58
2.	**Skin Changes**	
	• Xerosis	55
	• Purpura	15
	• APD	4
	• Bullous lesions	3
	• Keratosis pilaris	2
3.	**Pigmentary Changes**	
	• Pallor	93
	• Brown hyperpigmentation	29
	• Hyperpigmented macules on palms and soles	18
	• Grey - yellow discolouration	7
4.	**Hair Changes**	
	• Alopecia	26
	• Fine/Brittle hair	21
5.	**Nail Changes**	
	• Onychodystrophy	19
	• Absence of lunula	19
	• Half- and- half nail	18
	• Longitudinal ridging	11
	• Beau's line	5
	• Onycholysis	3
6.	**Infections**	
	• Onychomycosis	10
	• Pyoderma	9
7.	**Decreased Sweating**	27

of cases. Similar results were reported by Dyachenko *et al* (21) who found onychomycosis in 10.4% of their patients. Udayakumar *et al* (5) also found onychomycosis to be the commonest skin infection in their study. CRF patients have impaired cellular immunity due to decreased T-lymphocyte cell count; this could explain the increased prevalence of fungal infections in such patients (15). Twenty seven percent cases in the present study complained of decreased sweating. It was more frequently complained by patients with severe CRF and ESRD.

Table 5. Histopathological Findings in CRF Patients

S.No.	Histopathological Changes	No. of Patients
1.	**Epidermal Changes**	
	• Hyperkeratosis	91
	• Epidermal atrophy	89
	• Increased basal layer pigmentation	52
2.	**Dermal Changes**	
	• Perivascular lymphocytic infiltrate	62
	• Microangiopathy	
	- Basement membrane thickening	30
	- Endothelial cell activation/proliferation	25
	• Fragmentation of elastin	21
3.	**Adnexal Changes**	
	• Sweat gland atrophy	36
	• Increased number of nerve bundles	16

Table 4. Dermatological Manifestations in Relation to Severity of CRF

S. No.	Dermatological manifestations	Group I (Mild CRF + Moderate CRF) n = 57		Group II (Severe CRF + ESRD) n = 43		χ^2	*P value
		No.	Percentage	No.	Percentage		
1.	Pruritis	29	50.87	29	67.44	2.76	0.09
2.	Skin changes						
	• Xerosis	30	52.63	24	55.81	0.02	0.88
	• Purpura	10	17.54	5	11.62	1.53	0.21
	• APD	2	3.50	2	4.65	0.05	0.82
	• Bullous lesions	2	3.50	1	2.32	0.06	0.80
	• Keratosis pilaris	-	-	2	4.65	-	0.18
3.	Pigmentary changes						
	• Pallor	50	87.71	43	100	3.95	0.04
	• Brown hyperpigmentation	15	26.31	14	22.22	0.12	0.72
	• Hyperpigmented macules on palms and soles	8	14.03	9	20.09	0.83	0.36
	• Grey-yellow discolouration	5	8.77	2	4.65	0.16	0.68
4.	Hair changes						
	• Alopecia	16	28.07	10	23.25	0.30	0.58
	• Fine/Brittle hair	9	15.78	12	27.90	2.17	0.14
5.	Nail changes						
	• Onchodystrophy	11	19.29	8	15.09	0.50	0.48
	• Absence of lunula	7	12.28	12	27.90	3.89	0.04
	• Half and half nail	8	14.03	10	23.25	1.41	0.23
	• Longitudinal ridging	6	10.52	5	11.62	0.02	0.88
	• Beau's line	-	-	5	11.62	4.74	0.02
	• Onycholysis	2	3.50	1	2.32	0.06	0.80
6.	Infections						
	• Onychomycosis	8	14.03	2	4.65	2.07	0.14
	• Pyoderma	7	12.28	2	4.65	0.94	0.33
7.	Decreased sweating	11	19.29	16	37.20	3.99	0.04

**p value >0.05 = Non-significant; <0.05 = Significant*

Table 6. Histopathological changes in relation to severity of CRF

S.No.	Histopathological changes	Group I (Mild CRF + Moderate CRF) n = 57		Group II (Severe CRF & ESRD) n = 43		X^2	*p value
1.	Epidermal changes						
	• Hyperkeratosis	52	91.22	39	90.69	0.07	0.79
	• Epidermal atrophy	49	85.96	40	93.02	0.63	0.42
	• Increased basal layer pigmentation	30	52.63	22	51.16	0.02	0.88
2.	Dermal changes						
	• Perivascular lymphocytic infiltrate	31	54.38	31	72.09	3.26	0.07
	• Microangiopathy						
	➢ Basement membrane thickening	12	21.05	18	41.86	5.05	0.02
	➢ Endothelial cell activation/ Proliferation	9	15.78	16	37.20	6.00	0.01
	• Fragmentation of elastin	10	17.54	11	25.58	0.01	0.32
3.	Adnexal changes						
	• Sweat gland atrophy	15	26.13	21	48.83	5.40	0.02
	• Increased number of nerve bundles	5	8.77	11	25.58	5.15	0.02

p value >0.05 = Non-significant; <0.05 = Significant

Gilchrest and associates reported it in only 7.5% cases (13). There occur alterations of the cutaneous structures underlying the epidermis in CRF patients. These, among others, include atrophy of the secretory and ductal portions of the sweat glands as well as a decrease in the number of the glands. This could explain the impairment of sweating in such patients (22). Histopathological changes in the skin of patients with CRF have been rarely reported in the literature. The most prevalent histopathological finding observed in our study was hyperkeratosis with no significant correlation with the severity of renal failure. Gilchrest et al observed hyperkeratosis in all their CRF patients without any correlation with the severity of CRF (13). Singh *et al* reported it in 46% cases with no correlation with the severity of CRF (12).

Epidermal atrophy was seen in 86% cases in the present study and its prevalence did not differ statistically with the severity of renal failure. This observation is comparable to that of Singh *et al* (12) where it was seen in 80% cases. Gilchrest et al also reported it in 52% of their cases (13). Both these studies demonstrated no correlation with the severity of CRF, as is the case with the present study. However, Lundin *et al* (23) correlated epidermal atrophy with the severity of CRF. Increased basal layer pigmentation was observed in 52% cases in our study. Difference in prevalence did not correlate with the severity of renal failure. Singh et al have reported this finding in 93% of their cases; however they observed it to correlate with the severity of CRF (12). In the present study the most common dermal change was perivascular lymphocytic infiltrate seen in 62% cases and it showed no significant correlation with the severity of renal failure. . . . . *et al* observed it in 40.7% cases (13). Release of inflammatory mediators by capillaries and lymphatics in response to injury by toxic metabolite accumulation in CRF is thought to be the possible cause of perivascular lymphocytic infiltrate. Basement membrane thickening and endothelial cell activation were seen in 30% and 25% cases, respectively in the present study and their prevalence was seen to be significantly higher in patients with severe CRF and ESRD. Gilchrest *et al* observed basement membrane thickening in 37% cases and endothelial cell activation in 40.7% cases in their study; however these findings did not correlate with the severity of CRF (13). We found fragmentation of elastin in 21% of our cases with no statistically significant correlation with the severity of renal failure. Gilchrest et al demonstrated this feature in 44.4% of their cases with no correlation with the severity of renal failure. Fragmentation of elastin was thought to be due to release of elastase from perivascular inflammatory cells (13). Sweat gland atrophy was seen in 36% cases in our study and it was significantly more prevalent in severe CRF and ESRD. Cawley *et al* observed small eccrine sweat glands in 57% of their cases and attributed it to the toxic effects of elevated blood levels of some electrolytes or metabolites seen in CRF and also possibly to a factor produced by the damaged kidneys (24). An increased number of nerve bundles was seen in 16% of our cases and this was significantly more common in severe CRF and ESRD. This finding has been rarely reported in the literature before. Johansson *et al* demonstrated sprouting of nerve fibres in uremic patients which was thought to

be responsible for pruritis in them (25).

Conclusion

It may be concluded from the present study that CRF is associated with a number of dermatological manifestations, some of which are related with the severity of renal disease. Dialysis may often perpetuate many of these conditions. Although, most of the dermatological disorders in CRF are relatively benign, a few rare skin diseases have the potential to cause serious morbidity and mortality. Early recognition and management of some of these dermatological manifestations may reduce the associated morbidity and vastly improve the cutaneous outcome in these patients.

Reference

1. Naldi L. The field and its boundaries. In: Williams H, Bigby M, Diepgen T,Herxheimer A, Rzany B (eds.) Evidence based Dermatology, I[st] ed: BMG Books, London. 2003; .pp. 3-4.
2. Amatya B, Agrawal S, Dhali T, Sharma S, Pandey SS. Pattern of skin and nail changes in chronic renal failure in Nepal: a hospital-based study. *J Dermatol* 2008; 35: 140-45.
3. Sweeney S, Cropley TC. Cutaneous changes in renal disorders. In: Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI (eds.) Fitzpatrick's Dermatology in General Medicine. 6th ed: Mc Graw Hill, New York. 2003.pp. 1622-24.
4. Hajheydari Z, Makhlough A. Cutaneous and mucosal manifestations in patients on maintenance hemodialysis: a study of 101 patients in Sari, Iran. *Iranian J Kidney Dis* 2008; 2: 86-90.
5. Udayakumar P, Balasubramanian S, Ramalingam KS, Lakshmi C, Srinivas CR, Mathew AC. Cutaneous manifestations in patients with chronic renal renal failure on hemodialysis. *Ind J Dermatol Venereol Leprol* 2006, 72(2): 119-25.
6. Falodun O, Ogunbiyi A, Salako B, George A. Skin changes in patients with CRF. *Saudi J Kidney Dis Transpl* 2011; 22: 268-72.
7. K/DOQI clinical practice guidelines for chronic kidney disease: evaluation, classification seand stratification. Kidney Disease Outcome Quality Initiative. *Am J Kidney Dis* 2002; 39(2 Suppl 2): S1-246.
8. Khan R, Quaiser S, Haque SF, Sachdeva S. Cutaneous manifestations in patients of chronic kidney disease. *Int J Cur Bio Med Sci* 2011; 1(13); 113-15.
9. Mirza R, Wahid Z, Talat H. Dermatological manifestations in chronic renal failure patients on haemodialysis. *JLUMHS* 2012; 11: 25-28.
10. Sanad EM, Sorour NE, Saudi WM, Elmasry AM. Prevalence of cutaneous manifestations in CRF patients on regular hemodialysis: a hospital based study. *Egyptian J Dermatol Venerol* 2014; 34: 27-35.
11. Sheikh M, Malik LM, Jahangir M. Cutaneous manifestations of chronic renal failure. *J Pak Assoc Dermatol* 2014; 24(2): 150-155.
12. Singh G, Verma AK, Singh SJ, *et al*. Cutaneous changes in chronic renal failure. *Ind J Dermatol Venereol Leprol* 1992; 58: 320-22.
13. Gilchrest BA, Rowe JW, Mihm MC Jr. Clinical and histological skin changes in chronic renal failure: evidence for a dialysis-resistant, transplant responsive microangiopathy. *Lancet* 1980; 2(8207): 1271-75.
14. Sultan MM, Mansour HM, Wahby IM, Houdery AS. Cutaneous manifestations in Egyptian patients with CRF on regular hemodialysis. *J Egypt Women Dermatol Soc* 2010; 7: 49-55.
15. Pico MR, Lugo-Somolinos A, Sanchez JL, Calderon R. Cutaneous alterations in patients with chronic renal failure. *Int J Dermatol* 1992; 31(12): 860-63.
16. Graham RM, Cox NH. Systemic disease and the skin. In: Burns DA, Breathnach SM, Cox N, Griffiths CE (eds.) Rook's textbook of dermatology, 7th ed: Wiley-Blackwell, Oxford. 2004.pp. 59-75.
17. Jamal A, Subramanian PT. Pruritis among end-stage renal failure patrients on hemodialysis. *Saudi J Kidney Dis Transpl* 2000; 11: 181-85.
18. Siddappa K, Nair BK, Ravinder K, Siddesh ER. Skin in systemic disease. In: Valia RG, Valia AR (eds) IADVL textbook and atlas of dermatology. 2nd ed: Bhalani publishing house, Mumbai. 2000 .pp. 938-84.
19. Abdelbaqi-Salhab, MShalhub S, Morgan MS. A current review of the cutaneous manifestations of renal disease. *J Cutan Pathol* 2003; 30: 527-38.
20. Tercedor J, Hernandez BL, Rodenar JM. Nail diseases in hemodialysis patients. *Br J Dermatol* 2001; 144: 445-46.
21. Dyachenko p, Monselise A, Shustak A, Ziv M, Rozenman D. Nail disorders in patients with chronic renal failure and undergoing haemodialyssi treatment: a case control study. *J Eur Acad Dermatol Venereol* 2007; 21: 340-44.
22. Tsukuhara K, Takama Y, Moriwaki S, *et al*. Dermal fluid translocation is an important determinant of the diurnal variation in human skin thickness. *Br J Dermatol* 2001; 145: 590-96.
23. Lundin AP, Fani K, Berlyne GM, Friedman EA. Dermal angiopathy in hemodialysis patients: the effect of time. *Kidney Int* 1995; 47(6): 1775-80.
24. Cawley EP, Hoch-Ligeti C, Bond GM. The eccrine sweat glands of patients in uremia. *Arch Dermatol* 1961; 84(6): 889-97.
25. Johansson O, Hilliges M, Stahle-Backdahl M. Intraepidermal neuron-specific enolase (NSE)-immunoreactive nerve fibres: evidence for sprouting in uremic patients on maintenance hemodialysis. *Neurosci Lett 1*989; 99(3): 281-86.