Research Article

# Mucocutaneous manifestations in a sample of Iraqi adults patients with end-stage renal disease on haemodialysis

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## ABSTRACT

**INTRODUCTION**: The effects of end-stage renal disease are complex and can lead to the dysfunction of multiple organs, including the skin. It has been found that 50-100% of patients with end-stage renal disease have at least one associated cutaneous change.

**OBJECTIVE**: To study the various cutaneous manifestations and their prevalence in patients on maintenance haemodialysis at Al-Yarmouk haemodialysis unit in Baghdad.

**METHODS**: At the Haemodialysis Unit in Al-Yarmouk Hospital in Baghdad, a hundred adults with ESRD on regular haemodialysis patients were recruited in this cross-sectional study. Detailed renal and dermatological history and clinical examination were done with relevant laboratory tests. All symptoms, signs, and dermatological conditions were searched for accurately. Then, an association between these manifestations and some demo-clinical parameters were examined.

**RESULTS**: The mean age of the study group was 51.1± 14.1 years. All study participants (100%) had at least one mucocutaneous manifestation. Diabetes mellitus was the most common cause of end-stage renal disease in our sample. Xerosis was the most common cutaneous change in all patients. Xerosis, pruritus and eczema correlated with age ($p < 0.05$), and hair fall correlated only with gender. Duration of dialysis for > 5 years was associated with hair fall, ecchymosis, and dermatological infections ($p < 0.05$). Xerosis associated with dialysis time of 9 per week comparing to12 hours per week ($p < 0.05$). Eczema was associated with high calcium-phosphate byproduct and lower dialysis adequacy (kt/v <1.2) ($p < 0.05$). The lower the adequacy, the more macroglossia and onycholysis.

**CONCLUSION**: The frequency of cutaneous manifestations is high in adult haemodialysis patients. Xerosis is the most common mucocutaneous manifestations in those patients. Primary renal disease and dialysis adequacy have the greatest influence on the frequency of dermatological symptoms and signs.

**Key words**: Skin, mucocutaneous, ESRD, Haemodialysis.

## INTRODUCTION

Chronic kidney disease (CKD) is a progressive loss of renal function over months or years through five stages.[1] In end-stage renal disease (ESRD), with the progressive decline of glomerular filtration rate, the kidney fails to maintain normal levels of waste products of protein metabolism such as urea and creatinine, in addition to the disturbance of sodium, calcium, and phosphate which are the major agents involved in the pathogenesis of skin changes in severe kidney disease.[2]

In CKD, skin manifestations can be observed from the onset of the disease to the terminal stage, in uraemia, and after renal transplantation. [3,4] It has been found that 50-100% of patients with ESRD have at least one associated cutaneous change. Development of skin and skin appendages changes in ESRD depends on climatic conditions of the region, race and socioeconomic conditions of the patients,

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the accuracy of the diagnosis, and the light of environment in which cutaneous examination have been done.[5]

Cutaneous changes reported in patients with ESRD include xerosis, pruritus, pigmentary changes, pallor, acquired perforating disorders, purpura and ecchymoses, cutaneous infections, uraemic frost, calcification and calciphylaxis, cancerous and precancerous lesions, nephrogenic fibrosing dermopathy (NFD), and others. While mucosal changes include xerostomia, angular cheilitis, and coated tongue, uraemic fetor. Nails are not spared with many lesions like Lindsay's nails, fungal nail infections, leukonychia, koilonychia, subungual hyperkeratosis, onycholysis, Mees' lines, Merck's lines, Beau's lines. In addition to diffuse hair loss of the scalp.[5,6]

In our nephrology unit, we do not have a registry to record mucocutaneous manifestations reported in patients with ESRD on regular haemodialysis (HD) probably because changes of skin and mucous membrane are relatively mild without a major impact on health comparing to the involvement of other systems in the body. So, this study is aimed to measure the frequency of mucocutaneous symptoms and signs in prevalent patients with end-stage renal disease on regular haemodialysis at Al-Shifaa Hemodialysis Unit, Al-Yarmook Teaching Hospital in Al-Karkh Health Directorate in Baghdad, and to find any association between them and factors like age, gender, cause of ESRD, and dialysis parameters like dialysis duration and adequacy measured by Kt/V.

## METHODS

**Study design and setting**: A hospital-based cross-sectional study conducted at Al-Shifaa Haemodialysis Unit, Al-Yarmook Teaching Hospital in Al-Karkh Health Directorate in Baghdad form 1st September 2015, to 31st January 2016. A hundred adult prevalent HD patients recruited.

**Ethical consideration**: The study was approved by the research committee, and verbal consent was taken from all participants after explaining the aims of the study.

**Case definition inclusion and exclusion criteria**: In this study, we included a patient who was diagnosed with ESRD and on regular haemodialysis for at least 3 months and registered in Al-Shifaa Haemodialysis Unit. All patients included were receiving HD through Gambro machines model AK96 and filter brand name polyflux (polyurethane material) of KoA (1026) and KUF (12.5), and a surface area of 1.7$m^2$. Patients who were known to have mucocutaneous diseases like psoriasis, dermatitis, or persistent skin infection or cutaneous symptoms before the development of ESRD and using haemodialysis were excluded from this study.

**Sampling**: the sample was selected consecutively during the time of the study.

**Data collection and procedure**: A detailed medical (renal) history has been obtained with special attention to the cause of ESRD, the duration of illness before proceeding to HD, the duration of haemodialysis, number of hour of dialysis per week and full drug history. This part of the study was conducted by an experienced nephrologist. The dermatological part of the study was conducted by two experienced dermatologists. The examination included a full and thorough check of the skin, hair, nail, and mucous membranes. On finding a lesion, a full history of its duration, its initial site of distribution, and symptoms if any was collected. In the dialysis unit, a monthly check of biochemical laboratory tests was recorded and we used these recorded data as needed to achieve the purpose of this study.

Dialysis adequacy expressed as urea reduction ratio (URR) and Kt/V. The latter (fractional urea removal rate) was identified as a dimensionless numeric construct, which could best model urea clearance. Here, **T** means time, **V** is the volume of distribution of a given molecule, urea, while **k** is the dialyzer urea clearance. The desired targets for URR and kt/v are 60% and 1.2 respectively which can be used to quantify the dose of dialysis and ensure that it is adequate. [7]

**Outcome**: The frequency of mucocutaneous

symptoms and signs in prevalent haemodialysis patients and to find an association between them and age, gender, causes of ESRD, and dialysis parameters like dialysis duration and adequacy.

**Statistical analysis**: Analysis of data was carried out using the available statistical package of SPSS-24, IBM Corp. Released 2016. IBM SPSS Statistics for Windows, Version 24.0. Armonk, NY: IBM Corp. Data were presented in simple measures of frequency, percentage, mean, standard deviation, and range (minimum-maximum values). The significance of the difference of different percentages (qualitative data) was tested using the Pearson Chi-square test ($X^2$-test) with the application of Yate's correction or Fisher Exact test whenever applicable. Statistical significance was considered whenever the P-value was equal to or less than 0.05.

## RESULTS

The number of patients enrolled in the study is 100, all of them has shown at least one dermatological manifestations. The mean age of them is 51.1±14.1 year with range of 19-80 years. Male patients were 62 (62 %), while females were 38 (38 %). Diabetes mellitus was the commonest cause of end-stage renal disease reported in 30 patients (30 %). For other baseline characteristics of the patients see table 1. Table 2 shows the basic laboratory data of the patients.

Pruritus is the commonest symptoms reported by 48 patients (48%), while xerosis is the commonest sign followed by skin scratch reported in 83 (83 %) and 48 (48%) respectively. Table 3 shows other mucocutaneous manifestations.

Out of all reported mucocutaneous manifestations reported in table 3, pruritus, scratches, xerosis and ecchymosis have shown a statistically significant association with age with p values 0.033, 0.033, 0.036, and 0.041 respectively see table 4. While only hair fall, ecchymosis, and dermatological infection have shown a statistically significant association with duration of haemodialysis with p-values 0.043, 0.014, and 0.006 respectively, table 5. Hair fall was reported in 8.21 % of female compared to 6.5 % of males, p-value 0.029. Table 6 shows that the only statistically significant mucocutaneous manifestations associated with adequa-

**Table 1** | The baseline characteristics of the study group.

| The characterestics | | No | % |
|---|---|---|---|
| **Age (years)** | < 40 | 22 | 22.0 |
| | 40---59 | 43 | 43.0 |
| | ≥ 60 | 35 | 35.0 |
| ***Mean age in years±SD (Range)*** | | 51.1±14.1 (19-80) | |
| **Gender** | Male | 62 | 62.0 |
| | Female | 38 | 38.0 |
| **Possible causes of ESRD** | Diabetes | 30 | 30.0 |
| | Hypertension | 19 | 19.0 |
| | Obstructive uropathy | 22 | 22.0 |
| | Glomerulonephritis | 2 | 2.0 |
| | Others* | 4 | 4.0 |
| | Unknown | 23 | 23.0 |
| **Duration (years)†** | <5 | 74 | 74.0 |
| | ≥5 | 26 | 26.0 |
| ***Mean duration±SD (Range)*** | | 3.7±2.2 (1-13) | |
| **HD time (hour/week)** | 9 | 25 | 25.0 |
| | 12 | 75 | 75.0 |

**ESRD**: end-stage renal disease, **RTA**: renal tubular acidosis, **HD**: haemodialysis. *: Polycystic, RTA, Analgesia nephropathy. † Duration of the disease before proceding to HD.

**Table 2** | Basic laboratory data of the study group.

| Laboratory Data | | No | % |
|---|---|---|---|
| **Virology** | ***HBV*** | 15 | 15.0 |
| | ***HCV*** | 31 | 31.0 |
| | ***Negative*** | 54 | 54.0 |
| **URR (%)** | ***Abnormal (<60%)*** | 17 | 17.0 |
| | ***Normal*** | 83 | 83.0 |
| **Kt/v** | ***Inadequate (<1.2)*** | 25 | 25.0 |
| | ***Adequate*** | 75 | 75.0 |
| **PCV (%)** | ***<30*** | 58 | 58.0 |
| | ***≥ 30*** | 42 | 42.0 |
| **Ca mg/dl** | ***Low < 8.5*** | 48 | 48.0 |
| | ***Normal (8.5-10.5)*** | 52 | 52.0 |
| **PO4 mg/dl** | ***Low < 4.5*** | 26 | 26.0 |
| | ***Normal (4.5-7.0)*** | 64 | 64.0 |
| | ***High > 7.0*** | 10 | 10.0 |
| **Byproduct (CaxPO4)** | ***Risk (>55)*** | 14 | 14.0 |
| | ***Not*** | 86 | 86.0 |

**URR**: urea reduction ratio, **PCV**: packed cell volume, **Ca**: calcium, **po4**: phosphate

**Table 3** | Mucocutaneous manifestations of the study group.

| | No | % |
|---|---|---|
| **Symptoms** | | |
| *Pruritus* | 48 | 48.0 |
| *Hair fall* | 12 | 12.0 |
| **Signs** | | |
| *Xerosis* | 83 | 83.0 |
| *Scratch* | 48 | 48.0 |
| *White nail* | 26 | 26.0 |
| *Hyperpigmentation* | 19 | 19.0 |
| *Koilonychia* | 19 | 19.0 |
| *Ecchymosis* | 13 | 13.0 |
| *Acne* | 3 | 12.0 |
| *Macroglossia* | 9 | 9.0 |
| *Onycholysis* | 4 | 5.0 |
| *uremic frost* | 2 | 5.0 |
| *Half Nail* | 5 | 5.0 |
| *aphthous ulcer* | 2 | 5.0 |
| *Furry Tongue* | 5 | 5.0 |
| **Diseases** | | |
| *Eczema* | 9 | 4.0 |
| *Dermatologic infections* | 12 | 3.0 |
| *Ictheiosis* | 2 | 2.0 |
| *Kyle's disease* | 5 | 2.0 |
| *Diabetic Dermatopathy* | 2 | 2.0 |
| *Subangual hyperkeratosis* | 5 | 2.0 |
| *Photosensitivity* | 1 | 1.0 |
| *Angular Stomatitis* | 1 | 1.0 |

cy of haemodialysis measured by Kt/V were onycholysis and macroglossia, p values 0.018 and 0.026 respectively.

The dialysis time in hours per week was significantly associated with xerosis; 16 patients out of 25 (64%) in those receiving > 9 hours per week comparing to 67 patients out of 75 ( 89.3%) for those receiving 12 hours per week, P-value 0.003.

High PO3*Ca product (target <55)was significantly associated with eczema; 2 out of 14 patients with the product more than 55 (13.3%), while 2 out of 86 patients (2.3%) with product less than 55 (P-value 0.034).

## DISCUSSION

This study reveals how prevalent mucocutaneous manifestations in ESRD patients on maintenance HD program. Xerosis and pruritus were the most common features. Dialysis adequacy was significantly associated with the prevalence of these manifestations.

The mean age of CKD patients in the present study 51.1±14.1 years. There was a significant correlation between age and the prevalence of pruritus, ecchymosis, and xerosis because with age there is more atrophy of the sweat gland. This was comparable to other studies like that by Mirza et al (50.58).[8]

Hypertension and diabetes mellitus are more in men with ESRD than in females. In the current study, there is male preponderance and this is consistent with many other studies as that by Kolla et al.[9]

The most common possible cause of ESRD in this study was diabetes mellitus (30%) which

**Table 4** | The distribution of the dermatologic manifestations and diseases in relation to age.

| Mucocutaneous manifestation | | Age (years) | | | | | | P-value |
|---|---|---|---|---|---|---|---|---|
| | | <40 | | 40---59 | | =>60 | | |
| | | No | % | No | % | No | % | |
| **Pruritus** | *Yes* | 8 | 36.4 | 17 | 39.5 | 23 | 65.7 | 0.033* |
| | *No* | 14 | 63.6 | 26 | 60.5 | 12 | 34.3 | |
| **Scratch** | *Yes* | 8 | 36.4 | 17 | 39.5 | 23 | 65.7 | 0.033* |
| | *No* | 14 | 63.6 | 26 | 60.5 | 12 | 34.3 | |
| **Xerosis** | *Yes* | 15 | 68.2 | 35 | 81.4 | 33 | 94.3 | 0.036* |
| | *No* | 7 | 31.8 | 8 | 18.6 | 2 | 5.7 | |
| **Ecchymosis** | *Yes* | - | - | 5 | 11.6 | 8 | 22.9 | 0.041* |
| | *No* | 22 | 100 | 38 | 88.4 | 27 | 77.1 | |

*Significant difference between proportions using Pearson Chi-square test at 0.05 level.

**Table 5** | The Significance of the dermatologic manifestations and diseases in relation to the duration (Y) of haemodialysis.

| Mucocutaneous manifestation | | Duration (years) | | | | P-value |
|---|---|---|---|---|---|---|
| | | <5 | | ≥5 | | |
| | | No | % | No | % | |
| Hair fall | *Yes* | 6 | 8.1 | 6 | 23.1 | 0.043* |
| | *No* | 68 | 91.9 | 20 | 76.9 | |
| Ecchymosis | *Yes* | 6 | 8.1 | 7 | 26.9 | 0.014* |
| | *No* | 68 | 91.9 | 19 | 73.1 | |
| Dermatological infection | *Yes* | 5 | 6.8 | 7 | 26.9 | 0.006* |
| | *No* | 69 | 93.2 | 19 | 73.1 | |

**Table 6** | The distribution of the dermatological manifestations and diseases in relation to the adequacy of haemodialysis Kt/V

| Mucocutaneous manifestation | | Kt/v | | | | P-value |
|---|---|---|---|---|---|---|
| | | Inadequate (<1.2) | | Adequate | | |
| | | No | % | No | % | |
| Onycholysis | *Yes* | 3 | 12.0 | 1 | 1.3 | 0.018* |
| | *No* | 22 | 88.0 | 74 | 98.7 | |
| Macroglossia | *Yes* | 5 | 20.0 | 4 | 5.3 | 0.026* |
| | *No* | 20 | 80.0 | 71 | 94.7 | |

*Significant difference between proportions using Pearson Chi-square test at 0.05 level.

is consistent with that of Thomas et al in 2012,[10] and Khanna et al in 2010.[11]

### Skin Manifestations

Xerosis is the most common finding in this study (83%) of the patients which is consistent with that of Udaykumar et al (79%),[6] and Singh G et al (90%).[12] This can be attributed to a reduction in the size of eccrine sweat glands, a decrease in the use of emollients by the treating nephrologist, and the use of high doses of diuretic in dialysis patients. There was a significant correlation between the dialysis times/week (9hrs versus 12hrs) and the prevalence of xerosis.

Pruritus with scratch is the second most common finding in this study (48%); a finding that was seen also by Thomas EA et al in 2012.[10] The possible reason for this variation may be a difference in individual tolerance and threshold for itch due to racial and ethical background. Haemodialysis has been the initiating factor of pruritus in some patients; in some, it improves pruritus. Many of the patients with pruritus have concomitant xerosis. In our study, 75% of patients with pruritus reported exacerbation during sleep. However, the majority of the patients with pruritus reported no change during rest in the daytime. Our findings were in agreement with the data of Zucker et al.[13] The probable cause of worsening of pruritus at night is at least in part is the physiologic changes with diurnal rhythm, which could be related to the expression of circadian rhythms of peptides and their receptors in neurons.

A positive correlation between xerosis and pruritus was suggested by Khanna et al[11] and reported 87% of their patients with pruritus had xerosis. Similarly, in this study 75% of patients with pruritus had xerosis.

Hyperpigmentation is the 3rd most common manifestation seen in 19% which is less compared to that of Khanna D et al (50.5%). [11] This difference might be due to difficulty in appreciating hyperpigmentation in dark-coloured individuals unless it is extensive.

As most of the patients in this study have prolonged sun exposure, which also makes it difficult to differentiate from occupational/photo melanosis and kidney disease induced. The diffuse brownish-black hyperpigmentation on sun-exposed areas can be attributed to the retention of chromogens and deposition

of melanin in the basal layer and superficial dermis due to the failure of the kidneys to excrete beta-Melanocyte Stimulating Hormone (β-MSH).[11,14]

Acquired perforating dermatoses (APD) are seen in 5% with more prevalence in diabetic patients.[10,11] This was consistent with data from Kolla PK et al (6.9%)[9] but with less frequency than that reported by Udaykumar et al(21%).[6]

Dermatological infections were seen in 12 % of patients in the present study which is consistent with that reported by Falodun O et al (16.6%). [15] Thomas EA et al[10] has shown that infection is seen in 26.26% which is more comparable to the present study. Among fungal infections, Pityriasis Versicolor was the most common in the present study as heat and humidity are more in this region. There was a significant correlation between the duration of dialysis and dermatological infection. This may be related to more access for infection and more disturbance in immunity that occur with a long history of CKD and prolong history of dialysis.[10]

There was a significant correlation between the duration of dialysis and ecchymosis. It may be related to the prolonged use of heparin or abnormality in the number and function of platelets and clotting factors.[16]

Eczema was significantly correlated with the Ca*PO4 byproduct. Many authors have suggested elevated calcium and phosphate levels as contributing factors for the development of pruritus in CRF patients. However, no correlation has been reported between pruritus and elevated calcium and elevated phosphorus level in our study. Khanna et al[11] and Amatya et al[17] and did not show any relation between pruritus and serum calcium and phosphate.

### Mucosal manifestations

Macroglossia was seen in (9%); the same as that reported by Thomas et al[9] (9.09%), but Sultan MM, et al [14] in their study reported the prevalence of macroglossia to be 42%. Despite the small prevalence in our study, there was a significant correlation between macroglossia and urea reduction ratio (URR) and Kt\V. This may be attributed to diabetes as part of an infiltrative process or due to deposition of beta 2 micro-globulins specifically in patients with inadequate dialysis; low URR or Kt\V. [16]

### Hair and nail manifestations

There was a significant correlation between hair fall and gender and the duration of dialysis. Hormonal effects play a role. In this study, hair changes were more compared to those reported by Falodun et al 15 (12% vs. 2.5%). Sparse body hair and diffuse alopecia with lusterless hair have been attributed to decreased secretion of sebum.[13]

There was a significant correlation between the Kt\V and the prevalence of onycholysis. The nail changes in this group (59%) were comparable to other studies like that by Deshmukh et al (60%).[18] In our study, Leukonychia has reported in 26%, and it may be related to the high prevalence of pallor in chronic kidney disease patients. Half and half nails reported in 5% of patients and this might be related to deposition of melanin in the nail plate due to stimulation of matrix melanocyte, increase in capillaries and thickening of their walls. The proximal half of the nail appears white because of oedema.[19]

## CONCLUSION

The frequency of cutaneous manifestations is high in adult haemodialysis patients and xerosis is the most common. Primary renal disease and dialysis adequacy have the greatest influence on the frequency of dermatological symptoms and signs.

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**Abbreviations list**: Beta-Melanocyte Stimulating Hormone (**β-MSH**), Calcium phosphate (**Ca*PO4**),Chronic kidney disease (**CKD**), End-stage renal disease (**ESRD**), Fibrosing dermopathy (**NFD**), Haemodialysis (**HD**), Statistical package of social sciences (**SPSS**), Urea reduction ratio (**URR**).

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