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ORIGINAL ARTICLE

Nail disorder among patients on maintenance hemodialysis

Malihe Charkhchian [1], Akram Beheshti [2], Amir-Abdollah Zangivand [3,*], Afsaneh Sedighi [3]

[1] Department of Nephrology, Qazvin University of Medical Sciences, Qazvin, Iran
[2] Department of Dermatology, Qazvin University of Medical Sciences, Qazvin, Iran
[3] School of Medicine, Clinical Research Develop Unit, Qazvin University of Medical Sciences, Qazvin, Iran

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ABSTRACT

Background/Objective: Chronic renal failure can lead to nail disorders. The aim of this study was to investigate nail disorders and laboratory data in patients on constant hemodialysis (HD) in a hospital in Qazvin, Iran.

Methods: A case-controlled study was performed. End stage renal disease patients ($n = 149$) undergoing regular HD and 147 randomly selected individuals were examined for nail disorder. All participants were examined by two trained students and a single dermatologist. Specific investigations such as nail biopsy, potassium hydroxide mount, and fungal culture were done if necessary. Laboratory data were completed for HD patients. Demographic characteristics, the causes of end stage renal disease, and laboratory data were tested in a multivariate analysis.

Results: In this study, 62 HD patients had at least one nail disorder, with leukonychia being the most common in both groups. Clinical onychomycosis, absent lunula and half and half nail were the other common findings in HD patients. Positive mycological culture was noted in four HD patients and in none of the control individuals. The mean duration of HD was a significant predictor associated with the positive clinical onychomycosis ($p < 0.05$). Although there was no significant correlation between nail disorders and hypertension or heart failure, multiple logistic regression analysis indicated that gender, age $\geq$ 65 years, and diabetes mellitus (DM) were associated with nail disorder.

Conclusion: The prevalence of nail disorder in this study was correlated with age, DM, and gender. To decrease the prevalence of nail disorder, attention to duration of HD, age, male sex, and DM is very important.

Introduction

Chronic renal failure (CRF) can lead to skin and nail disorders. Changes in skin color, xerosis, pruritis, metastatic calcinosis, bullous dermatosis, and perforating disorders have been seen in patients with CRF.[1] These abnormalities may develop before or after initiation of hemodialysis (HD).[2] Many of these uremic related dermatologic abnormalities improve after kidney transplantation.[1] The prevalence of nail disorders may be as high as 71.4 %. [3] Various studies have reported skin and nail disorders in patients with chronic renal disease undergoing dialysis; however, few of these were controlled studies conducted to compare the prevalence of these disorders in patients undergoing dialysis and in healthy individuals in the general population.[1,4–6] The nail disorders most commonly found in patients with CRF are: half and half nails (HHN),[1,5,7] absent lunula (AL),[1,5] and splinter hemorrhages.[1,5,8] In HHN, the proximal half is white, while the distal portion is red to brown.[9] AL is a condition characterized by absence of the visible portion of the nail matrix, while splinter hemorrhages appear as dark red, filiform, longitudinal lines in the distal region of the nail plate and may also be associated with antiphospholipid antibody syndrome, bacterial endocarditis, trichinosis, onychomatricoma, and external trauma.[9] The pathogenesis of nail involvement in patients with renal failure is poorly defined.[4] The aim of our study was to investigate nail disorders and laboratory data in patients on constant HD in hemodialysis centers of a hospital in Qazvin, Iran and compare them with a paired sample of individuals selected at random from the general population.

Methods

A case-controlled study was performed. There were 149 end-stage renal disease (ESRD) patients undergoing chronic HD for at least

* Corresponding author. School of Medicine, Clinical Research Develop Unit, Boo Ali-Sina Hospital, Qazvin University of Medical Sciences, Qazvin, Iran. Tel.: +98 9362768827; fax: +98 2812222974.
E-mail address: zangivand@gmail.com (A.-A. Zangivand).

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3 months and 147 individuals who were randomly selected from the friends and relatives accompanying patients at the hospital who were examined for nail disorders in Boo-Ali-Sina Hospital in Qazvin. Exclusion criteria included: history of renal transplant, active malignancy, collagen vascular diseases, active infection, cirrhosis, immunosuppressive medication, human immune deficiency virus infection, and alcohol abuse. A questionnaire that included age, sex, underlying cause of ESRD, coexistence diseases, duration of HD, medication, dialysis quality (Kt/V), and laboratory data, including hemoglobin, leukocyte count, calcium, phosphorous, albumin, creatinine, blood urea nitrogen (BUN), alkaline phosphatase (ALP), alanine aminotransferase, aspartate aminotransfrase, iron, ferritin, total iron binding capacity, and parathyroid hormone (PTH), was completed for each HD patient. Blood samples were drawn from the patients and controls under fasting conditions and immediately before the dialysis session in patients. All patients and the control group were examined by two trained students and a single meticulous dermatologist. Specific investigations such as nail biopsy, culture and sensitivity for potassium hydroxide (KOH) mount, and fungal culture were done if necessary.

After a thorough examination of the fingers and toenails, nail scrapings were obtained from 38 HD patients and 11 control individuals who expressed suspicious nail changes. If onychomycosis (OM) was suspected, microscopic examination of the nail scrapings was performed with the use of 20% KOH solution. (The KOH test was performed on all 38 HD patients and 11 controls.) Samples were cultured on Sabouraud dextrose agar (Sigma Chemical Co., St Louis, MO, USA). Cultures were incubated at 26°C and examined twice a week for a total duration of 4 weeks. If a mould was isolated, it was regarded as pathogenic when direct microscope examination was positive and culture, repeated three times at 7 day intervals, led to isolation of a pure culture of the mould positive in a number of inoculations. The criteria for the diagnosis of OM were the same as all moulds isolated in the study period. Dermatophytes and moulds were identified on the basis of macro- and microscopic characters of colonies according to the criteria of Rebell and Taplin for dermatophytes and De Hoog et al for moulds.[10] Phosphorus, creatinine, and BUN were determined with a standard autoanalyzer. Ionized calcium was determined using a calcium-specific electrode. Total ALP was determined using a commercial enzyme linked immunoassay kit (ELISA; normal range 40–190 IU/L). PTH was determined using an immunofluorimetric assay that detects the intact PTH molecule (normal range 10–70 pg/mL).[11] A colorimetric method was used to determine serum albumin. The quality of HD was assessed during the study period by calculating Kt/V using the Daugirdas formula, as described in the Dialysis Outcomes Quality Initiative guidelines.[12]

The collected data were analyzed using SPSS software (version 11.0; SPSS Inc, Chicago, IL, USA). The Fisher's exact Chi-square test and the Student *t* test were used to assess statistical relationships between variables. Demographic characteristics, medical data, and laboratory test data were subjected to a multivariate analysis. Continuous data are presented as mean ± standard deviation. A p-value <0.05 was considered significant.

The study was approved by the ethics committee of the university before its initiation, and the protocols used conformed to the ethical guidelines of the 1975 Helsinki Declaration. All patients were informed about the study protocol and the written consent was obtained from all participants.

Results

Of 149 HD patients, 96 (64.4%) were male. Mean age was 55.9 ± 16.1 years (range 13–91 years) and the mean dialysis duration was 40.85 ± 42.64 months (range 3–228 months). In the control group, 88 (59.8%) were male and mean age was 55.7 ± 17.9 years (range 8–75 years). The causes of ESRD in the patient cohort are shown in Figure 1.

Overall, 62 HD patients and 36 control individuals had at least one nail disorder. There were 96 nail lesions identified in HD patients and 38 in the control group, as some of the patients had more than one nail disorder. The prevalence rates of the different types of nail disorders are shown in (Table 1).

Of the 62 HD patients (all HD cases had nail disorders), 47 were male, 24 were age ≥ 65 years, 31 were positive for diabetes mellitus (DM), 28 were positive for hypertension, and 11 were positive for heart failure. The presence of nail disorders in HD patients was shown to be statistically related to sex, DM, and age (Table 2).

Leukonychia was the most common nail change in both patients and controls. Other common findings in HD patients were clinical OM, AL, and HHN followed by splinter hemorrhage, onycholysis, pitting, culture positive OM, thin nail, undiagnosable lesion, subungual hyperkeratosis, koilonychia, cyanosis, pincer nail, melanonychia, and clubbing. In the control group, after leukonychia, AL and onycolysis were the most common nail disorders. Furthermore, the prevalence of clinical diagnosis of OM was established in 11 HD patients and two controls according to the presence of both positive clinical signs (such as discoloration of nails, changes in nail thickness) and positive KOH test. Positive mycological culture was noted in four HD patients in case group and in none of patients in control group (Table 3). None of the patients had a positive familial history or history of nail trauma, tight and high heeled or traumatic shoes, and excessive sweating of foot during activity. The clinical and biochemical characteristics of the HD patients are shown in Table 4. The results of our study showed that the mean duration of HD in patients with positive clinical OM was more than that in those without ($p < 0.05$). Apart from serum ALP, alanine aminotransferase, aspartate aminotransfrase, and total iron binding capacity ($p < 0.05$), the other clinical and biochemical parameters had no statistically significant differences in either group.

Discussion

CRF is a known cause for several nail pathologies. Nail abnormalities have been reported in 60% to 76% of patients undergoing HD.[4,6]

In a case-control study, Saray et al reported at least one type of nail pathology in 69.8% of HD patients and 39.2% of a control group.

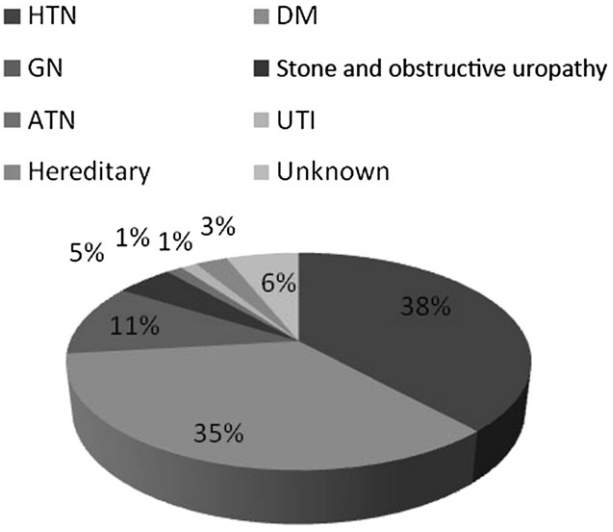

Figure 1 The causes of ESRD in the patients of the present study. ATN = acute tubular necrosis; DM = diabetes mellitus; GN = glomerulonephritis; HTN = hypertension; UTI = urinary tract infections.

Table 1 The prevalence rates of nail lesions in hemodialysis and control.

Nail disorder	Control ($n = 147$)	Case ($n = 149$)	p
Leukonychia	10 (6.8%)	23 (15.4%)	0.017*
Absent lunula	6 (4%)	11 (7.3%)	0.220
Clinical onycomycosis	2 (1.3%)	11 (7.3%)	0.020*
Half and half	2 (1.3%)	10 (6.7%)	0.035*
Splinter hemorrhage	3 (2%)	8 (5.3%)	0.218
Onycholysis	5 (3.4%)	7 (4.7%)	0.571
Pitting	3 (2%)	5 (3.3%)	0.723
Culture (+) onycomycosis	0	4 (2.7%)	0.122
Thin nail	3 (2%)	3 (2%)	1.000
Undiagnosable lesion	2 (1.3%)	3 (2%)	1.000
Subungual hyperkeratosis	1 (0.6%)	3 (2%)	0.622
Koilonychia	0	2 (1.3%)	0.498
Cyanosis	1 (0.6%)	2 (1.3%)	1.000
Pincer nail	0	2 (1.3%)	0.498
Melanonychia	0	1 (0.7%)	1.000
Clubbing	0	1 (0.7%)	1.000
Total	38 (25.8%)	96 (64.4%)	0.000*

Clinical onycomycosis: if there was the presence of both positive clinical signs (such as discoloration of nails, changes in nail thickness) and positive KOH test. Negative clinical onycomycosis: if either positive clinical signs (such as discoloration of nails, changes in nail thickness) or positive KOH test were not present.
*A p-value <0.05 was considered significant.

In this study AL, OM, and splinter hemorrhage were the most common disorders. The overall prevalence of nail pathology in this study was not correlated with age, sex, and HD duration, although they showed a possible relationship between HD duration and OM ($p = 0.05$).[1]

In another study Dyachenko et al reported nail disorder in 11.6% of controls, 60.3% of CRF and 62.3% of HD patients. The most common disorders in controls, in CRF patients, and in patients on HD were: OM; AL, OM, and HHN; and HHN, AL, and OM, respectively. Male gender, age above 65 years, DM, hypertension, heart failure, and PTH above 220 μEq/mL were the most important risk factors in this study but duration of HD was not important.[4]

Salam et al reported at least one nail disorder in 76% of HD patients and 30% of controls. In this study HHN was the most common finding followed by AL, onycholysis, brittle nail, beau's nail, clubbing, longitudinal ridging, OM, and other disorders. They did not find significant correlation between nail pathology and duration of HD.[6]

In the study by Maha et al on 100 patients undergoing regular HD, koilonychia, HHN, and splinter hemorrhages were the three common diseases[13] (Table 5 summarizes the results of our study and the other studies).

We found 62 HD patients (41.6%) and 36 controls (24.5%) with nail disorders. Leukonychia (15.4%), AL (7.3%), clinical OM (7.3%), HHN (6.7%), splinter hemorrhage (5.3%) and onycholysis (4.7%) were the most common findings in HD patients, while leukonychia (6.8%) and AL (4%) were the most common in the control group.

Although there was no significant correlation between nail disorders and hypertension [odds ratio (OR) = 1.735, 95% confidence interval (CI) 0.886–3.400] and heart failure (OR = 1.125, 95% CI 0.473–2.676), multiple logistic regression analysis indicated that male sex (OR = 2.430, 95% CI 1.184–4.988), DM (OR = 3.143, 95% CI 1.562–6.324) and age ≥ 65 years (OR = 1.331, 95% CI 0.674–2.629)

Table 2 Multivariate logistic regression analysis for overall nail disorders.

Factors	OR (95% CI)	p
Male	2.430 (1.184-4.988)	0.010
DM	3.143 (1.562-6.324)	0.001
HTN	1.735 (0.886-3.400)	0.108
Age ≥ 65 y	1.331 (0.674-2.692)	0.041
HF	1.125 (0.473-2.676)	0.792

DM = diabetes mellitusis; HF = heart failure; HTN = hypertension.

Table 3 The frequency of isolated fungi toenail scraping cultures in case group.

Isolated fungus	n (%) of culture(+)
Trichophyton rubrum D	2 (1.4%)
Trichophyton mentagrophytes D	1 (0.7%)
Epidermophyton D	1 (0.7%)

D = dermatophyte.

were associated with nail disorders. These results clearly indicate a relationship between nail disorders and DM and gender in HD patients.

Leukonychia or white nail is the most common form of color change, where the nail appears opaque and white, probably owing to the diffraction of light in the abnormal keratotic cells; with polarized light, the nail structure appears disrupted owing to disorganization of the keratin fibrils.[14] This condition may be present under clinical circumstances such as renal failure, pneumonia or heart disease or induced by the use of cytotoxic drugs or poisoning with arsenic. Some considerations to keep in mind regarding leukonychia are that its presence is not a sign of a lack of vitamin or calcium in the diet, it is harmless and may be caused simply from a minor injury that occurs when the nail is growing, and that it is much more common on fingernails than toenails. This disorder was found to have high prevalence in our study both in patients and controls, although the difference in prevalence between the two groups was not significant ($p = 0.446$).

Clinical OM was the second most common disorder in HD patients in our study. The prevalence of OM in general population is about 2% to 11%[15–18] and in HD patients it rises to 6.2% to 52%.[5,8] This higher frequency of OM may stem from impaired cellular immunity in these patients.[19]

The risk factors that have been associated with OM are older age, swimming, tinea pedis, psoriasis, DM, immunodeficiency, and living with family members who have OM.[15,20,21] OM is an infection of the nail apparatus with fungi including dermatophytes, non-dermatophyte moulds, and yeasts (mainly *Candida* spp.). The toenails are affected in 80% of all cases with OM; dermatophyte infection, mostly due to *Trichophyton rubrum*, is the cause in over 90% of cases.[10] OM may eventually progress to total nail dystrophy in which the nail plate is almost completely destroyed. Treatment should not be instituted on clinical grounds alone. Although 50% of all cases of nail dystrophy are fungal in origin it is not always possible to identify such cases accurately.[22]

Table 4 The frequency of isolated fungi toenail scraping cultures in case group.

Parameters	Positive clinical onycomycosis ($n = 11$)	Negative clinical onycomycosis ($n = 138$)	p
Age (y)	59.7 ± 16.6 (29–81)	55.6 ± 16.1 (13–91)	0.446
Sex	Male = 81.8%	Male = 63%	_
Duration (mo)	69.5 ± 40 (8–120)	38.6 ± 42.2 (3–228)	0.032*
Weekly Kt/V	2.5 ± 0.96 (1.2–4.2)	2.5 ± 0.91 (1.2–7.02)	1.000
Hb (g/dL)	10 ± 1.5 (7.6–12)	10.7 ± 1.8 (6.3–16)	0.168
AST (IU)	13 ± 4 (10–23)	19 ± 13 (8–86)	0.001*
ALT (IU)	14 ± 5 (10–26)	18 ± 12 (5–99)	0.040*
TIBC (μg/dL)	243 ± 30 (200–300)	289 ± 135 (122–1120)	0.003*
Fe (μg/dL)	127 ± 223 (30–800)	114 ± 158 (20–829)	0.853
Ca (mg/dL)	8.5 ± 1.1 (7–10.4)	8.5 ± 0.7 (6–10)	1.000
P (mg/dL)	6.6 ± 1.8 (4.4–10)	6.9 ± 2 (2–13)	0.608
Ferritin (μg/L)	438 ± 420 (117–1600)	293 ± 267 (17–2000)	0.286
ALP (IU/L)	663 ± 385 (208–1300)	398 ± 268 (56–2000)	0.049*
PTH (pg/mL)	761 ± 998 (24–2900)	458 ± 516 (26–3100)	0.343
Albumin (g/dL)	4.1 ± 0.3 (3.6–4.6)	4.2 ± 0.6 (2–6)	0.349

ALP = alkaline phosphatase; ALT = alanine aminotransferase; AST = aspartate aminotransferase; Duration = duration of hemodialysis; Hb = hemoglobin; Kt/V = quality of dialysis; PTH = parathyroid hormone; TIBC = total iron binding capacity.
*A p-value <0.05 was considered significant.

Table 5 Comparison of common nail disorders in our study and other studies.

Disorders	Our study	Saray et al[1]	Dyachenko et al[4]	Maha et al[13]	Salem et al[6]
	Iran	Turkey	Israel	Egypt	Egypt
Leukonychia	15.4%	10.4%	7.8%	unknown	2%
Absent lunula	7.3%	31.9%	13%	unknown	17%
Culture (+) onycomycosis	2.7%	19.2%	10.4%	unknown	4%
Half and half	6.7%	7.7%	16.9%	28%	20%
Splinter hemorrhage	5.3%	13.7%	3.9%	16%	2%
Onycholysis	4.7%	1.1%	7.8%	3%	7%
Koilonychia	3.3%	2.7%	unknown	39%	3%

In the study by Kuvandik et al[23] on 109 HD patients: 81% of diabetic and 57.7% of non-diabetic HD patients had dystrophic nail changes; 26.6% of all patients showed OM according to both positive clinical sign and positive KOH test; toenail scraping cultures were positive in 19.7% of patients with dystrophic nail changes; and DM and duration of HD increased the prevalence of OM (OR 4.0232 and 1.2499).

In our study, clinical OM was diagnosed in 11 HD patients (7.3%). Although only four of them had a positive culture, *Trichophyton rubrum* was the most frequently isolated organism from the cultures, followed by *Trichophyton mentagrophytes* and *Epidermophyton*. In concordance with previous studies we found that three culture positive patients were diabetic[24,25]; however, the prevalence of culture positive OM in our study was low in comparison with other published studies.[4,23] Mean duration of HD in patients with positive clinical OM was higher than the same mean in negative clinical OM ($p < 0.05$). This result is in agreement with the Kuvandik et al study.[23]

HHN was the fourth most common disorder in HD patients in our study. This disorder, first reported by Bean in 1963,[26] is the white appearance of proximal half of the nail, due to nail bed edema associated with dilated capillaries despite the fact that the other half of the nail bed appears normal.[27] The etiology of this disorder remains unknown.[7,28] In some publications, HHN had been reported as representing the most common nail disorder in CRF patients on HD.[7,29] This disorder were the fourth common disorder in HD patients in the present study (6.7%), with a significant difference in prevalence compared with the control group ($p = 0.035$).

In our study, AL was the second most common finding in both case and control groups. This result can be explained by the varied etiology of this disorder such as anemia or malnutrition.

Our study suggests that nail disorders were most common in HD patients. Numerous factors influence the prevalence rate of these conditions and their diagnosis. The difference between our findings and the other similar studies on some specific nail manifestations in patients on HD may be due to education, genetics, occupation, and chance, in association with different physical and chemical agents in the studied population.

In conclusion the prevalence of nail disorders is increased among HD patients. In our study male sex, age $\geq$ 65 years, and DM were important risk factors for nail disorders, and dialysis duration and presence of DM were risk factors for OM. Leukonychia, OM, AL, and HHN were the most common lesions. Periodic dermatologic examination of nail in patients with ESRD is necessary. In addition, to decrease the prevalence of OM and other nail disorders attention to duration of HD, male sex, age $\geq$ 65 years, and DM is very important.

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