

## Frequency of Onychomycoses in Chronic Renal Failure Patients Undergoing Hemodialysis in Porto Alegre, Brazil

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Received: August 19, 2011

Accepted: February 15, 2013

**SUMMARY** – Onychomycosis is one of the most frequent infections affecting the fingernails or the toenails and it is caused mainly by dermatophytes. The aim of the study was to assess the frequency of onychomycoses in hemodialysis patients and to relate sex, age, duration of hemodialysis and causes of renal failure to the development of nail disorders. The study included 100 patients with chronic renal failure undergoing hemodialysis. The patients underwent detailed clinical examination of the toenails and those with any kind of clinical finding had nail scraping for mycological testing. In the study population, the frequency of onychomycosis was 39%. The most commonly isolated fungi were dermatophytes (69.23%), *Candida* spp. (15.38%) and nondermatophyte molds (15.38%). *T. interdigitale* was the most prevalent fungus followed by *Candida* ssp. and *T. rubrum*. The risk of onychomycosis increases by 1.9% for each additional year in age and diabetic patients are 88% more likely to develop onychomycosis than nondiabetic ones. The duration of hemodialysis treatment and sex were not associated with the development of onychomycosis. In conclusion, in hemodialysis patients, the frequency of onychomycosis was higher in those at advanced age and with diabetes.

**KEY WORDS:** dermatophytes, onychomycosis, renal failure, hemodialysis, diabetes mellitus

### INTRODUCTION

Onychomycosis is one of the most frequent infections affecting the fingernails or the toenails, accounting for 18-40% of all nail disorders and for 30% of all skin fungal infections (1). It is caused mainly by dermatophytes belonging to the following three genera: *Trichophyton*, *Microsporum* and *Epidermophyton*. Of these, the most common species that affect

nails are *Trichophyton* (*T.*) *rubrum*, *T. mentagrophytes* and *T. interdigitale*, followed by nondermatophyte molds and *Candida* spp., which account for 7% of infections (2-4). According to recent molecular studies, the anthropophilic subspecies of *T. mentagrophytes* are now grouped within the so called designated *T. interdigitale* complex (5). Individual risk factors for

onychomycosis include age, immunosuppression, diabetes mellitus, family history, peripheral vascular disease, and skin disorders such as hyperhidrosis, psoriasis, onychogryphosis and nail trauma (6,7).

In the general population, the prevalence of nail infection ranges between 2% and 11% and in diabetic patients, the prevalence of onychomycosis ranges from 1.2% to 26% (8,9). In these patients, fungal infection associated with neuropathy characterized by loss of sensitivity, and with angiopathy and poor perfusion in lower extremities may heighten the risk of diabetic foot syndrome. Functional loss of lower limbs impairs the quality of life and causes high health expenditures (8,11). Patients with chronic renal failure undergoing hemodialysis have several skin and nail disorders, the most frequent of which include nail lifting (koilonychia), absence of lunula, hemorrhage and onychomycoses, their prevalence ranging from 6.2% to 52% (12,13). Susceptibility to nail disorders in these patients occurs owing to histologic findings and lower immunity caused by uremia (2,3,12).

The aim of the present study was to assess the frequency of onychomycoses in hemodialysis patients and to relate sex, age, duration of hemodialysis treatment, and causes of renal failure to the development of nail disorders.

## METHODS

One hundred and eleven patients with chronic renal failure (CRF) undergoing hemodialysis at the Nephrology Outpatient Clinic of Hospital Santa Casa de Porto Alegre, southern Brazil, were initially selected. Of these, 100 patients were eventually included in the study. Ten patients refused to participate and one was excluded because of immunosuppressant use. Those patients with onychomycosis treated with topical or systemic antifungal and antimicrobial or cytostatic agents or those diagnosed with human immunodeficiency virus infection were excluded from the study.

All participating patients underwent hemodialysis treatment three times a week for 4 hours/day. The patients included in the study underwent detailed clinical examination of the toenails and nail scrapings were obtained for mycological testing from those with any kind of clinical finding. The mycological tests included direct microscopic examination (DME) and culture. Microscopic examination of nail scrapings was performed with the use of 20% potassium hydroxide solution. Samples were cultured in two test tubes, one with Sabouraud dextrose agar (HiMedia Laboratories) and one with cycloheximide (Merck) and chloramphenicol (Sigma). Cultures were incubated at 25 °C and fungal growth was assessed once

a week for up to five weeks. The identification of dermatophytes was based on their macroscopic examination of fungal colonies, microscopic examination of microculture and assessment of urease production. The following findings were considered to be positive: positive DME and positive culture; negative DME and positive culture, and positive DME and negative culture.

The procedures and methods employed are adapted to the current ethical standards of the committee responsible for experiments on human beings in *Complexo Hospitalar Santa Casa de Porto Alegre* and Helsinki Declaration.

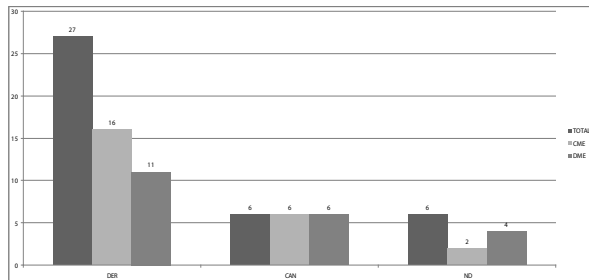
The SPSS for Windows version 17.0 was used for statistical analysis. A  $p$  value  $<0.05$  was considered statistically significant. Categorical variables were compared by the  $\chi^2$ -test. Student's  $t$  test and Mann-Whitney test were used to relate age and duration of hemodialysis treatment, respectively, with onychomycosis. Poisson regression with robust variances was used to calculate the prevalence ratios of the investigated factors associated with onychomycosis (11). Variables with  $p < 0.10$  in the bivariate analyses were considered for multiple Poisson regression.

## RESULTS

Among study patients, 59% were male, mean age was  $52.98 \pm 17$  years and mean duration of hemodialysis treatment was 4.29 years. Of these patients, 19.09% were diagnosed with diabetes mellitus (DM), 50.90% with hypertension, 6.36% with polycystic kidneys, 2.73% with glomerulopathy caused by immunoglobulin A (IgA), 2.73% with nephrosclerosis, 0.91% with kidney stones, 6.36% with recurrent infection, whereas 10.91% had an unknown etiology.

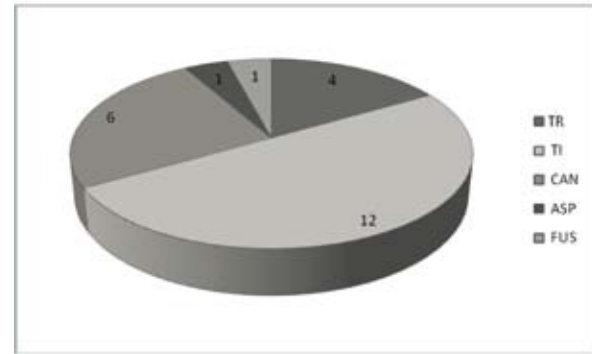
Dystrophic nail changes were observed in 71 patients. The major clinical manifestations were onycholysis (42%), distal hyperkeratosis (35%) and leukonychia (4%). Forty-one percent of the disorders affected the left lower limb and 32% were found in the right lower limb.

Among the 100 study patients, the diagnosis of onychomycosis was confirmed in 39 patients out of 71 who exhibited dystrophic nail changes according to the presence of DME and/or positive culture. Of these, 27 (69.23%) were caused by dermatophytes, 6 (15.38%) by *Candida* spp. and 6 (15.38%) by non-dermatophyte molds (Fig. 1). *T. interdigitale* was the most prevalent fungus ( $n=12$ ), followed by *Candida* spp. ( $n=6$ ) and *T. rubrum* ( $n=4$ ). Among non-dermatophyte molds, there was growth of *Aspergillus* spp. in one culture and of *Fusarium* spp. in another one (Fig. 2). In all negative DME there was no fungal growth



**Figure 1.** Positive direct mycological examination (DME) and cultural mycological examination (CME) diagnostic of onychomycosis.

DER = dermatophytes; CAN = *Candida* spp.; ND = nondermatophytes; TOTAL = positive mycological examination: positive DME and positive culture; negative DME and positive culture, and positive DME and negative culture.



**Figure 2.** Frequency of isolation of fungi from cultural mycological examination (CME).

TR = *Trichophyton rubrum*; TI = *Trichophyton interdigitale* complex; CAN = *Candida* spp.; ASP = *Aspergillus* spp.; FUS = *Fusarium* spp.; the frequency of each fungus in the CME positive cultures is given inside the pie chart.

(Table 1). Among the patients diagnosed with onychomycosis, 12 (30.77%) had diabetes mellitus and dermatophytes were the principal agent involved in the infection.

Adjusted analysis indicated the prevalence ratio (PR) for age to be 1.019 with 95% confidence interval of 1.00-1.03, whereas in diabetic patients it was 1.88% (95% CI: 1.21-2.92). Thus, the risk of onychomycosis increases by 1.9% for each additional year in age and diabetic patients are 88% more likely to develop onychomycosis than nondiabetic ones. Bivariate analysis showed that male sex was a significant factor for onychomycosis ( $p < 0.042$ ); however, multiple analysis did not confirm this finding (PR: 1.74, 95% CI: 0.98-3.08). Statistical analyses were not significant for female sex. In this study, the duration of hemodialysis treatment was not associated with the development of fungal infection.

**Table 1.** Results of direct mycological examination (DME) and cultural mycological examination (CME)

CME DME	TR	TI	CAN	ASP	FUS	NEG	Total
DER	4	12	-	-	-	11	27
ND	-	-	-	1	1	4	6
CAN	-	-	6	-	-	-	6
NEG	-	-	-	-	-	32	32
Total	4	12	6	1	1	47	71

DER = dermatophytes; ND = nondermatophytes; CAN = *Candida* spp.; NEG = negative; TR = *Trichophyton rubrum*; TI = *Trichophyton interdigitale* complex; ASP = *Aspergillus* spp.; FUS = *Fusarium* spp.

## DISCUSSION

Fungal infections are most frequent worldwide, affecting individuals in all age groups and impairing the quality of life of affected patients, while also increasing economic burden due to the cost of treatment. Few studies report the prevalence of onychomycosis in hemodialysis patients. According to literature data, the major nail disorders that affect these patients are nail lifting, absence of lunula and onychomycosis (12-14). Kuvandik *et al.* (8) demonstrated that 26.6% of 109 hemodialysis patients were diagnosed with onychomycosis and that 68.9% of these patients were diabetic. The same study showed the presence of diabetes and duration of hemodialysis to be significant predictors associated with the development of onychomycosis. A study conducted in Israel in 2007 compared CRF patients and hemodialysis patients and found male sex, advanced age, diabetes mellitus, hypertension and heart failure to be associated with nail disorders; however, the association with the duration of hemodialysis was not significant (15). In our study, the frequency of onychomycosis was 39% of all included patients; 54.92% of patients with dystrophic nail changes were diagnosed with onychomycosis and 30.76% of these patients were diabetic. The duration of hemodialysis as well as hypertension, polycystic kidneys, glomerulopathy caused by immunoglobulin A (IgA), nephrosclerosis, kidney stones, recurrent infection and unknown etiology were not associated with the development of fungal infection, but factors such as having diabetes and advanced age were significant for its development.

Several studies indicate that the development of onychomycosis in diabetic patients without renal disorders is also related to advanced age and male sex. In a multicenter study, Gupta *et al.* (16) showed advanced age and male sex to be associated with infection in diabetic patients, while male patients had a 2.99 higher likelihood to have onychomycosis than women. A study performed in DM1, DM2 and nondiabetic patients in Germany in 2007 showed a significant correlation of male sex and advanced age with fungal infection (17). In our study, although male sex was a significant factor in bivariate analysis, adjusted analysis did not associate it with the development of onychomycosis. This was probably due to the fact that in our sample, male patients were mostly older, so that age turned out to be a significant variable. Several studies report that onychomycosis is an age-related infection. In addition to poorer peripheral circulation and lower immunity, elderly patients are more frequently exposed to fungi over years and then have higher chances of transmission and infection (1).

According to the findings presented in this work, DME detected a higher number of positive cases compared to fungal culture. In 11 of 27 fungal nail infections caused by dermatophytes, the fungus was identified only by DME, while the cultures were negative. Consistent with these results, other studies also demonstrated that in case of infection by dermatophytes DME detects more cases of onychomycosis than culture. The authors believe that these findings might be explained by difficulty of cultivating dermatophytes in laboratory (18,19).

The main causative agent of onychomycosis was a dermatophyte, followed by *Candida* spp. and nondermatophyte molds. Among nondermatophyte molds, there was growth of *Aspergillus* spp. and *Fusarium* spp. in our study. This finding is consistent with the world literature, which describes dermatophytes as the main causative agents, whereas *Candida* spp. and nondermatophyte molds alternately occupy the third and fourth positions (1,3,7,20-23).

Among dermatophytes, *T. interdigitale* was most prevalent, followed by *T. rubrum*, corroborating the study performed in Lebanon in 2005, which included 772 patients with clinical suspicion of onychomycosis over a period of 5 years. The authors believed that the increase in antifungal resistance over years could have been the cause of this prevalence (24). Although we agree with this conclusion, in our group of patients impaired immunity could be the main explanation for the high fungal prevalence.

Hemodialysis patients are more susceptible to infections due to impaired cellular immunity, charac-

terized by lymphopenia and reduced B cell and T cell subpopulation activity (13). Moreover, in hemodialysis patients with diabetes, disorders such as angiopathy, vascular stasis with consequent tissue hypoxia and neuropathy with poorer sensitivity increase the probability of trauma and erosion. Chronic erosion usually develops into ulcer, cellulitis, and even amputation of the affected limb.

In this study, the frequency of onychomycosis was higher in CRF patients undergoing hemodialysis, and diabetes mellitus and age were found to be independent risk factors associated with the development of onychomycosis in these patients. Given that onychomycosis predisposes to more severe infections such as erysipelas, cellulitis and amputations, hemodialysis patients must be instructed in the care and hygiene of their toenails. In addition, education of hemodialysis patients about the importance of foot and nail care should be an essential component in their management.

### Acknowledgments

The authors are grateful to CAPES (Coordenação de Aperfeiçoamento de Pessoal de Nível Superior) and CNPq (Conselho Nacional de Desenvolvimento Científico e Tecnológico) for their financial support.

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