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RESEARCH ARTICLE

Prevalence of mixed dermatophyte and non-dermatophyte onychomycosis in surveillance of patients with diabetes living in a sub-tropical climate and association with selected diabetes foot ulcer risk factors

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Background: Onychomycosis (OM) is the infection of a fingernail or toenail by one or more of three types of pathogens: dermatophytic fungi, yeasts and non-dermatophytic moulds. Whereas previously dermatophytes were regarded as the primary causative agent, mixed infections of both dermatophyte onychomycosis (DOM) and non-dermatophyte onychomycosis (NDOM) have been reported with higher incidence in warm climates. Very few studies in Africa have tracked OM prevalence in populations living with diabetes.
Objectives: This study aimed to determine the prevalence of mixed OM and whether there was any association between mixed OM and four variables, namely, gender, pre-clinical peripheral arterial disease (prePAD), peripheral neuropathy (PN), and hallux dysfunction.
Method: A retrospective chart review was conducted on annual foot assessment records for 231 male and female adult diabetes patients in Umhlanga, KwaZulu-Natal.
Results: Prevalence of mixed OM was 54.5% and was associated with being male ($p = 0.028$). Patients presenting hallux dysfunction were less likely to have mixed OM (44% versus 61%). There was a strong association between prePAD and PN ($p < 0.001$) as those with prePAD were more likely to have PN (62.5% vs 30.8%). There was no association between mixed OM and the four variables captured in this small study.
Conclusion: A high prevalence of mixed OM exists in the diabetes population in this study. Mixed OM is less likely in hallux dysfunction and no association was found between mixed OM and the other variables. Pre-clinical PAD shows a strong association with PN.

Keywords: climate change, dermatophyte, diabetes foot ulcer, Doppler pedal pulses, hallux dysfunction, non-dermatophyte, onychomycosis, peripheral neuropathy, short first metatarsal, sub-tropical

Introduction

Onychomycosis (OM) is the infection of a fingernail or toenail by one or more of three types of pathogens: dermatophytic fungi, yeasts, and non-dermatophytic moulds. It can be understood to mean infection of the nail plate or matrix by any keratinophytic organisms that produce keratolytic proteases to digest nail keratin.[1] Whereas in the past dermatophytes were regarded as the primary causative agent, mixed infections of both dermatophyte onychomycosis (DOM) and non-dermatophyte onychomycosis (NDOM) are increasingly being identified.[2,3] While the CONSONANCE project (Consensus on Onychomycosis Assessment in Non-specialised Clinical Environments) found a wide variation in prevalence in Europe (from < 1% to 28%), a global scoping review revealed how few studies have been conducted in Africa.[4,5]

In patients living with diabetes, onychomycosis presents an ominous red flag, because studies prior to and after the Seattle Diabetic Foot Study in 2006 have shown onychomycosis to be a predictor of foot ulceration.[6–8] This is most important to understand in terms of patient foot ulcer risk prediction. Infiltration into and under the nail-plate layers by the keratinolytic elements leads to discolouration, thickening, desquamation, and separation from the nail bed.[9] Dermatophytes then trigger the release of cytokines and chemokines that contribute to the inflammatory response. By breaking down the protective keratin, transcription factors and signalling pathways that promote virulence are enabled. Spores are able ultimately to infect both nail and skin and can lead to invasive and deep infections via the nail sulcus, nail bed, and fissuring of interdigital spaces.[10] Fibrils anchor fungal cells within the membranes of the host keratinocytes. The weakening of the keratin nail plate by dermatophytes further increases the risk of invasion by environmental moulds.[4] Secondary bacterial infections are common once the integrity of outer protection is compromised, which lead the way to peri-ungual blistering, abscess formation and ulceration. Degradation of the nail plate can lead to "buckling" deformation in nail plate shape, implicated in ingrowing nails (onychocryptosis). Nail in-growth has been shown to be a strong predictor of foot ulceration risk.[11] In turn, foot ulceration in diabetes is a known complication that can ultimately lead to lower limb amputation.[12]

In one study on onychomycosis, Brazil was found to have more mixed infections than either Canada or Israel.[2] The study did not explore why this might be so but climate and climatic temperatures have previously been linked to the distribution of pathogens.[13] As the KwaZulu-Natal coastline in South Africa is sub-tropical in climate, not unlike that of sub-tropical parts of Brazil, this study sought to investigate whether any similarities could be found in local data.

At the same time and given that diabetes is a multi-faceted disease, other potential associations were considered. In a 2023 systematic review, although it did not find a direct association per se between onychomycosis and ulceration, a significant association ($p = 0.012$) was found between the occurrence of onychomycosis and diabetic neuropathy, itself a known risk factor for ulceration.[8] The presence of peripheral neuropathy in diabetes, apart from the associated impact on the vascular system, is implicated in localised trauma to the foot from loss of protective sensation (LOPS), giving rise to lesions that precede foot ulceration.

Poor foot haemodynamics are associated with hallux dysfunction, as well as abnormal or reduced pedal pulse Doppler waveforms.[14–16] The study thus investigated whether any statistical associations with these parameters might exist in the local data.

Aim

The study aims were twofold. First, to investigate foot surveillance data from clinical records to determine the prevalence of mixed dermatophyte and non-dermatophyte onychomycosis (as opposed to only dermatophytes). Second, to explore whether there was any association between mixed dermatophyte and non-dermatophyte onychomycosis with gender, hallux dysfunction, pre-PAD, and PN in a cohort of patients attending a multidisciplinary diabetes centre in Umhlanga, KwaZulu-Natal in South Africa.

Methodology

Study setting and population

The diabetes and endocrine centre in Umhlanga, situated on the sub-tropical coast north of Durban in KwaZulu-Natal, South Africa, draws patients from surrounding suburbs and small towns within a radius of 60 km. The majority (> 80%) of patients attending the diabetes centre are South Africans of Asian Indian heritage.

Ethical considerations

This study was approved by the Biomedical Research Ethics Committee at the University of KwaZulu-Natal Research Ethics office (Ref: BREC/00006101/2023). Privacy and confidentiality of the participants' clinical data were maintained.

Research approach and design

A quantitative approach and retrospective chart review was conducted on 231 podiatric clinical foot assessment records of male and female adult patients living with diabetes, for the period June 2020 to June 2021, to capture the following data:

- gender (male, female);
- hallux dysfunction (present, absent);
- mixed onychomycosis (present, absent);
- pre-clinical peripheral arterial disease (present, absent);
- peripheral neuropathy (present, absent).

The selected data parameters were chosen from within the four categories of clinical examinations that form a podiatric foot assessment of a person living with diabetes, namely musculoskeletal, dermatological, vascular and neurological.

Hallux dysfunction

Clinically presents as a decrease in range of motion and joint mobility such that dorsiflexion of the hallux at the first metatarsophalangeal joint is less than 40 degrees. These instances include hallux limitus, hallux rigidus, hallux valgus, and brachymetatarsia of the first metatarsal. Insufficient dorsiflexion of the hallux fails to engage the plantar fascia windlass mechanism, and this impacts negatively on the pumping action within the foot (venous foot return) and thereby on foot haemodynamics.[14,15]

Mixed onychomycosis

Clinical presentations are toenail plates that are thickened in comparison with fingernails (subungual hyperkeratosis caused by infiltration of fibrils into lamellae of the nail plate), changes in nail-plate colour such as yellow, white, black, grey, purple, and brown (visually different colour from nails and nailbeds on the hands), onycholysis (lifting of the nail plate), crumbling subungual debris, with or without longitudinal or transverse grooves, nail distortion, brittle nails, or cracks in the nails.[17] Further clinical classification of onychomycosis may be by presentation and route of invasion, as per Table 1.

Pre-clinical peripheral arterial disease

Clinical presentation is seen in the absence of normal triphasic pedal pulse waveforms on Doppler ultrasound (Huntley DMX doppler®). Pedal pulse biphasic or monophasic Doppler waveforms in this study were considered to be indications of early damage to the peripheral vascular system, independent of classical PAD signs and symptoms, hence the classification in this study of pre-clinical PAD.

Peripheral neuropathy

Clinical presentation is loss of protective sensation (LOPS) of any one or more of the following: light touch indicated by the 10 g Semmes–Weinstein monofilament test, proprioception,

Table 1: Clinical descriptions of fungal and mould toenail infection[4,18]

Distal and lateral subungual OM (DLSO)	Most common form Commences by invasion at distal or lateral edge of the nail, and underside of the nail at the hyponychium Results in thickening and detachment of the nail plate from the nail bed Can be Trichophyton rubrum, Epidermophyton floccosum
Proximal subungual OM (PSO)	Occurs when organisms invade the proximal nail fold/cuticle area, penetrate new nail and migrate distally Common agent is *T rubrum* Common in immune-compromised patients
White superficial OM (WSO)	Occurs when pathogens invade the top layer of the nail plate directly Recognised by white "islands" t spread as disease progresses. Nail becomes rough, soft, and crumbles easily. Can lead to thick, brittle nails. White "stains" are typical of *fusarium sp.*
Candida nail infections	May first appear as oedematous, erythematous paronychia Penetrates the nail plate only after it has attacked the soft tissue around the nail Can present with transverse lines (Beau's lines), pseudo-clubbing

Table 2: Frequency of all variables

Factor		Count	%
Gender	Female	105	45.5%
	Male	126	54.5%
Hallux-DYSF	No	140	60.6%
	Yes	91	39.4%
Mixed mycosis	No	105	45.5%
	Yes	126	54.5%
Pre-PAD	No	39	16.9%
	Yes	192	83.1%
PN	No	99	42.9%
	Yes	132	57.1%

vibration (128 Hz tuning fork), temperature differentiation (TipTherm® instrument), sharp/blunt differentiation (Neuropen® instrument), absent patellar reflex, absent ankle reflex.[19]

Data analysis

The Statistical Package for the Social Sciences (version 27; ®IBM Corp, Armonk, NY, USA) was used to analyse the data. Frequencies were assessed and are presented in Table 2. Chi-square tests were used to assess associations between the variables at a two-sided significance level of 0.05.

Results

Table 3 shows a similar distribution between male and female patients. Male patients represented 54.5% while females represented 45.5% of participants in the study. Almost 40% of patients in the study presented with hallux dysfunction. Clinical signs of mixed mycosis were present in 54.5% of patients, while prePAD was recorded in 83% of patients, and PN in 57% of patients.

In Table 3, it can be seen that mixed mycoses were associated with being male ($p = 0.028$) while no other associations with gender were found.

In Table 4 it can be seen that there was an association between mixed mycoses and hallux dysfunction ($p = 0.009$). There was no association between hallux dysfunction and either prePAD or PN.

Similarly, when examining any possible relationship between mixed OM, pre-PAD, and PN, no association was found, as shown in Table 5.

In Table 6, the results showed a strong association between prePAD and PN ($p < 0.001$). Those patients with prePAD were more likely to have PN (62.5% vs 30.8%).

Discussion

The most important result of this small study is the revelation of a high prevalence of mixed dermatophyte and non-dermatophyte nail infection (54.5%) in the studied patient population. This is in stark contrast to onychomycosis prevalence of between 1% and 28% in the CONSONANCE European project.[4]

In this study, mixed mycoses were associated with being male ($p = 0.028$), which echoes the suggestion of the Nail Society of India that male patients with diabetes are 2.5–2.8 times more likely to develop OM.[20]

The study found an association between mixed mycoses and hallux dysfunction ($p = 0.009$) in that those who had hallux

Table 3: Association between gender and all variables

		Gender				
		Female		Male		
Factor		Count	Column, *n* %	Count	Column, *n* %	p-*value*
Hallux-DYSF	No	59	56.2%	81	64.3%	0.210
	Yes	46	43.8%	45	35.7%	
Mixed Mycosis	No	56	53.3%	49	38.9%	0.028
	Yes	49	46.7%	77	61.1%	
Pre-PAD	No	13	12.4%	26	20.6%	0.095
	Yes	92	87.6%	100	79.4%	
PN	No	50	47.6%	49	38.9%	0.182
	Yes	55	52.4%	77	61.1%	

Table 4: Association between hallux dysfunction and other variables

		Hallux-DYSF				
		No		Yes		
Factor		Count	Column, *n* %	Count	Column, *n* %	p-*value*
Mixed mycosis	No	54	38.6%	51	56.0%	0.009
	Yes	86	61.4%	40	44.0%	
Pre-PAD	No	26	18.6%	13	14.3%	0.396
	Yes	114	81.4%	78	85.7%	
PN	No	55	39.3%	44	48.4%	0.174
	Yes	85	60.7%	47	51.6%	

Table 5: Association between mixed mycosis and the variables

		Mixed mycosis				
		No		Yes		
Item		**Count**	**Column, *n* %**	**Count**	**Column, *n* %**	p-*value*
Pre-PAD	No	20	19.0%	19	15.1%	0.423
	Yes	85	81.0%	107	84.9%	
PN	No	51	48.6%	48	38.1%	0.109
	Yes	54	51.4%	78	61.9%	

Table 6: Association between prePAD and PN.

		Pre-PAD				
		No		Yes		
Item		**Count**	**Column, *n* %**	**Count**	**Column, *n* %**	***p*-value**
PN	No	27	69.2%	72	37.5%	< 0.001
	Yes	12	30.8%	120	62.5%	

dysfunction were less likely to have mixed mycosis (44% vs 61%). In hallux dysfunction, there is insufficient dorsiflexion of the hallux, a movement that in normal gait would usually result in the distal toenail touching the upper lining of the shoe. As footwear is a common reservoir of contagion by fungal spores and infected nail debris, hallux dysfunction could ostensibly result in diminished contagion via this vector.[21]

In exploring the consideration that a diminished venous foot pump mechanism (due to dysfunctional hallux dorsiflexion) might be associated with reduced blood flow that, in turn, could also impact neural function, the current study showed no association between hallux dysfunction and either prePAD or PN.

Onychomycosis in diabetes is relentlessly progressive, represents a decline from full health, and thus places the foot at risk of complications.[22] A common complication is onychocryptosis (ingrown nail) as the nail structure is weakened, becomes deformed, and may grow into the side sulcus tissue, which can lead to secondary infection. In a study in Tanzania, nail ingrowth was found to be a strong indicator of diabetic foot ulceration risk. However, no detail was provided as to the aetiology of such nail-plate distortion.[11]

The organisms that cause OM are often the same that in turn infect the skin, causing tinea pedis (and vice versa). Further, fungal nail infection can be uncomfortable, painful, and interfere with walking and necessary exercise, as well as the fit of footwear.[23] Untreated patients can contaminate family and communal areas.

A further potential complication is that of the development of onychogryphosis, in which the nail plate layers grossly thicken in response to fungal activity within the layers (Figure 1).

In some instances, the gross nail overgrowth can cause dorsal pressure onto the nail bed due to the reduced space at the toe box of footwear, increasing the risk of subungual abscess and ulcer formation. Invasion of deeper layers of dermis and hypodermis that can cause deep infection in diabetic and immunocompromised patients have been reported.[24]

It is noted with concern that global warming is seen to be a factor in increasing prevalence of fungal infections.[10] In addition, there are now reports of increasing antifungal resistance in dermatophytes, with combination therapy being suggested.[25,26]

Figure 1: DLSO mixed onychomycosis with onychogryphotic nail-plate thickening.

Clinician reticence to treat clinical onychomycosis may stem from prior instances of adverse effects from oral agents, long dosing required by some antifungal agents, perceived poor results, and cost. In South Africa, the cost of pathology testing and treatment is a grudge expense, borne by patients either from medical insurance savings or out of pocket or not readily available at state primary care facilities.[17]

The need to sanitise footwear and the use of prophylactic topical antifungal agents should be part of any treatment protocol, prevention of recurrence, and reinfection.[21,27–29] Whereas a detailed discourse on the many oral and device-based treatments available is not within the ambit of this study, it may be noted that in the clinic in this study, a three-pronged combination topical treatment approach has shown

Figure 2: Nail-plate reduction with ceramic burr and vacuum extraction.

Figure 3: Pre nail reduction.

success. A weekly application of amorolfine 5% is combined with daily 0.0005% aqueous solution spray of fungistatic detergent used on footwear, hosiery, and toenails daily (Medipod Fungisolve® 5 ml dissolved in 1 000 ml water), together with strict bi-monthly podiatric nail plate thickness reduction, dermabrasion, and cleansing of the diseased nail plate to expose the active infection site without damage to the nail bed (Figures 2, 3 and 4).

Nail plate reduction allows for continued adequate penetration of the topical medication. For patients with severe OM, a more aggressive approach includes the combination of both topical and systemic therapy with terbinafine as well as the fungistatic detergent and regular bi-monthly nail reduction. Environmental treatment with the fungistatic detergent is integral to treatment

Figure 4: Post nail reduction.

because environmental factors in households of affected members such as sharing footwear and walking barefoot on carpets or floors have been shown to increase transmission risk up to 44–47%.[30] One can imagine that infected toenails could contaminate prayer mats used in a kneeling position, such that decontamination of such mats would also need to be undertaken.

Conclusion

A high prevalence of fungal nail infection (54.5%) was found in the diabetes population in this study. The current study found an association between OM and being male. Our results showed no association between PN and mixed onychomycosis, in contrast to the findings in the systematic review by Navarro-Perez et al.[8] Mixed OM was shown to be less likely in hallux dysfunction while pre-clinical PAD shows a strong association with PN.

Complications of infection by both dermatophytes and non-dermatophytes of both skin and nails include invasive and deep infections of the nail sulcus, nail bed, and interdigital spaces; secondary bacterial infections; reduced self-image, reduced ability to self-care, reduced immune response; cellulitis; abscess and ulcer formation; osteomyelitis; tissue necrosis and amputation, with emotional, socioeconomic and psychological consequences.

This study highlights the need to evaluate all forms of onychomycosis in the diabetic population as well as to include surveillance and treatment as part of the standard of diabetes care to prevent the known complications.

Limitations

A shortcoming of the current exploratory study is that data were not collected regarding age of the patients, duration of diabetes, exposure to soil via formal or informal agriculture and/

or gardening, obesity, triglyceride levels, renal function, activity levels, and HBA1c, which might have enabled an extended comparison with other studies.[2,5,31] In addition, it was not possible due to cost considerations to implement OM and NDM diagnostic testing instead of the clinical diagnosis used. Future studies are needed that include the aforementioned variables, such as exposure to agriculture, physical activity, footwear type, and footwear flexion in addition to age, duration of diabetes, previous attempts at self-treatment (which may contribute to resistance), and all diabetes markers such as HbA1c, lipids, and renal function, should provide further insights and enable comparisons with other populations.

These aspects will be addressed in future studies, as findings that determine the burden of fungal infections are necessary to determine treatment approaches and influence medical care policy regarding this important aspect of diabetic foot care.

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