

# Can the use of a topical antifungal nail lacquer reduce risk for diabetic foot ulceration? Results from a randomised controlled pilot study

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## ABSTRACT

The purpose of this study was to determine whether the routine use of a topical antifungal nail lacquer (AFL) could reduce the risk for ulceration by theoretically increasing the frequency of patient self-inspection. In this randomised controlled trial, 70 persons at high risk for diabetic foot ulceration were enrolled into a preventative care program involving daily self-inspection with the possible use of an AFL (ciclopirox 8%) versus self-inspection instructions alone (NAFL). Patients were followed for 12 months or until ulceration. Using an intent to treat analysis, there was no significant difference in proportion of persons ulcerating in the AFL versus the NAFL groups (5.9% versus 5.6%  $P = 0.9$ ). There was also no difference in the number of unexpected visits ( $P = 0.2$ ) or missed appointments ( $P = 0.7$ ) between treatment arms. Interestingly, while there was no difference in proportion of patients with clinically diagnosed hyperkeratosis or tinea pedis on entry into the study ( $P = 0.2$ ), a significantly lower proportion of AFL patients had a clinical diagnosis on study termination (52.9% versus 77.8%  $P = 0.03$ , OR = 1.7, 95% confidence interval = 1.1–2.7). The results of this study suggest that there may be no immediate prophylactic benefit through the use of AFL to prevent wounds. The incidental finding of a potential reduction in hyperkeratosis and tinea pedis is a compelling one and may deserve further investigation.

**Key words:** Ulcer • Onychomycosis • Diabetes • Amputation

## Key Points

- diabetic foot ulceration is one of the most common reasons for hospitalization
- most common mechanism for ulceration involves pre-existing neuropathy, deformity, stress and subsequent inflammation

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## INTRODUCTION

The infected diabetic foot ulcer is one of the most common reasons for hospitalisation and amputation among persons with diabetes, worldwide (1–7). The most common mechanism for the development of ulceration involves pre-existing neuropathy, deformity, repetitive stress, subsequent inflammation and tissue breakdown (8–10). Providing a simple self-care modality may empower patients to examine their feet and a more regular, consistent basis and potentially modify their behaviour and activity so as to reduce

the extraordinarily high incidence of lower extremity ulceration and potential subsequent amputation in this high-risk population through increased self-efficacy.

Furthermore, to this very high incidence of complications, onychomycosis is very common in persons with diabetes. With a conservative estimated prevalence of 30% in this population, it is logical to postulate that onychomycosis can act as a reservoir for more proximal fungal and even bacterial superinfections – particularly in persons who may be immunocompromised and might therefore be a risk factor for deleterious complications (11–13). Systemic and topical therapies for onychomycosis have been present and actively utilised by specialists for more than a generation in the developing world. While systemic treatments may show efficacy in this population, topical therapies offer a potentially unexplored additional benefit. Perhaps the act of application of a topical agent in a high-risk population might increase the chances for daily self-examination of the foot, thereby reducing complications. We are unaware of any randomised controlled trials which have evaluated this technique for its potential utility. Therefore, the purpose of this study was to determine whether the routine use of a topical antifungal nail lacquer (AFL) could reduce the risk for ulceration by increasing the frequency of patient self-inspection.

## METHODS

In this randomised controlled trial, 70 persons at high risk for diabetic foot ulceration were enrolled into a preventative care program involving daily self-inspection with the possible use of an AFL (ciclopirox 8%) versus self-inspection instructions alone (NAFL). The screening process involved review of the patient's past medical history to confirm the diagnosis of diabetes and a lower extremity physical examination. A staff podiatrist examined each patient to identify lower extremity complications and risk factors, such as history of lower extremity pathology (previous foot ulceration and amputation), peripheral sensory neuropathy, peripheral vascular disease, foot deformities and abnormal foot pressures using previously published methods (7,14). Peripheral neuropathy was evaluated using a 10-g Semmes-Weinstein monofilament

(Touch-Test Sensory Evaluator, North Coast Medical Inc., Morgan Hill, CA, USA), and Vibration Perception Threshold testing (VPT Tester, Salix Medical, San Antonio, TX, USA) was performed using the methods previously described by Armstrong and Lavery (15). Neuropathy with loss of protective sensation was based on either a vibration perception threshold level of  $>25$  V or the inability to accurately detect the Semmes-Weinstein monofilament. Lower extremity vascular disease was defined as a non palpable foot pulse (dorsalis pedis or posterior tibial arterial pulse) and ankle brachial index of  $<0.80$  in either foot. We used the International Diabetic Foot Classification system to facilitate risk group assignment (16). Persons enrolled in this study fit into foot risk category 2 (neuropathy/deformity) or category 3 (history of ulceration or amputation). Subjects were excluded if they were unable to ambulate without the assistance of a wheelchair or crutches, if they were sight impaired to the extent that they were legally blind and if they were unable or unwilling to give consent to participate in this project.

Patients were randomised through a computerised randomisation schedule. Randomisation was performed after the initial screening. Patients were followed every 3 months for 12 months or until ulceration in a multidisciplinary high-risk diabetic foot clinic. Patients were also given the contact information for a 'foot hotline'. This phone was staffed 24 h a day by a clinician familiar with the care and status of these patients. Furthermore, this clinician had the charge and ability to rapidly appoint patients into pre-assigned emergency visit slots in each daily clinic schedule.

We evaluated the influence of continuous variables' effect between groups generally using a Mann-Whitney *U*-test. Dichotomous variables were evaluated with a chi-squared test with odds ratio and 95% confidence interval (CI).

## RESULTS

Descriptive characteristics for the study population are illustrated in Table 1. Using an intent to treat analysis, there was no difference in proportion of persons ulcerating in the AFL versus the NAFL groups (5.9% versus 5.6%  $P = 0.9$ ). There was also no difference in the

### Key Points

- there is a high incidence of amputation with this high risk population
- onychomycosis is common in persons with diabetes and can act as a reservoir for bacterial super infections
- randomised controlled trial in 70 persons at high risk of diabetic foot ulceration testing an anti-fungal lacquer against a non anti-fungal lacquer
- peripheral neuropathy was evaluated by monofilament
- International Diabetic Foot Classification used to facilitate risk group assignment
- patients randomised by computer

**Key Points**

- daily foot self inspection is part of an important proactive approach in the prevention of foot ulcers with diabetes mellitus
- patient education is important but needs to be frequent
- studies of educational intervention and self assessment programs have not shown wide spread success, however

**Table 1** Population descriptive characteristics

Group	<i>n</i>	Age (year)	Gender (% male)	Duration of DM (year)	Risk category 3 (%)	VPT (volts)	Ulcerated at 12 months (%)	One or more unexpected visits (%)	One or more missed visits (%)	Tinea/HK at study entry (%)	Tinea/HK at end of study (%)
Total	70	69.9 ± 11.5	97.1	11.9 ± 8.6	57.1	40.0 ± 20.7	5.7	24.3	28.6	85.7	65.7
AFL	34	69.5 ± 13.6	100	12.8 ± 9.0	55.9	37.0 ± 17.4	5.9	17.6	30.6	91.2	52.9*
NAFL	36	70.3 ± 9.3	94.4	11.2 ± 8.2	58.3	43.4 ± 23.4	5.6	30.6	26.5	80.6	77.8

AFL, antifungal lacquer group; DM, diabetes mellitus; HK, hyperkeratosis; NAFL, no antifungal lacquer (control); Risk category 3, International Diabetic Foot Risk Category 3; VPT, vibration perception threshold. Data are mean ± SD. \**P* < 0.05.

number of unexpected visits ( $P = 0.2$ ) or missed appointments ( $P = 0.7$ ) between treatment arms. Interestingly, while there was no difference in proportion of patients with clinically diagnosed hyperkeratosis or tinea pedis on entry into the study ( $P = 0.2$ ), a significantly lower proportion of AFL patients had a clinical diagnosis on study termination (52.9% versus 77.8%  $P = 0.03$ , OR = 1.7, 95% CI = 1.1–2.7).

**DISCUSSION**

Patients' daily foot self-inspection is part of an important proactive approach in the prevention of foot ulcers with diabetes mellitus (17–20). Patient education is considered most effective when it is encouraged throughout a diabetic patient's medical care and becomes incorporated into lifestyle habits (21). However, previous studies, limited by potential confounding and conflicting results, suggest that patient education may have positive but short-lived effects on foot care knowledge (22) and that strategies are needed to improve the delivery of preventive foot care services to older persons with diabetes (23). Providing a simple self-care modality may empower patients to more frequently examine their feet and potentially modify their behaviour and activity so as to reduce the extraordinarily high incidence of lower extremity ulceration and potential subsequent amputation in this high-risk population through increased self-efficacy.

While the idea that enhancing self-efficacy through education or self-evaluation appears to be an inherently beneficial enterprise, there are remarkably few data to support effectiveness of these strategies. Studies of educational interventions and self-assessment programs have not shown widespread success in this population. This is because of several factors. In a large randomised trial of educational and behavioural intervention to prevent lower extremity morbidity, Litzelman and co-workers (24) reported approximately 60% fewer complications in the group receiving the intervention. However, this same group also received frequent telephone calls and postcard reminders ensuring that they were complying with their regime, making it difficult for the clinician to tease out the effective intervention (or combination of interventions). Birke and Rolfsen (25) reported that

self-administration of a sensory test had a 73% concordance with the actual clinician-administered test. Interpretation of this study (26) subsequently inferred that widespread dissemination of simple monofilaments could potentially lessen lower extremity morbidity. However, no direct evidence in the study or in subsequent trials has suggested this to be the case. It appears as though the desire for a validation of what is inherently common sense may have led the clinical community to see data where none presently exists in a robust form. Currently, much of the robust randomised data existing in the literature suggesting that self-inspection and subsequent intervention may be beneficial in reducing long-term morbidity lies in two trials (one published and one currently in abstract form) using so-called personal dermal thermometers designed to identify inflammation and prompt the patient to contact their caregiver (27,28).

In the present randomised trial comparing the proportion of ulceration in persons dispensed an AFL (ciclopirox 8%) with instructions to inspect their foot daily versus self inspection instructions alone, the results suggested that there may be no immediate prophylactic benefit. It may be entirely possible that use of this lacquer may have some potential benefit and that this potential utility may have been obscured due to type I error in this study. While our initial power analysis suggested that we could detect a respectable difference between groups using a commonly cited prevalence of recurrent complications of 50–60% (29), the overall 1-year incidence of ulceration in both the treatment arms (under 6%) was extraordinarily low. One could suggest that this result was a consequence of the 43% prevalence of foot risk category 2 patients (those with neuropathy and deformity but without a previous history of ulceration) equally distributed between groups. However, the lowest identified yearly incidence of persons in this risk stratum is approximately 7%. When combined with the 57% prevalence of category 3 patients, the expected rate of ulceration/reulceration would be much higher than what was encountered. Therefore, it may be surmised that the overall low incidence may have been a positive unintended consequence of the

close care and follow-up afforded to these patients through the course of study.

Interestingly, a significantly lower proportion of AFL patients had clinical signs and symptoms of hyperkeratosis and tinea pedis on termination of the study, while there was no difference in proportion of patients with clinically diagnosed hyperkeratosis or tinea pedis on entry into the study. Perhaps the AFL's reduction of onychomycotic reservoir may ultimately reduce the risk for deleterious complications including more proximal fungal and even bacterial superinfections, particularly in persons who may be immunocompromised. However, as this was a secondary analysis in this study, shortcomings include that microscopy and fungal culture were not performed to confirm the clinical diagnosis of onychomycosis and tinea pedis during the course of the study.

In conclusion, the results of this study do not support the contention that daily lacquer application may reduce risk for ulceration by theoretically increasing the rate of consistent self-monitoring. The secondary finding of a potential reduction in hyperkeratosis and tinea pedis of the foot itself solely through consistent use of an AFL is a compelling one and may deserve further investigation.

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#### Key Points

- self administered sensory tests had a 73% concordance with those clinically administered
- personal dermal thermometers designed to identify inflammation have been used by patients to determine when to contact their caregivers
- better close care of patients may have increased benefit of AFL
- the AFL's reduction of onychomycotic reservoir may ultimately reduce the risk for deleterious complications
- in conclusion the results of this study do not support the use of daily lacquer, increasing the rate of consistent self monitoring

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