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# Prevalence and epidemiology of toenail onychomycosis in diabetic subjects: a multicentre survey

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**Summary** The number of individuals diagnosed with diabetes mellitus is increasing. The diabetic may present with complications involving all systems of the body. While onychomycosis is often observed in diabetics, there have been no large studies on the prevalence of the condition in this patient group. We examined the prevalence of onychomycosis in diabetics attending diabetes and dermatology clinics in London, Ontario, Canada and Boston, MA, U.S.A. Diabetic subjects seen in dermatology offices were for unrelated dermatoses; those referred specifically for the management of onychomycosis were excluded from the sample. A total of 550 diabetic subjects was evaluated (283 males and 267 females), age 56·1 ± 0·7 years (mean ± SEM). Patients with type I diabetes constituted 34% of the sample. The racial origin was: 531 Caucasians, 17 Asians, one African-American and one American-Indian. Abnormal-appearing nails and mycological evidence of onychomycosis (mostly due to dermatophytes) were present in 253 (46%) and 144 (26%), respectively, of 550 subjects. The development of onychomycosis was significantly correlated with age ($P<0·0001$) and male gender ($P<0·0001$). Males were 2·99 times more likely to have onychomycosis compared with females (95% confidence interval, CI 1·94–4 61). After controlling for age and sex, the risk odds ratio for diabetic subjects to have toenail onychomycosis was 2·77 times compared with normal individuals (95% CI 2·15–3·57). After controlling for age and sex, a stepwise logistic regression demonstrated that significant predictors for onychomycosis included a family history of onychomycosis ($P=0·0001$), concurrent intake of immunosuppressive therapy ($P=0·035$) and peripheral vascular disease ($P=0·023$). Toenail onychomycosis was present in 26% of the sample and is projected to affect approximately one-third of subjects with diabetes. Predisposing factors include increasing age, male gender, family history of onychomycosis, concurrent intake of immunosuppressive agents and peripheral vascular disease.

Diabetes mellitus (DM) affects all populations and age groups with an estimated 60 million people worldwide,[1] 16 million in the U.S.A. and 1·5 million in Canada. The World Health Organization estimates that the total number of people with diabetes the world over will double to 200 million by the year 2010. The number of individuals with diagnosed DM has increased fivefold between 1958 and 1993.[2] In the U.S.A. it is estimated that the yearly incidence of new cases of insulin-dependent DM (IDDM) and non-insulin-dependent DM (NIDDM) is 30,000[3] and 625,000,[4], respectively.

DM can result in complications affecting all systems of the body. Of particular relevance is lower extremity

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arterial disease (LEAD) which is relatively common in DM.[5] It is the result of decreased perfusion of the lower extremity and may manifest as intermittent claudication and/or absence of peripheral pulses in the feet. The presence of LEAD in diabetics may be compounded by infections such as onychomycosis and bacterial sepsis, and peripheral neuropathy. The rate of neuropathy in subjects with NIDDM may be five times higher compared with normal individuals.[6,7] Ulcers are another complication more likely to develop in diabetics with LEAD, peripheral neuropathy or other concomitant systemic disease.[8–10]

Onychomycosis may be the most common disease of nails, representing 18–40% of all onychopathies[11,12] and 30% of all cutaneous mycotic infections.[13] Toenail onychomycosis often exists with interdigital or plantar tinea pedis.[14] Nails with fungal infection may become thick and distorted, sometimes with sharp edges. Such nails can abrade or ulcerate adjacent skin. The potential for serious sequelae is increased in diabetics with vascular disease of the extremity, peripheral neuropathy, and those with poorly fitting shoes. The abrasion or ulceration can increase in size, become chronic, and act as a portal of infection for bacteria, fungi or other organisms. Impaired wound healing may result in increased morbidity, possible amputation of the lower extremity or even mortality.

Given the potential for morbidity that may result from fungal infections of the extremities, we have determined the prevalence of toenail onychomycosis and the factors predisposing to its development in diabetic subjects.

## Subjects and methods

*Study population*

Consecutive, consenting individuals with a diagnosis of diabetes were recruited from diabetes clinics where they presented for regular follow-up. Subjects with gestational diabetes were not included in the survey. The clinics were at Victoria Hospital and St Joseph's Hospital in London, Ontario, Canada and the New England Medical Center in Boston, MA, U.S.A. Furthermore, patients seen at two dermatologists' offices, one in London, Ontario, Canada (A.K.G.) and the other in Boston, MA, U.S.A. (N.K.) for a variety of dermatoses were included if they had diabetes. Subjects were excluded from the survey if their referring diagnosis was onychomycosis. All patients provided consent and the protocol was approved by Institution Review Boards at the University of Western Ontario, London, Ontario, Canada and the New England Medical Center, Boston, MA, U.S.A.

*Assessment of parameters that may predispose to onychomycosis*

For subjects with diabetes, the following information was obtained: age, gender, racial origin, duration and type of diabetes, list of medications taken by the patient, family history of onychomycosis, and history of vascular disease, peripheral neuropathy, nephropathy and retinopathy. From the patients' charts the laboratory parameters ascertained included glycosylated haemoglobin ($HbA_{1c}$) readings over the past 3 years, serum creatinine, proteinuria, triglycerides and cholesterol. Examination included measurement of the brachial and ankle blood pressures, evaluation of the dorsalis pedis and posterior tibial pulses, assessing the degree of capillary refill and testing for peripheral neuropathy using the Semmes–Weinstein 5·07 monofilament. The severity of onychomycosis was evaluated globally for all toenails as: minimal (<25% of nail plate and bed involvement), moderate (26–75% diseased nail plate and bed) and severe (>75% nail plate and bed or matrix involvement).

*Mycological sampling of toenails*

The toenails of all diabetic subjects enrolled in the survey were examined. Nail specimens were collected from each individual; if all toenails appeared clinically normal then both big toenails were sampled. If one or more of the toenails appeared clinically abnormal, then the two toenails that were clinically most likely to have onychomycosis were sampled.

*Mycological evaluation of toenails*

All nail specimens were sent to a mycology laboratory, where they were examined in a blinded manner without the operator being aware of the clinical details. Light microscopic (KOH) examination was performed for the presence of fungal filaments. The nail specimens were also cultured in both cycloheximide and non-cycloheximide containing media. The media used were Sabouraud peptone–glucose agar, with added cycloheximide, chloramphenicol and gentamicin (CCG), casaminoacids erythritol albumin agar with CCG and Littman oxgall agar with added streptomycin.

For a mycological report from a nail specimen to be regarded as being significant, it was necessary to

observe fungal filaments under the light microscope, except when a dermatophyte was cultured. In the case of a yeast or non-dermatophyte mould, congruous and recognizably non-dermatophytic fungal spores, filaments or pseudomycelium had to be observed under the microscope, in addition to the culture being positive for these organisms. In the instances where the culture grew a yeast or other non-dermatophyte with negative light microscopic (KOH) examination, or where a non-dermatophyte grew as a probable contaminant from specimens positive for filaments consistent with those of a dermatophyte, the non-dermatophyte was regarded as not being causative for onychomycosis and therefore excluded from the list of organisms implicated in causing onychomycosis. It was not within the scope of this study to have patients return for repeat sampling of their toenails.

*Prevalence of onychomycosis in normal individuals*

The prevalence of onychomycosis in diabetic subjects was compared with that in normal individuals. The latter group comprised 2001 subjects visiting dermatologists' offices whose nails were clinically examined by a dermatologist and all abnormal-appearing nails were sampled mycologically.[15] In this sample the prevalence of onychomycosis was 9·1%. When corrected for the age and sex distribution in the Ontario population using census data, the estimated prevalence of onychomycosis in normal individuals in Ontario, Canada is 6·8%.[15] The distribution of organisms was: dermatophytes 92·9%, *Candida* species 2·8% and non-dermatophyte moulds 4·3%.

*Statistical analysis*

To determine the factors that predispose diabetic patients to the development of onychomycosis, a series of maximum-likelihood logistic regression models was analysed. For each model, the mycological presence of toenail onychomycosis served as the dependent measure of the prevalence of onychomycosis. Variables related to the duration and type of diabetes, medications taken by the patient, family history of onychomycosis, and history of vascular disease, peripheral neuropathy, nephropathy and retinopathy were entered into separate models to determine if these were associated with the development of onychomycosis, after controlling for age and sex of the patient. Odds ratios (ORs) and 95% confidence intervals (CIs) were computed with the use of β coefficients and standard errors obtained from the logistic analyses. CIs not containing the value 1·0 are statistically significant at $P = 0{\cdot}05$.

## Results

*Patients*

A total of 550 subjects (283 males and 267 females), age $56{\cdot}1 \pm 0{\cdot}7$ years (mean ± SEM), was surveyed. The duration of diabetes in patients without and with onychomycosis was $13{\cdot}8 \pm 0{\cdot}6$ years and $15{\cdot}3 \pm 1{\cdot}2$ years (mean ± SEM), respectively ($P > 0{\cdot}05$). The racial origin of the 550 subjects was: 531 Caucasian, 17 Asian, one African-American and one American-Indian.

*Prevalence, type and distribution of onychomycosis*

Abnormal-appearing toenails and mycological evidence of onychomycosis were observed in 253 (46%) and 144 (26%), respectively, of 550 subjects (Table 1). Type I diabetes was present in 34% of the sample. The prevalence of onychomycosis in this subset was 13%. Distal and lateral subungual onychomycosis (DLSO) was confirmed mycologically in 120 of 550 subjects (Table 2). In 10 of the 120 individuals DLSO was found concomitantly with white superficial onychomycosis (WSO). Fifteen (3%) of 550 subjects had WSO alone (Table 2). In eight (1·5%) of 550 subjects the toenail appeared clinically normal; however, upon mycological examination there was evidence of onychomycosis. While DLSO usually involved the big toenail, WSO was observed most commonly on the surface of the third and fourth toenails (Fig. 1). The organisms implicated in causing toenail onychomycosis are indicated in Table 2. Most were dermatophytes (88%), with *Candida* species in 3% and non-dermatophyte moulds accounting for 9% of cases.

The development of onychomycosis in diabetic subjects was found to be significantly correlated with increasing age ($P < 0{\cdot}0001$) and the male gender ($P < 0{\cdot}0001$) (Fig. 2). Males were 2·99 times more likely to have onychomycosis compared with females (95% CI 1·94–4·61). After controlling for age and sex, the risk OR for diabetic subjects to have toenail onychomycosis was 2·77 times compared with normal individuals (95% CI 2·15–3·57). In the subset of patients with type I diabetes the corresponding figure was 1·69 (95% CI 0·98–2·91).

Some possible sources of bias resulting from somewhat different sampling techniques will be addressed. Diabetics were seen in hospital clinics when they presented

**Table 1.** Age distribution of diabetics with abnormal-appearing nails and onychomycosis

| Age group (years) | Patients in age group | | Patients with abnormal-appearing nails | | | Patients with onychomycosis | | |
|---|---|---|---|---|---|---|---|---|
| | Male/female | Total number | Male/female | Total number | % of age group | Male/female | Total number | % of age group |
| 10–19 | 2/2 | 4 | 0/0 | 0 | 0 | 0/0 | 0 | 0 |
| 20–29 | 17/21 | 38 | 2/2 | 4 | 11 | 1/2 | 3 | 8 |
| 30–39 | 31/27 | 58 | 6/4 | 10 | 17 | 5/0 | 5 | 9 |
| 40–49 | 51/31 | 82 | 20/6 | 26 | 32 | 10/1 | 11 | 13 |
| 50–59 | 45/46 | 91 | 23/22 | 45 | 49 | 14/7 | 21 | 23 |
| 60–69 | 79/74 | 153 | 52/42 | 94 | 61 | 31/13 | 44 | 29 |
| 70–79 | 52/58 | 110 | 34/30 | 64 | 58 | 32/21 | 53 | 48 |
| ≥ 80 | 5/9 | 14 | 3/7 | 10 | 71 | 4/3 | 7 | 50 |
| Totals | 282/268 | 550 | 140/113 | 253 | 46 | 97/47 | 144 | 26 |

for regular follow-up visits which generally occur two to three times a year. Additional diabetics were seen at two dermatologists' offices. Diabetics who presented to the dermatologists' offices for the management of onychomycosis were excluded from the sample. On the other hand, 'normal individuals' were patients seen in dermatologists' offices for a wide range of dermatoses excluding referrals for tinea unguium (in order to avoid an obvious bias endemic to dermatology offices).[15] In North America, patients seen in dermatologists' offices are broadly similar to those who attend a dermatology out-patient clinic in a hospital in the ambulatory setting. It is therefore likely that no meaningful bias was introduced because some diabetics and 'normal individuals' have been sampled from different settings. Furthermore, in a sample of 15,000 patients visiting dermatologists' offices, excluding those referred for the management of onychomycosis, after controlling for age and sex the risk OR for diabetics to have onychomycosis was 3·24 (95% CI 2·15–4·88) (Gupta AK, unpublished observations). In normal individuals only abnormal-appearing nails were sampled whereas in the diabetics toenails were sampled from each patient whether or not they appeared clinically abnormal. It is probable that only a very small proportion of normal-appearing toenails in normal individuals have onychomycosis. This is based on data from a separate study involving psoriasis patients in whom mycological evidence of

**Table 2.** Fungal organisms causing toenail onychomycosis in patients with diabetes ($n = 550$)

| Fungal organism | Patients with clinically normal-appearing toenails | Patients with clinically abnormal-appearing toenails | | | | |
|---|---|---|---|---|---|---|
| | | DLSO | WSO | DLSO plus WSO | WSO plus PSO | Total (% of 550) |
| Dermatophytes[a] (97 of 110 positive cultures) = 88% | | | | | | |
| *Trichophyton rubrum* | 2 | 48 | 1 | 1 | – | 52 (9·5%) |
| *Trichophyton mentagrophytes* | 5 | 27 | 5 | 5 | 1 | 43 (7·8%) |
| *Epidermophyton floccosum* | – | – | 1 | – | – | 1 (0·2%) |
| *Trichophyton rubrum* plus *Scopulariopsis brevicaulis* | – | 1 | – | – | – | 1 (0·2%) |
| *Candida* species[a] (3 of 110 positive cultures) = 3% | | | | | | |
| *Candida* species | – | 1 | 2 | – | – | 3 (0·5%) |
| Non-dermatophyte moulds[a] (10 of 110 positive cultures) = 9% | | | | | | |
| *Acremonium* species | – | 3 | 1 | 2 | – | 6 (1·1%) |
| *Aspergillus niger* | – | – | 1 | – | – | 1 (0·2%) |
| *Aspergillus sydowii* | – | 1 | – | – | – | 1 (0·2%) |
| *Scopulariopsis brevicaulis* | – | 2 | – | – | – | 2 (0·4%) |
| KOH-positive, no fungus grown | 1 | 27 | 4 | 2 | – | 34 (6·2%) |
| Total | 8 | 110 | 15 | 10 | 1 | 144 (26·2%) |

DLSO, distal and lateral subungual onychomycosis; WSO, white superficial onychomycosis; PSO, proximal subungual onychomycosis. [a] Of 550 patients, 144 had onychomycosis. In 34 of the 144 individuals, light microscopic examination was positive and culture negative (6% of 550 patients). In 13 (2%) of 550 patients, direct light microscopic examination was negative with a dermatophyte grown on culture.

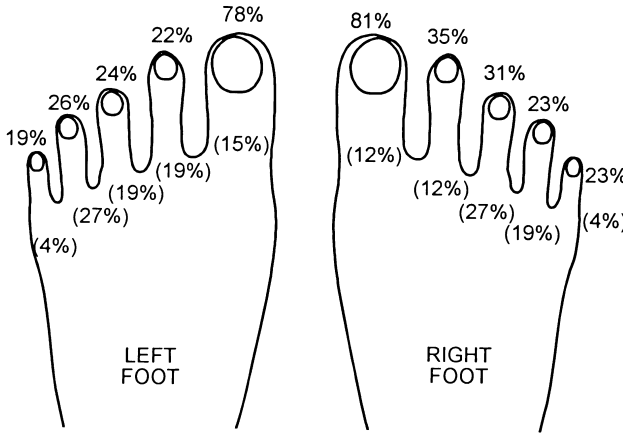


**Figure 1.** Distribution of distal and lateral subungual onychomycosis and white superficial onychomycosis (WSO) involving the toes of the left and right feet. Values for WSO are given in brackets.

onychomycosis was present in only 0·4% of individuals with normal-appearing toenails.[16]

In order to estimate the prevalence of onychomycosis in the general diabetic population in Ontario, Canada, the age-adjusted prevalence of diabetes in Manitoba, Canada was taken to be representative of Ontario.[17] For Massachusetts, the source of data was a study that used the medical records of residents in Rochester, MN.[18] The prevalence of toenail onychomycosis in diabetic subjects in Ontario and Massachusetts is estimated to be 32·3% (95% CI 28·3–36·2%) and 34·9% (95% CI 30·8–38·9%), respectively.

*Variables predisposing to the development of onychomycosis*

A stepwise logistic regression was carried out to determine the variables that were significant predictors for the development of onychomycosis in diabetic subjects, after controlling for age and sex. The type and duration of diabetes were not significant predictors for onychomycosis; however, the severity of onychomycosis was significantly associated with the duration of diabetes ($P = 0{\cdot}043$). Other significant predictors for onychomycosis in diabetics included a family history of onychomycosis ($P = 0{\cdot}0001$), concurrent intake of immunosuppressive therapy ($P = 0{\cdot}035$), reduced or absent peripheral pulses in the feet (dorsalis pedis or posterior tibial) ($P = 0{\cdot}0018$), reduced or absent capillary refill ($P = 0{\cdot}023$), and reduced ankle blood pressure ($P = 0{\cdot}0005$) with a resultant decrease in the ankle/brachial blood pressure ratio ($P = 0{\cdot}018$). The following were non-significant predictors for onychomycosis ($P > 0{\cdot}05$): a history of myocardial infarction, angina, hypertension, coronary artery bypass graft or intermittent claudication, history of paraesthesiae or dysaesthesiae, brachial diastolic and systolic blood pressure, absence of peripheral neuropathy as measured using the Semmes–Weinstein 5·07 monofilament, presence of proliferative retinopathy, the average glycosylated haemoglobin over the previous 3 years, the percentage of glycosylated haemoglobin over the upper range of normal for the previous 3 years, presence of proteinuria (% increase over upper limit of normal), creatinine (absolute value), and hypertriglyceridaemia or hypercholesterolaemia.

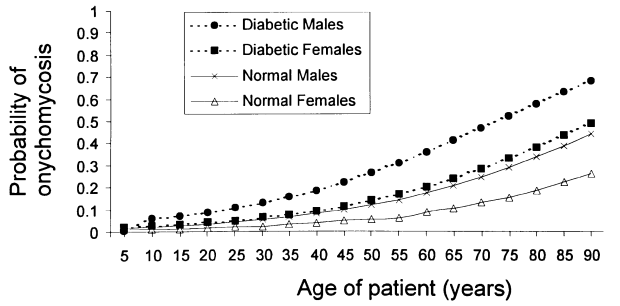


**Figure 2.** Probability of developing onychomycosis in diabetic and normal males and females at different ages.

## Discussion

There have only been a few studies that have determined the prevalence of onychomycosis in diabetic subjects. To our knowledge, the present study is the largest one of its kind and the only one that has systematically looked for the factors that predispose to the development of onychomycosis in diabetic subjects. Buxton *et al.*[19] in the U.K. determined the prevalence of onychomycosis in 100 subjects with well-controlled IDDM and compared their results with a control group of 100 non-diabetic subjects matched for age and sex. These investigators did not include individuals with NIDDM in their sample, the subset that accounts for the majority of diabetic subjects. Mycologically confirmed onychomycosis was present in 12% of diabetics vs. 11% in the control group. In the present study, type I diabetes was present in 34% of 550 subjects. Compared with age- and sex-matched normal individuals, the risk OR for type I diabetics to have toenail onychomycosis was 1·69 (95% CI 0·98–2·91). Lugo-Somolinos and Sánchez[20] reported onychomycosis in 12 (39%) of 31 diabetic subjects. In the present study the prevalence of onychomycosis in diabetics was 26%. Alteras and Saryt[21] reported the prevalence of organisms in toe-webs and toenails combined; however, separate data were not provided for toenails.

The results of our two-centre study indicate that

toenail onychomycosis is common, estimated to be present in approximately one-third of diabetic subjects. After controlling for age and sex, the risk OR for diabetic subjects to have toenail onychomycosis is 2·77 times compared with normal individuals (95% CI 2·15–3·57). Men with diabetes in the higher age groups are particularly prone to developing onychomycosis. A family history of onychomycosis and concomitant intake of immunosuppressive agents for other coexisting medical disorders (e.g. methotrexate for rheumatoid arthritis) are also important pointers. Another important predictor for onychomycosis is the presence of peripheral vascular disease. Microangiopathy with compromised perfusion to the feet can contribute to poor tissue oxygenation of the extremities.[22] Thus, diabetic subjects with one or more predisposing factors for the development of onychomycosis should have their feet and nails examined particularly carefully.

When toenails in diabetic subjects appeared abnormal, the prevalence of onychomycosis was 57% (144 of 253 subjects). In comparison, among normal individuals, only 40% of abnormal-appearing toenails were due to onychomycosis with the remainder of the nail changes being due to causes such as trauma, ageing and psoriasis that can mimic onychomycosis.[15] It is interesting to note that in eight (3%) of the 297 diabetic subjects in this study who had clinically normal-appearing nails there was mycological evidence of onychomycosis. Mycological evidence of onychomycosis was present in 0·4% of patients with psoriasis who had normal-appearing toenails.[16] Therefore, it is possible that in the early stages of onychomycosis, invasion of the nail bed and plate by fungal organisms is not accompanied by gross changes that are clinically detectable. The data further support the advisability of regular foot examinations and appropriate education pertaining to foot care in individuals with diabetes.

The degree of glycaemic control over the preceding 3 years was not a significant predictor for the development of onychomycosis in this study. Improved glycaemic control in diabetic subjects, particularly those with IDDM, reduces the risk for developing microangiopathy and diminishes the rate of progression of established microvascular disease.[23] In the present study it was not feasible to estimate the degree of glycaemic control in the majority of diabetic subjects over a period longer than the preceding 3 years because most patient charts did not have records of the glycosylated haemoglobin going back beyond 3 years. We therefore could not determine whether the degree of control of diabetes over the time-span of the disease is a predictor for the development of onychomycosis. While the duration of diabetes was not a significant predictor for onychomycosis, the severity of onychomycosis was significantly associated with the length of time for which the individual had had diabetes. Thus, early intervention while onychomycosis is less severe may be advisable because of the potentially progressive nature of the fungal infection. Higher cure rates for onychomycosis are more likely when a small area of nail plate and bed is diseased, in the absence of nail matrix involvement.

The availability of the newer antifungal agents itraconazole, terbinafine and fluconazole provides an opportunity for effective treatment of toenail onychomycosis.[24] This is a particularly important consideration in diabetes where approximately one-third of individuals can be expected to have onychomycosis. Furthermore, the consequences of not treating the onychomycosis may have a more serious potential for complications compared with normal individuals. Griseofulvin is the traditional agent that has a narrow spectrum with relatively poor efficacy for toenail onychomycosis; therefore, it has been largely superseded by the newer generation of antimycotic drugs. These agents have a high benefit to risk ratio with shorter treatment times compared with griseofulvin, thereby resulting in higher compliance. The role of patient education pertaining to measures to reduce reinfection once an effective response has been obtained cannot be overemphasized,[25] especially in patient groups at higher risk for the development of onychomycosis.

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