Prevalence, Risk Factors, and Type of Organism in Fungal Foot Infection and Toenail Onychomycosis in Thai Diabetic Patients

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Background: *Diabetes mellitus (DM) is a known and important predisposing factor for toenail onychomycosis and fungal foot infection. DM also increases the risk of patient developing secondary bacterial infection if fungal infection goes unrecognized and untreated.*

Objective: *To assess the prevalence and risk factors of toenail onychomycosis and fungal foot infection in Thai diabetic patients.*

Material and Method: *This single center cross-sectional observational study recruited type 1 and type 2 diabetic patients older than 18 years who attended Siriraj Hospital between October 1, 2012 and November 30, 2013. Patient demographic data, clinical data, and medical history were collected by questionnaire and assessed. Diagnosis of fungal infection was confirmed by potassium hydroxide investigation and fungal culture was performed to identify the type of organism.*

Results: *One hundred forty four diabetes outpatients were enrolled and 38.9% were men. The mean (±SD) age was 59.6±12.7 years. Fungal infection was diagnosed 46 cases (31.9%). There were 28 cases (61%) with only toenail onychomycosis, two cases (4%) with only fungal foot infection, and 16 cases (35%) with co-infection (fungal foot infection and toenail onychomychosis). The organisms identified as causing fungal foot infection and toenail onychomycosis were dermatophytes (44.4% and 34.1%, respectively), non-dermatophytes (44.5% and 47.7%, respectively), and Candida species (5.6% and 4.5%, respectively). Risk factors found to be significantly correlated with toenail onychomycosis and fungal foot infection were male gender ($p = 0.001$), age older than 60 years ($p = 0.006$), agriculture-related activities ($p = 0.006$), family history of dermatophytosis ($p = 0.034$), and co-morbidity coronary heart disease ($p = 0.044$). No significant association was found for BMI, duration of DM, HbA1c, and diabetes related complications.*

Conclusion: *Prevalence of fungal foot and toenail infection in Thai diabetes patient was 31.9%. We found higher prevalence of non-dermatophyte organisms as the cause of dermatomycosis and toenail onychomycosis. Accordingly, clinical diagnosis without proper culture identification may result in treatment failure.*

Keywords: *Fungal foot infection, Toenail onychomycosis, Diabetes mellitus*

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Toenail onychomycosis and fungal foot infection (tinea pedis caused by dermatophytes and dermatomycosis caused by non-dermatophyte molds) are generally asymptomatic and are usually unrecognized in most patients. Prevalence of these infections among diabetic patients is higher than in the general population and there is increased risk of developing secondary bacterial infection if the fungal infection goes unrecognized and untreated. Diagnosis of fungal foot infection is usually made from clinical presentation of dystrophic nails or foot abnormalities. However, appropriate diagnostic techniques, including potassium hydroxide (KOH) test and fungal culture, can help to ensure a more accurate diagnosis. Treatment of toenail onychomycosis and fungal foot infection depends on both severity and causative fungus[1]. *Scytalidium dimidiatum* is a leading cause of fungal foot infection and toenail onychomycosis in Thailand[2]. Clinical diagnosis alone without proper culture identification, can lead to treatment failure and complications. According to our review of the literature, no studies have reported data on the prevalence, risk factors, and

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type of organism of fungal foot infection and toenail onychomycosis among Thai diabetic patients. Accordingly, the primary objective of this study was to examine the prevalence of toenail onychomycosis and fungal foot infection in Thai diabetic subjects. The secondary objective was to determine the risk factors associated with these infections.

Material and Method

Patients

We recruited type 1 and type 2 diabetic patients older than 18 years old who attended Siriraj Hospital between October 1, 2012 and November 30, 2013 study period. Patients who had gestational diabetes or who were uncooperative were excluded from the study. Demographic and clinical data were recorded, including age, gender, body mass index (BMI), comorbidities, and laboratory data. All patients were assessed for the type and duration of diabetes, HbA1c level, diabetes-related factors, and chronic complications of diabetes (retinopathy, nephropathy, sensory neuropathy, and peripheral vascular disease) by review of patient history from the medical record and neuropathy examination by Semmes-Weinstein monofilament test. Sensory neuropathy was diagnosed if monofilament perception was abnormal. By questionnaire, we also assessed risk factors associated with fungal foot infections, including obesity, smoking, alcohol consumption, agriculture-related activities, previous history of repeated foot trauma, family history of fungal infection, history of walking barefoot, and history of animal contact. This study was approved by the Siriraj Institutional Review Board (SIRB) and all patients provided written informed consent.

Sample size

Sample size was calculated using estimating proportion of one group formula. Based on the literature review, prevalence of onychomycosis and fungal foot infection in one cohort was 26%, we calculated sample size of 150 patients (margin of error = 7%, confidence level = 95%).

Clinical examinations and mycological examinations

Clinical evidence of fungal foot infection and toenail onychomycosis was identified by careful inspection of the feet by experienced physicians. Photographic images of suspected or affected feet were also recorded and evaluated. In patients suspected of having fungal infection, mycological sampling was performed by specialized clinicians. Presence of toenail onychomycosis and/or fungal foot infection was demonstrated by direct microscopy with KOH preparation. Fungal culture was performed by the mycological laboratory for confirmation of diagnosis and species identification.

Statistical analysis

Descriptive data were expressed as mean ± SD for continuous data and number and percentage for categorical data. Prevalence and type of organism responsible for causing fungal foot infection and toenail onychomycosis were expressed as percentage. To evaluate the factors related to the presence or absence of toenail onychomycosis and/or fungal foot infection, Chi-square test or Fisher's exact test was used for categorical data and t-test or Mann-Whitney U test was used for continuous data. A p-value <0.05 was considered to be statistically significant. In this study, we used SPSS version 12.0 for analysis.

Results

This was a cross-sectional observational study. One hundred forty four ambulatory diabetic patients were enrolled. Fifty-six subjects (38.9%) were male and mean age of the study population was 59.6±12.7 years. Demographic and clinical characteristics are shown in Table 1. Fungal foot infection and/or toenail onychomycosis were diagnosed in 46 cases (31.9%). There were 28 cases (61%) with toenail onychomycosis only, two cases (4%) with fungal foot infection only, and 16 cases (35%) with co-infection (fungal foot infection and toenail onychomycosis). Risk factors found to be significantly correlated with fungal foot and toenail infection were male gender (p = 0.001), age older than 60 years (p = 0.006), agriculture-related activities (p = 0.006), family history of dermatophytosis (p = 0.034), and co-morbidity coronary heart disease (p = 0.044). No significant association was found for BMI, duration of DM, HbA1c, or diabetes-related complications, including lower extremity peripheral arterial disease, neuropathy, nephropathy, and retinopathy (Table 1, 2).

Organisms responsible for causing fungal foot infection included dermatophytes (8 cases, 44.4%), non-dermatophytes (8 cases, 44.5%), and *Candida* species (1 case, 5.6%). The organisms identified as causing toenail onychomycosis were dermatophytes (15 cases, 34.1%), non-dermatophytes (21 cases, 47.7%) and *Candida* species (2 cases, 4.5%). Among non-dermatophytes infection, *S. dimidiatum* was the leading pathogen, with *Trichophyton rubrum* and

T. mentagrophytes being the predominant dermatophytes identified in this study (Table 3).

Discussion

Prevalence of toenail onychomycosis and fungal foot infection among diabetic patients is higher than in the general population. Prevalence of fungal infection in diabetic subjects is 26%, which is 2.5 times higher than in normal individuals[3]. Patients with long-standing, poorly-controlled diabetes often have problems with their feet. This is due mainly to neuropathy and arterial insufficiency, which causes decreased perfusion to the lower extremities and can lead to either or both toenail onychomycosis and fungal foot infection. Infected nails become irregular, thick, and distorted - sometimes with sharp edges. Nails in this condition can abrade or ulcerate adjacent skin, causing secondary bacterial infection. Potential for serious sequalae, such as amputation, is increased if the fungal infection is unrecognized and left untreated. In a previous study, Gupta et al reported that male gender, old age, immunocompromised status, family history of fungal infection, duration of diabetes, poor glycemic control, high triglycerides levels, and diabetic

Table 1. Dermographic and clinical characteristics in 144 diabetes patients

Baseline characteristics	Total (n = 144)	No fungal infection (n = 98)	Fungal foot and nail infection (n = 46)	*p*-value
Male	56 (38.9)	29 (29.6)	27 (58.7)	0.001*
Obesity (BMI >25 kg/m^2)	70 (48.6)	51 (52.0)	19 (41.3)	0.275
Immunocompetent host**	137 (95.1)	93 (94.9)	44 (95.7)	0.964
Type 2 diabetes mellitus	139 (96.5)	91 (92.9)	46 (100)	0.597
FBS (mg/dl)	148.1±47.6	149.6±49.6	144.8±43.6	0.524
HbA1c (%)	7.8±1.5	7.9±1.7	7.7±1.3	0.367
Co-morbidity diseases				
Hypertension	108 (75.0)	74 (75.5)	34 (73.9)	0.995
Dyslipidemia	128 (88.9)	87 (88.8)	41 (89.1)	0.672
Coronary heart disease	10 (6.9)	4 (4.1)	6 (13.0)	0.044*
Cerebrovascular disease	6 (4.2)	4 (4.1)	2 (4.3)	1.000

BMI = body mass index; FBS = fasting blood sugar; HbA1c = hemoglobin A1c
Data were expressed as number (%) or mean ± SD, unless otherwise specified
* *p*-value ≤0.05 indicates statistical significance
** Immunocompetent host mean subject who did not take any immunosuppressive agents

Table 2. Factor related with fungal foot and toenail infection in 144 diabetes patients

Variables	Total (n = 144)	No fungal infection (n = 98)	Fungal foot and nail infection (n = 46)	*p*-value
Age ≥60 year old	70 (48.6)	40 (40.8)	30 (65.2)	0.006*
Diabetes-related factors				
Duration of DM >5 years	101 (70.1)	70 (71.4)	31 (67.4)	0.689
HbA1c >7%	101 (70.1)	71 (72.4)	30 (65.2)	0.479
Diabetic retinopathy	97 (67.4)	67 (68.4)	30 (65.2)	0.422
Diabetic nephropathy	92 (63.9)	56 (57.1)	36 (78.3)	0.055
Diabetic neuropathy	35 (24.3)	20 (20.4)	15 (32.6)	0.095
Impaired peripheral pulse	11 (7.6)	6 (6.1)	5 (10.9)	0.299
Agriculture-related	112 (84.7)	83 (84.7)	29 (63.0)	0.006*
Recurrent onychomycosis	10 (6.9)	5 (5.1)	5 (10.9)	0.287
Repeated foot trauma	15 (10.4)	11 (11.2)	4 (8.7)	0.775
History of walking barefoot	58 (40.3)	38 (38.8)	20 (43.5)	0.521
Family history of dermatophytosis	5 (3.5)	1 (1.0)	4 (8.7)	0.034*
Animal contact	61 (42.4)	38 (38.8)	23 (50.0)	0.324
Foot deformities	21 (14.6)	14 (14.3)	7 (15.2)	0.714

DM = diabetes mellitus
Data were presented as number (%), unless otherwise specified
* *p*-value ≤0.05 indicates statistical significance

Table 3. Prevalence of organisms that caused fungal infection in this study

Organisms	Fungal foot infection (%) (n = 18)	Onychomycosis (%) (n = 44)
Dermatophytes		
T. rubrum	-	1 (2.3)
T. mentagrophytes	8 (44.4)	14 (31.8)
Non-dermatophytes		
S. dimidiatum	7 (38.9)	11 (25.0)
Fusarium spp.	1 (5.6)	10 (22.7)
Candida species	1 (5.6)	2 (4.5)
Unidentified	1 (5.6)	6 (13.6)

n = number of infections
All data were presented as number (%)

complication, such as diabetic retinopathy and nephropathy were predisposing factors for fungal foot infection and toenail onychomycosis in diabetic patients[3-6]. From this study, risk factors significantly associated with fungal foot infection and toenail onychomycosis were male gender, age older than 60 years, agriculture-related activities, family history of dermatophytosis, and co-morbidity coronary heart disease. Gait changes, foot deformity, repeated trauma, circulatory problems, and failure to maintain hygiene of the feet and nails increased susceptibility to toenail onychomycosis in elderly. In our study, no significant correlation was found for duration of diabetes, glycemic control (HbA1c) or diabetes-related complications, including lower extremity peripheral arterial disease, neuropathy, nephropathy, and retinopathy.

Organisms found to be responsible for causing toenail onychomycosis and fungal foot infection[1] were dermatophytes (such as *T. rubrum*, *T. mentagrophytes*, *T. interdigitale*, and *Epidermophyton floccosum*), non-dermaphytes (*Acremonium* spp., *Aspergillus* spp., *Fusarium* spp., *Onychocola canadensis*, *Scopulariopsis brevicaulis*, and *S. dimidiatum*), and yeasts. Prevalence and type of organisms that cause fungal foot infection vary from country to country. Previous studies have reported that 90% of toenail onychomychosis and fungal foot infection cases were caused by dermatophytes[1,4]. In contrast, a study in Thailand[5] reported prevalence of dermatophyte-related toenail onychomycosis and fungal foot infection to be 36% (Table 4).

Prevalence of fungal foot infection and toenail onychomycosis in diabetic outpatients in our study was 31.9%, which is similar to data from previous report[3]. Consistent with other studies, the pathogens found to most commonly cause fungal foot infection in our study were dermatophytes (88%)[2-4,9,10]. We also found a higher prevalence of non-dermatophyte organisms than reported previous study[7]. In the present study, *S. dimidiatum* was the most common cause of dermatomycosis and toenail onychomycosis among Thai diabetic outpatients.

S. dimidiatum is a recognized pathogen in tropical countries that can commonly be found in fruit trees. This organism can cause chronic disease of the soles, toe spaces, palms and nails, and it is clinically indistinguishable from other dermatophyte infections. The higher prevalence in Asia is due to geographical distribution and climate[2,5]. Without proper identification by fungal culture, clinical diagnosis may not be made or may not be accurate thus, lead to treatment failure and complications. In addition, dermatomycosis from *S. dimidiatum* does not respond to oral or tropical antifungal agents. The limitations of this study were its cross-sectional observational design and the

Table 4. Comparison of organisms that cause fungal infection worldwide, in Thailand, and in this study

Organism	Worldwide (%)		Thailand[5] (%)		This study (%)	
	Fungal foot infection[8]	Onychomycosis[4]	Fungal foot infection	Onychomycosis	Fungal foot infection	Onychomycosis
Dermatophyte	100	88.0	36.8	36.3	44.4	34.1
T. rubrum	84.0	47.0	13.2	30.3	0	2.3
T. mentagrophytes	7.2	39.0	18.4	3.0	44.4	31.8
E. floccosum	5.9	0.9	5.2	3.0	0	0
Non-dermatophytes	0	9.0	57.9	51.6	44.5	47.7
S. dimidiatum	0	0	54.0	36.4	38.9	25.0
Fusarium spp.	0	0	3.9	15.2	5.6	22.7
Acremonium spp.	0	6.0	0	0	0	0
Yeasts (*Candida albicans*)	0	3.0	2.6	6.0	5.6	4.5
Mixed infection	0	1.0	0	3.0	0	0
Unidentified	0	34.0	2.6	3.0	5.6	13.6

acknowledged fact that we did not repeat fungal culture of nails in case of non-dermatophyte toenail onychomycosis, according to proposed criteria[11].

Conclusion

Onychomycosis and fungal foot infection are typically asymptomatic and go unrecognized in most patients. Diabetic patients with one or more predisposing factors for the development of fungal infection should have their feet and nails examined carefully and regularly. These patients should also receive appropriate foot care education to promote detection and prevention of fungal infection.

The prevalence of fungal foot infection and toenail onychomycosis in Thai diabetes outpatients was 31.9%. Our study found higher prevalence of non-dermatophyte organisms, predominantly *S. dimidiatum*, as the cause of dermatomycosis and toenail onychomycosis. Clinical diagnosis without microbiological confirmation could result in misdiagnosis and subsequent treatment failure. Significant risk factors for toenail onychomycosis and fungal foot infection were male gender, age older than 60 years, agriculture-related activities, family history of dermatophytosis, and co-morbidity coronary heart disease.

What is already known on this topic?

Already know. Diabetes mellitus is an important predisposing factor for fungal foot infection and onychomycosis worldwide.

What this study adds?

Prevalence of fungal foot and nail infection in Thailand was 32%. Half of patients with fungal infection were caused by non-dermatophytes that were resistant to oral medical treatment.

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Potential conflicts of interest

None.

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อุบัติการณ์ ปัจจัยเสี่ยง และชนิดเชื้อราก่อโรค ในผู้ที่มีโรคติดเชื้อราบริเวณเท้าและเล็บเท้าในคนไทยที่เป็นเบาหวาน

รสิตา อัศดามงคล, ระวีวรรณ เลิศวัฒนารักษ์, ทวีศักดิ์ วรรณชาลี, สุมนัส บุณยะรัตเวช, จรัสศรี พียาพรรณ, ลลิตา มัฏฐาพันธ์

ภูมิหลัง: *เบาหวานเป็นโรคที่เพิ่มความเสี่ยงต่อการเกิดการติดเชื้อราที่ผิวหนังและเท้า และเพิ่มความเสี่ยงต่อการติดเชื้อแบคทีเรียมากขึ้น โดยเฉพาะถ้าไม่สามารถให้การวินิจฉัยการติดเชื้อราได้อย่างถูกต้องและไม่ได้รับการรักษาที่เหมาะสม*

วัตถุประสงค์: *เพื่อศึกษาอุบัติการณ์ ปัจจัยเสี่ยง และชนิดเชื้อราก่อโรคในผู้ที่มีโรคติดเชื้อราบริเวณเท้าและเล็บเท้าในคนไทยที่เป็นโรคเบาหวาน*

วัสดุและวิธีการ: *ผู้เป็นเบาหวานชนิดที่ 1 และเบาหวานชนิดที่ 2 ที่มีอายุมากกว่า 18 ปีขึ้นไป และรับการตรวจรักษาในโรงพยาบาลศิริราช ตั้งแต่วันที่ 1 ตุลาคม พ.ศ. 2555 ถึง 30 พฤศจิกายน พ.ศ. 2556 โดยผู้ร่วมการศึกษาจะได้รับการสัมภาษณ์ประวัติ ตรวจร่างกาย ตรวจเท้า โดยแบบสอบถาม และถ้ามีหลักฐานสงสัยว่าเป็นโรคติดเชื้อราบริเวณเท้าหรือเล็บเท้า จะได้รับการส่งตรวจทางห้องปฏิบัติการเพิ่มเติม โดยการขูดตรวจเชื้อรา potassium hydroxide preparation (KOH) เพื่อยืนยันการติดเชื้อ และส่งตรวจหาเชื้อก่อโรคเพิ่มเติม*

ผลการศึกษา: *ผู้เป็นเบาหวานเข้าร่วมการศึกษา 144 ราย เป็นเพศชายร้อยละ 38.9 อายุเฉลี่ย 59.6±12.7 ปี พบการติดเชื้อราบริเวณเท้าและเล็บเท้า 46 ราย คิดเป็นร้อยละ 31.9 โดยในจำนวนที่มีการติดเชื้อรา 28 ราย คิดเป็นร้อยละ 61 พบมีโรคติดเชื้อราบริเวณเล็บเท้า 2 ราย คิดเป็นร้อยละ 4 พบโรคติดเชื้อราที่เท้า และอีก 16 ราย คิดเป็นร้อยละ 35 พบทั้งการติดเชื้อราบริเวณเล็บเท้าและเท้าร่วมกัน เชื้อก่อโรคที่พบในโรคติดเชื้อราบริเวณเล็บเท้าและเท้าได้แก่ dermatophytes, non-dermatophytes และ Candida species โดยเชื้อดังกล่าวเป็นเชื้อก่อโรคที่เล็บเท้าและเท้าคิดเป็นร้อยละ 44.4, 34.1 และ 44.5, 47.7 และ 5.6, 4.5 ตามลำดับ ปัจจัยเสี่ยงที่มีนัยสำคัญต่อการติดเชื้อราที่เล็บเท้าและเท้าจากการศึกษานี้ได้แก่ ผู้เป็นเบาหวานเพศชาย (p-value = 0.001) ผู้ที่มีอายุมากกว่า 60 ปี (p-value = 0.006) ผู้ที่ประกอบอาชีพเกษตรกรรม (p-value = 0.006) ประวัติการติดเชื้อราในครอบครัว (p-value = 0.034) และการมีประวัติโรคหลอดเลือดหัวใจร่วมด้วย (p-value = 0.044) อย่างไรก็ตามจากการศึกษานี้ไม่พบความสัมพันธ์ที่มีนัยสำคัญทางสถิติของการติดเชื้อราที่เล็บเท้าและเท้ากับดัชนีมวลกาย ระยะเวลาที่เป็นโรคเบาหวาน ระดับน้ำตาลสะสม และภาวะแทรกซ้อนเรื้อรังชนิดต่าง ๆ ของโรคเบาหวาน*

สรุป: *พบอุบัติการณ์ของการติดเชื้อราที่เล็บเท้าและเท้าในคนไทยที่เป็นเบาหวานร้อยละ 31.9 จากการศึกษานี้พบอุบัติการณ์ของเชื้อก่อโรค non-dermatophyte สูงใกล้เคียงกับ dermatophyte ดังนั้นถ้าผู้ติดเชื้อราดังกล่าวไม่ได้รับการตรวจหาชนิดของเชื้อราก่อโรคจำเพาะโดยการทำการเพาะเชื้อ การวินิจฉัยจากอาการและอาการแสดงเท่านั้นส่งผลให้การรักษาไม่มีประสิทธิภาพหรือรักษาไม่หายขาด*