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Uncontrolled blood sugar tends to increase prevalence of dermatomycosis in diabetic type 2 patients

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ABSTRACT

BACKGROUND
The prevalence of type 2 diabetes mellitus (DM) is increasing. Diabetic patients have a higher risk of getting dermatomycosis. Dermatomycoses, although a common health problem amongst DM, is often misdiagnosed and consequently undertreated. Studies on the association between dermatomycosis and type 2 diabetes are lacking, especially in Indonesia. Therefore, the aim of this study was to determine the prevalence, etiology, and association of dermatomycosis with diabetic control of type 2 DM.

METHODS
A cross-sectional study was performed involving 87 subjects with type 2 DM. Demographic and clinical data, including age, sex, and blood glucose level, were collected. If a dermatomycosis lesion was found, a specimen would be taken for identification. Determination of serum glucose level was conducted using Roche c111 analyzer®. Statistical analysis was performed with the chi-square test and Kolmogorov-Smirnov two-independent sample test.

RESULTS
Seventeen (19.55%) subjects had dermatomycosis. The predominant age group affected was 51 - 60 years (42.4%). The number of clinically apparent dermatomycosis was greater in the uncontrolled than in the controlled blood sugar group, but the difference was statistically not significant ($p > 0.05$). The lesions were mostly found on the nails (74%) and the most common etiology was candida (50%) followed by dermatophyte (25%) and non-dermatophyte molds (25%).

CONCLUSION
Uncontrolled blood sugar tends to increase the risk of dermatomycosis in type 2 DM patients. Fungal skin infections are common in type-2 DM patients, especially in those with poor glycemic control.

Keywords: Candida, dermatomycosis, dermatophytes, diabetes mellitus type 2

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INTRODUCTION

Diabetes mellitus (DM) describes a group of metabolic disorders characterized by high blood glucose level.[1] In type 2 DM, this condition is caused by both insulin resistance and insulin secretion defect that affect glucose metabolism.[2] The International Diabetes Federation (IDF) estimated that there were 451 million people (age 18-99 years) with diabetes in the world in 2017. This number is predicted to increase to 693 million by 2045. Nearly 9.9% of the population aged 20-79 years is estimated to have DM in 2045.[1] The World Health Organization (WHO) predicted that there will be an increase from 8.43 million in 2000 to 21.3 million patients in 2030 in Indonesia.[2]

Dermatomycosis is a skin disease caused by fungi. It might appear under various clinical pictures, such as dermatophytosis, candidiasis, piedra, pytiriasis versicolor, tinea nigra, onychomycosis, and paronychia.[3] Dermatomycosis affects more than 20-25% of the world population.[3,4] These numbers continue to increase along with demographic and social economic changes, and the emerging of comorbid diseases and treatment options. The causative agents of dermatomycosis are dermatophytes, yeasts, and non-dermatophyte molds (NDM).[5,6]

People with type 2 DM might be more susceptible to dermatomycosis because of the state of their immune system.[5,7,8] One study showed that patients with type 2 DM tended to have a higher prevalence of dermatomycosis than patients with type 1 DM, which could be possibly explained by the delay in the disease detection and following glycemic control.[9] A chronic hyperglycemic condition affects cellular immunity and disrupts the function of phagocytes throughout the body, including the skin. This is one of the reasons why the skin becomes more easily colonized by the fungi.[10] Most of the dermatomycosis features found in people with type 2 DM are dermatophytosis (66%) and candidiasis (24.1%).[11] The agents causing the clinical manifestations are changing according to time and place.[3] And the fact that these skin infections are more prevalent in people with uncontrolled type 2 DM raises the need of attention to their presence.[12]

Specifically, onychomycosis is one of the most frequent form of dermatomycosis found in Asia.[13] This condition is more prevalent in people with DM, about 1.9 – 2.8 times higher than in normal people.[14] The most common agents causing onychomycosis are the dermatophytes, chiefly *Trichophyton rubrum*. [5] Ninety percent of onychomycosis in toenails is caused by dermatophytes, while onychomycosis in fingernails is caused by yeasts, especially *Candida albicans*.[15,16] In the last two decades, there has been an increasing trend of nondermatophyte molds (NDM). Some species such as *Scopulariopsis brevicaulis, Aspergillus spp., Fusarium spp., Scytalidium spp, Alternaria alternata,* and many more were found to be the cause of onychomycosis. [17-19] This may be the result of an increasing population with an immunocompromized state, peripheral vascular disorders, and other conditions.[20]

Data related to the epidemiology of dermatomycosis in diabetic patients in our country are scarce. This study was developed in order to find the prevalence and the most frequent causative agents of dermatomycosis in people with type 2 DM. Therefore, the aim of this study was to determine the prevalence, etiology, and association of dermatomycosis with the diabetic control of type 2 DM patients.

METHODS

Research design

The design of this study was cross-sectional. This study was conducted in the Internal Medicine wards and the Parasitology Laboratory, School of Medicine and Health Sciences, Atma Jaya Catholic University of Indonesia, from October 2016 - March 2017.

Study subjects

Patients with type 2 DM who underwent hospitalization were included in the study. The inclusion criterion was type 2 DM patients who were hospitalized in the Internal Medicine wards of Atma Jaya Hospital from October 2016 until January 2017. A total of 91 patients were hospitalized during that period. Of these, 4 patients were excluded due to insufficient data or because they had been admitted twice to the hospital, leaving 87 patients included in this study.

Data collecting

Demographic and clinical data such as age, sex, patient's diagnosis, blood glucose level and microbiological test results were collected. Age and sex were collected from the medical records. The diagnosis of type 2 DM was made by an internist, while the diagnosis of dermatomycosis was made by a dermatologist. The blood glucose level was collected from the medical records (collection of blood glucose samples was described below). Mycological tests were conducted in all patients suffering from dermatomycosis.

Laboratory analysis

A venous blood sample was collected from each patient. Serum was then separeated from other blood components. Determination of blood glucose level was conducted on serum using a Roche c111 analyzer®. The patient's blood glucose level was grouped into uncontrolled and uncontrollable blood glucose. Controlled blood glucose was defined by fasting blood glucose (FBG) <130 mg/dl and postprandial blood glucose (PBG) <180 mg/dl.[2]

Isolation and identification of isolates

Each patient underwent a thorough skin examination by a dermatologist to determine the presence of dermatomycosis clinical lesions. Dermatomycosis lesions were wiped with alcohol swabs then scraped with sterile glass slides. The samples from skin and nail scrapings were inoculated onto three types of media, i.e. Sabouraud Dextrose Agar (SDA) (Oxoid, Hampshire, England), SDA containing chloramphenicol (Indofarma, Jakarta, Indonesia), and SDA containing 0.4 mg/ml chloramphenicol and 0.5 mg/ml cycloheximide (Amresco, Ohio, USA).[21,22] If pytiriasis was suspected, the sample would be inoculated onto SDA containing chloramphenicol and overlaid with 2% olive oil. [23] Inoculated samples were incubated at 25°C - 30°C. The onychomycosis samples were inoculated at 16 points in those media. If no dermatophyte or candida was detected, the cause of dermatomycosis was determined from the most-growing colonies.[24] The cultures were examined daily until the growth of the fungus was observed and was declared negative if there was no growth within 4 weeks. If the isolates formed mold colonies, the samples were continued in slide culture with SDA. But, if the isolates formed yeast colonies, the samples were continued in slide culture with rice cream and culture on Hi-Chrom Agar (HiMedia Laboratories, Mumbai, India) for identification.[22]

Statistical analysis

The statistical tests used were chi-square and Kolmogorov-Smirnov 2-independent sample test, to analyze the relationship between several variables, such as gender, age, blood glucose level, and dermatomycosis case. The software used was SPSS for Windows version 17.

Ethical clearance

This study has obtained ethical approval from the Institute of Ethics Studies of Atma Jaya and has received permission from Atma Jaya Hospital. The number of ethical clearance was 01/02/KEP-FKUAJ-2016.

RESULTS

Of the 87 diabetic patients, 50 (57.5%) were female and the predominant age group affected was 51 - 60 years (42.4%) (Table 1). From the clinical examination, 17 (19.55%)

Table 1. Distribution of features characteristic of research subjects (n=87)

Characteristic	n (%)
Sex	
Male	37 (42.5)
Female	50 (57.5)
Age (years)	57.93 ± 9.14
≤40	4 (5)
41 - 50	15 (17.1)
51 - 60	37 (42.4)
>60	31 (35.5)
Dermatomycosis	
Yes	17 (19.55)
No	70 (80.05)
Type of dermatomycosis*	
Onychomycosis	13 (72.22)
Tinea	2 (11.11)
Candidiasis	3 (16.67)
Blood glucose (mg/dL)	
Fasting	169.59 ± 69.66
Controlled	103.63 ± 11.5
Uncontrolled	184.45 ± 68.66
2 h-Postprandial	217.84 ± 104.37
Controlled	127.94 ± 24.99
Uncontrolled	238.09 ± 104.81

*Based on clinical diagnosis by dermatologist (1 patient could have more than 1 diagnosis)

patients had dermatomycosis, and no significant difference between dermatomycosis and sex or age (Table 2). The number of clinical dermatomycosis was greater in uncontrolled FBG or PBG than in controlled FBG or PBG, but the difference was statistically not significant (p=0.394 and p=0.658 respectively) (Table 2).

Of the body sites affected with dermatomycosis 74% were nails and out of all dermatomycosis cases 50% were due to candida. *Candida glabrata* was the most commonly found candida species (40%) and the most common dermatophyte was *Trichophyton rubrum* (75%), followed by *Trichophyton mentagrophytes* (25%). Other fungi that have been isolated were NDM and *Rhodotorulla glutinis*. The NDMs found were aspergillus, *Onychocola canadensis*, *Neoscytalidium dimidiatum*, and geotrichum.

DISCUSSION

This study showed that the prevalence of dermatomycosis in females was higher than in males, but the difference was statistically not significant. Other studies showed that men are more likely have dermatomycosis than women, but the difference was not statistically confirmed.[8,9,25] Dermatomycosis is associated with the physical activities and habits of the patient, such as water-related work, and physical activities that cause injuries.[12,25,26]

The hyperglycemic state disrupts skin homeostasis by inhibiting keratinocyte proliferation or migration, protein biosynthesis, inducing apoptosis, reducing nitric oxide synthesis, disturbing phagocytosis and cell

Table 2. The relationship between dermatomycoses and sex, age, and blood glucose control

Variables	Dermatomycoses		p value
	Yes	No	
Sex			
Male	6 (16.2%)	31 (83.8%)	0.472*
Female	11 (22%)	39 (78%)	
Age group (years)			
≤40	0 (0%)	4 (100%)	1.000#
41–50	3 (20%)	12 (80%)	
51–60	9 (24.3%)	28 (75.7%)	
>60	5 (16.1%)	26 (83.9%)	
FBG			
Uncontrolled	13 (22%)	46 (78%)	0.394*
Controlled	4 (14.3%)	24 (85.7%)	
PBG			
Uncontrolled	10 (21.3%)	37 (78.7%)	0.658*
Controlled	7 (17.5%)	33 (82.5%)	

*: Chi-square test; #: Kolmogorov-Smirnov 2-independent sample test; FBG: fasting blood glucose; PBG: 2-h postprandial blood glucose

chemotaxis. These conditions promote skin disorders in diabetes, including skin fungal infection.[27]

The results of our study showed that the prevalence of dermatomycosis tends to be higher in uncontrolled diabetic patients than in controlled ones. This result is in concordance with Sugandhi et al.[28] in that poor glycemic control was significantly associated with fungal infection. Type 2 diabetes was previously known as predisposing factor for fungal infection especially *Candida* infection and dermatophytosis of the foot and nail.[7,9,29]

Akkus et al.[12] stated that tinea pedis and onychomycosis were more frequent in uncontrolled diabetic patients and patients with vascular disturbance. Tzar et al.[30] also found that the most frequent fungal infection is onychomycosis. Uncontrolled blood glucose level is also associated with onychomycosis.[7] The result of the present study is in concordance with other previous studies, in that the most frequent dermatomycosis was onychomycosis. This study found that candida was the most common cause of dermatomycosis, followed by dermatophytes, NDM, and *R. glutinis.* The high prevalence of candida infection was supported by many studies stating that the most frequent etiology of dermatomycosis in DM was candida infection, followed by dermatophytes, especially in nails and their surroundings.[31,32] Candida is part of the normal flora in humans that is a potential opportunistic pathogen. In the diabetic condition, there are an increased blood glucose level and an impaired immune system. The high blood glucose level provides the optimal condition for fungal growth. The impaired immune system results in the incapability of the host immune system to counter candida in cutaneous invasion.[32] Different results were obtained by Nenoff et al.[7] who found that the most common etiology of dermatomycosis was dermatophytes, rather than candida.

The most common dermatophyte found in this study was *T. rubrum,* followed by *T. mentagrophytes*. This result is in concordance with previous knowledge that dermatophytosis is commonly caused by *T. rubrum* and *T. mentagrophytes*.[7] Studies in Asian countries such as India and Japan, as reviewed by Hayette et al.,[5] also confirmed that these species are the main agents causing dermatophytosis. Parada et al.[9] also found that *T. rubrum* and *T. mentagrophytes* were the cause of dermatomycosis in the lower limb of patients with type 2 diabetes. Reddy et al.[25] stated that the high incidence of *T. rubrum* is related to its ability to form colonies in hard keratin structures. It is also known that *T. rubrum* more commonly affects people with predisposing factors such as DM.[7]

Of the 30% sample in this study it was found that the etiological agents were non-dermatophyte and non-candida fungi, such as *Aspergillus*, *R. glutinis*, *O. canadensis*, *N. dimidiatum*, and *Geotrichum*, the most common being *Aspergillus*. Besides candida and dermatophytes, the other fungi have also been known as the causative agents of onychomycosis, such as *Scopulariopsis brevicaulis, Aspergillus spp., Fusarium spp., Scytalidium spp, Alternaria alternata,* and many more.[17-19] Nondermatophyte molds may invade nails damaged by occupational trauma, such as in young persons, immunocompromized individuals, those with impaired peripheral circulation, and those with peripheral neuropathy.[20] However, NDM may also present as contaminants that grow saprophytically in nails. To diagnose NDM as the etiology of onychomycosis, is challenging.

There are several methods that may be used to decide NDM as the etiology of onychomycosis cases. In this study, samples have been cultured on 16 spots in media. If candida or dermatophytes appeared, they would be decided as the etiology of onychomycosis. But, if they did not, the etiology would have been decided from the most populous colony of fungi that grew in the media.[23] Gupta et al.[24] suggested 6 criteria for diagnosing NDM as the etiology of onychomycosis cases accurately:

detecting NDM by direct microscopic examination from clinical samples with potassium hydroxide (KOH), positive culture of NDM, re-positive culture of NDM (at different points in time), the density of colony, absence of dermatophytes, and histologic examination. Minimally 3 of those criteria have to be obtained. It is important to bear in mind some limitations of this study. First, the true frequency of onychomycosis in the group of patients might have been underestimated due to negative cultures for fungi. Second, the cross-sectional design of this study prevents the finding of the true causal relationship between dermatomycosis and poor blood glucose control.

Since dermatomycosis is common in DM patients, the management of type 2 DM should also address this problem to improve the patient's quality of life. Future research studies with similar objectives should be designed as cohort studies with larger sample sizes to find a more precise causal relationship between dermatomycosis and diabetic control.

CONCLUSIONS

Uncontrolled blood sugar tends to increase dermatomycosis in patients with type 2 diabetes mellitus. The most common cases of dermatomycosis are the onychomycoses and the most common etiology is candida.

CONFLICT OF INTEREST

The authors declare they have no conflict of interest.

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CONTRIBUTORS

SSS contributed to conceiving and presenting the research idea, conducting laboratory work, conducting statistical analysis, constructing article. MH contributed to collecting research data, constructing article. MW contributed to collecting research data, conducting laboratory work, conducting statistical analysis, constructing article. P contributed to collecting research data. HY contributed to finding research grant, conducting statistical analysis, constructing article. All authors have read and approved the final manuscript.

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