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Prevalence and factors associated with cutaneous manifestations of type 2 diabetes mellitus

ABSTRACT

Background. Type 2 diabetes mellitus (T2DM) is known to cause multiple systemic manifestations. However, there are limited studies describing cutaneous manifestation among T2DM in Malaysia. The objective of this study was to determine the prevalence of cutaneous manifestation among T2DM patients, types of lesions and its associated factors.

Methods. A cross-sectional study was conducted among 271 T2DM patients at a primary care clinic in Kuala Lumpur.

Results. More than one third (63.5%) of patients were found to have cutaneous manifestations of T2DM. The most common manifestation was infections (34.7%) followed by Skin Diseases with Weak to Strong Association with Diabetes (SDWSAD) (31.7%), Skin Manifestation of Diabetic Complication (SMDC) (2.2%) and others cutaneous lesions (22.1%). Among the infections, onychomycosis was the commonest type of infection (27.7%) while diabetic dermopathy was the commonest lesion of SDWSAD (29.7%). Males had almost two times the odds of developing cutaneous manifestations of T2DM, compared to females (adjusted odds ratio [AOR]: 1.871, 95% CI: 1.108–3.160; P = 0.019). There was no association between glycemic control and cutaneous manifestations. However, males and those with T2DM duration of five years and more had 2.6 times the odds of developing SDWSAD (AOR: 2.646, 95% CI: 1.506–4.648 P = 0.001) and (AOR: 2.635, 95% CI: 1.107–6.268, P = 0.028) respectively. Those with diabetic neuropathy and peripheral vascular disease (PVD) had very high odds of developing SMDC such as diabetic foot and trophic ulcers (AOR: 23.259, 95% CI: 1.191–454.2, P = 0.038) and (AOR: 102.36, 95% CI: 4.013–2610, P = 0.005), respectively.

Conclusion. The knowledge of these cutaneous manifestations increases physician's awareness and prompts early screening to reduce morbidity improve quality of life. (Clin Diabetol 2020; 9; 6: 461–468)

Key word: diabetes mellitus, skin manifestations, glycated hemoglobin A, prevalence

Introduction

South-East Asia accounts for more than 60% of the world's diabetes population [1]. The rapid rise in type 2 diabetes mellitus (T2DM) prevalence in Malaysia is alarming with 70 to 80% of patients having poor glycemic control [2]. Cutaneous manifestations of diabetes mellitus appear at disease onset, after the disease is established or precede diabetes by many years. A cutaneous condition is defined as any medical condition that affects the system enclosing the body, including the skin, hair, nails, and related muscle and glands [3]. Cutaneous disorders due to T2DM are attributed to hyperglycemia which affects skin homeostasis resulting in altered keratinocytes metabolism and collagen properties [4, 5]. Relative insulin deficiency in T2DM causes poor growth and differentiation of keratinocyte [4, 5]. Certain conditions such as skin tags and acanthosis nigricans are linked to hyperinsulinemia in the prediabetic state while bullous diabeticorum, diabetic dermopathy and scleroderma are more often see in long stand-

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ing T2DM [6]. Microvascular complications, impaired wound healing and other undetermined mechanisms further contribute to cutaneous disease [7].

Prevalence of dermatological disorders due to T2DM ranges from 36% to as high as 88.3% [8, 9]. Factors associated with cutaneous manifestations are poor glycemic control (HbA_{1c} > 7%) [10, 11] and duration of diabetes [8]. Longer disease duration have higher incidence of diabetic dermopathy [8]. Profiling characteristics of T2DM and cutaneous manifestations may help in early diagnosis of diabetes, used as a surrogate marker for poor glycemic control and microvascular complications in other organs. Hence the aim of this study is to determine the prevalence of cutaneous manifestation among patients with T2DM and to determine its associated factors.

Methods

A cross-sectional study was performed between June and September 2019 at the primary care clinic of a university in Kuala Lumpur. Sample size of 246 was calculated using Kish formula, 80% was taken as the highest prevalence cutaneous manifestation of T2DM [8] with 95% confidence interval and 5% absolute precision. The final sample size was 271 as 10% was added to overcome possible incomplete data. Participants were selected using systematic random sampling (sampling interval of 2) from the list of T2DM patients who registered for consultation. Type 1 diabetes mellitus (T1DM), pregnancy and patients with dermatoses due to physical factors such as burns, and trauma were excluded. Written consent was obtained. A thorough physical examination from head to toe including genitalia was performed to evaluate the cutaneous manifestations.

A data collection form was designed to record the intended data, based on a literature search and expert opinion. Section A consists of socio-demographic information such as age, gender, ethnicity and clinical profile such as duration of diabetes, diabetic complication (neuropathy, nephropathy, retinopathy, and peripheral vascular disease), body mass index (BMI) and HbA_{1c} level. Information on HbA_{1c}, diabetic retinopathy, nephropathy and lipid levels was extracted from participant's electronic database. For the purpose of this study, HbA_{1c} level of > 6.5% was considered as poor glycemic control while ≤ 6.5% was considered as a good glycemic control [12]. Peripheral neuropathy was screened using 10-g monofilament, vibration sense using a 128-Hz tuning fork and ankle reflex [12]. Peripheral vascular disease (PVD) was objectively screened based on examination of distal pulses, capillary return time and skin color.

Section B recorded cutaneous manifestation of T2DM that was diagnosed on the consultation day. A list of skin manifestations associated with T2DM was derived from literature search and expert panel input [13, 14]. Cutaneous manifestations of diabetes mellitus were classified into 4 types which are skin diseases with weak to strong associations with diabetes (SDWSAD), skin infections (SI), skin manifestations due to diabetes complication (SMDC) and skin reaction to diabetic treatment [13, 14]. Skin reaction to diabetic treatment was excluded as the objective of this study was to determine the cutaneous manifestations purely due to T2DM and not due to effect of treatment or other secondary causes. Hence lesions which fulfilled these three categories were included:

— Skin Diseases with Weak to Strong Associations with Diabetes (SDWSAD): diabetic dermopathy, acanthosis nigricans, yellow skin, eruptive xanthoma, oral leukoplakia, lichen planus, necrobiosis lipoidica, granuloma annulare and diabetic bullae. Diabetic dermopathy is described as asymptomatic well circumscribed pinkish or brownish atrophic (depressed) lesion on shin, thigh, forearm, scalp or trunk. Lesion may arise in crops gradually resolve, reappear and sometimes ulcerate;
— Skin infections (SI): impetigo, ecthyma, cellulitis, folliculitis, furunculosis, carbuncles, erysipelas, viral warts, tinea capitis, tinea pedis, tinea corporis, tinea cruris, tinea versicolor, tinea manuum, paronychia, onychomycosis, candidiasis. Infections of both dermal and mucosa surfaces were taken into consideration encompassing all types of bacterial and viral infections. All four clinical types of onychomycosis i.e. total dystrophic, white superficial, candida, proximal and distal subungual onychomycosis were all included under the broad term of onychomycosis;
— Skin manifestation of diabetic complication (SMDC): microangiopathy, macroangiopathy, neuropathy e.g. diabetic foot and trophic ulcers.

Patients presenting with of any of the cutaneous disorders related to T2DM was labelled as having cutaneous manifestations of T2DM. Other cutaneous lesions were recorded if found to be present. The primary researcher received hands-on training from a qualified dermatologist and a family medicine specialist with qualification in family practice dermatology prior to the commencement of this study. Clinical diagnosis was made by the primary investigator. Inter-rater reliability for the clinical diagnosis between the 3 investigators was performed using images of the lesions and measured using Cohen's Kappa to ensure the reliability of the diagnosis.

The data collected was analyzed using SPSS (version 25). Descriptive analysis was performed using frequencies and percentage. Simple and multiple logistic regression analyses were used to determine the association between type of cutaneous manifestation with sociodemographic characteristics and clinical profile. Cohen's Kappa was used to determine the agreement between the researchers' diagnoses of the skin condition. This research was approved by the Research and Ethics Committee of University Kebangsaan Malaysia Medical Centre (FF-2018-088) and registered with the National Medical Research Registry (NMRR-17-2555-38622).

Results

A total of 271 patients participated in this study. The median age was 66 (SD 13) years, ranging from 28 to 91 years. Almost half of the participants belonged to the Malay ethnic group 131 (48.3%) and 128 (47.2%) were obese. Female to male ration was almost equal (1:1.08). A large majority of participants 223 (82.3%) had T2DM for more than 5 years. The median HbA1c was 7.7 (2.4) and most 211 (77.9%) had poor glucose control (HbA1c >6.5). About half of them 142 (52.4%) had diabetes complication with nephropathy being the commonest 24 (27.3%) (Table 1).

The interrater agreement between the three investigators on the clinical diagnosis of the cutaneous lesions was good with a Cohen's Kappa value 0.91 (95% confidence interval). More than half of the participants (58.2%) presented with one type of lesion while the rest had two or more types of lesions. The prevalence of cutaneous disorders related to T2DM was 172 (63.5%) with infections being the commonest presentation 94 (34.7%). Fungal infection was commonest (39.9%) (Fig. 1A–E) presenting as onychomycosis (27.7%) (Fig. 1A–C). The most common SDWSADs were diabetic dermopathy (29.9%) (Fig. 1F) and necrobiosis lipoidica (2.6%). Only 0.4% had acanthosis nigricans (Table 2). Other cutaneous lesions observed were eczema 39 (14.4%) (Fig. 1C, G), xerosis 12 (4.4%) (Fig. 1A, H) and callus 5 (1.8%) (Fig. 1I).

Multivariate analysis using independent variables with P values of less than 0.25 and variables considered clinically important showed significant association between cutaneous manifestation and gender. Males were almost two times more likely to have cutaneous manifestation (1.89 [95%CI; 1.12–3.20], P = 0.02) compared to females (Table 3). Males (2.55 [95%CI: 1.46–4.43]) and those with duration of T2DM of more than 5 years (2.42 [95%CI: 1.03–5.70]) have 2 times the odds of having SDWSAD (Table 4).

Table 1. Sociodemographic and clinical characteristics of the study participants

Variables	n (%)	Median (IQR)
Age (years)		66 (13.0)
Gender		
Male	141 (52)	
Female	130 (48)	
Ethnicity		
Malay	131 (48.3)	
Chinese	116 (42.8)	
Indian	24 (8.9)	
Duration of DM in years		10 (10)
BMI [kg/m²]		27 (6)
HBA_{1c} (%)		7.7 (2.4)
LDL level [mmol/L]		2.4 (1.1)
Duration of DM		
< 5 years	48 (17.7)	
≥ 5 years	223 (82.3)	
Glycemic control		
Good control (HbA_{1c} ≤ 6.5%)	60 (22.1)	
Poor control (HbA_{1c} > 6.5%)	211 (77.9)	
BMI		
Underweight/normal (BMI < 22.9)	40 (14.8)	
Overweight (BMI 23–27.4)	103 (38.0)	
Obese (BMI ≥ 27.5)	128 (47.2)	
Diabetic complications		
Yes	142 (52.4)	
No	129 (47.6)	
Type of diabetic complications		
Retinopathy	71 (26.2)	
Neuropathy	47 (17.3)	
Nephropathy	24 (27.3)	
Peripheral vascular disease	6 (2.2)	

Regression analysis demonstrated significant associations between skin manifestations with SMDC such as diabetic neuropathy (P = 0.038) and peripheral vascular disease (P = 0.005). The presence of diabetic neuropathy has 23 times the odds of having SMDC (95% CI: 1.191–454.20, P = 0.038), while peripheral vascular diseases (PVD) 102 times the odds of having SMDC (95% CI: 4.013–2610, P = 0.005) (Table 5). However, these findings need to be interpreted cautiously in view of small number of cases with SMDC. There was no association between skin infection and other cutaneous lesions with the sociodemographic and clinical profile.

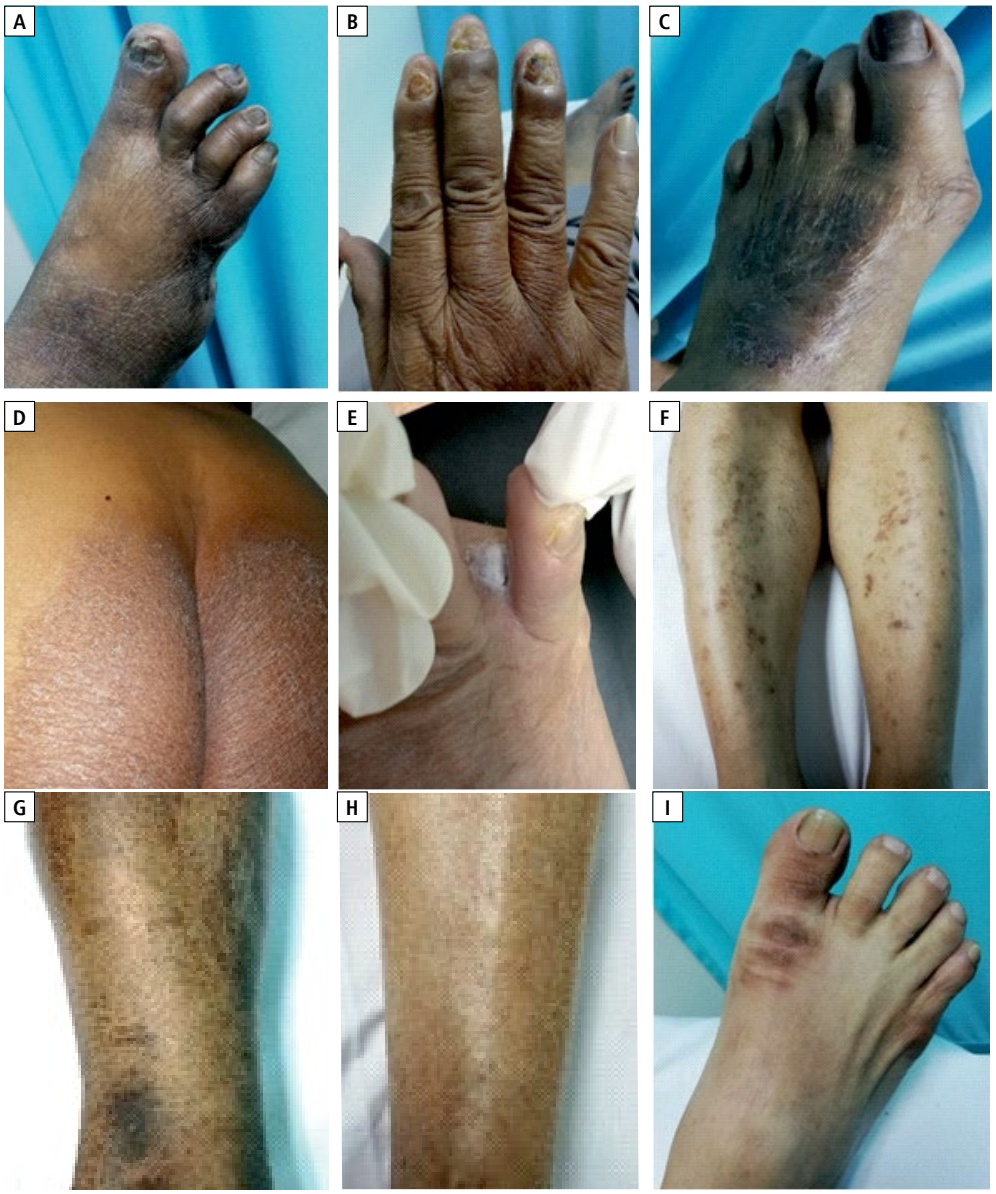

Figure 1. Cutaneous lesion in T2DM: **A** — amputated little toe with onychomycosis and xerosis; **B** — onychomycosis with chronic paronychia; **C** — onychomycosis of the big toe due to Aspergillus niger with eczema craquele over the dorsum of the foot; **D** — extensive tinea cruris over the gluteal regions extending to the upper thighs; **E** — maceration of the interdigital space due to fungal infection; **F** — diabetic dermopathy characterized by multiple discrete, hyperpigmented and atrophic macules and patches with thin scales; **G** — ichthyosis over the lower limb; **H** — xerosis with generalized thin scales over the lower limb; **I** — callosities over the first metatarsophalangeal and proximal interphalangeal joints

Discussion

Skin manifestations of T2DM vary in different parts of the world. An outline of common conditions and their etiology would help physicians manage T2DM patients in a holistic manner. We found a high prevalence of cutaneous manifestation of T2DM. The prevalence was similar to that in India, Pakistan and Hong Kong which is between 58 to 67% [10, 15, 16]. Skin infection was the most common cutaneous manifestation of T2DM in our patients, followed by SDWSAD with diabetic dermopathy. Infections and diabetic dermopathy are common cutaneous disorders associated with diabetes [8, 15, 16]. Diabetic foot and trophic ulcer were the most common manifestations of SMDC. Skin infection is common among T2DM patients due to lower immunity and defect in carbohydrate metabolism compared to the normal population [17]. Fungal infection presenting with onychomycosis was the most common pathogen among the infective conditions in our patients. The hot and humid local climate environment is favorable for fungal growth. Fungal infection alters skin barrier and predispose to complications such

Table 2. Prevalence and types of cutaneous manifestations

Variables	n (%)
Presence of cutaneous disorders related to T2DM	
Yes	172 (63.5)
No	99 (36.5)
Types of cutaneous manifestation	
Infections (fungal, bacterial or viral)	94 (34.7)
Skin diseases with weak to strong association with diabetes (SDWSAD)	86 (31.7)
Other cutaneous lesions	60 (22.1)
Skin Manifestation of Diabetic Complications (SMDC)	6 (2.2)
Types of skin diseases with weak to strong association with diabetes (SDWSAD)	
Diabetic dermopathy	81 (29.9)
Necrobiosis lipoidica	7 (2.6)
Acanthosis nigricans	1 (0.4)
Organisms causing skin infection	
Fungal	107 (39.6)
Bacterial	13 (4.7)
Viral	6 (2.2)
Types of infections	
Onychomycosis	75 (27.7)
Paronychia	10 (3.7)
Tinea pedis	8 (3)
Viral wart	6 (2.2)
Candidiasis	5 (1.8)
Tinea corporis	5 (1.8)
Folliculitis	5 (1.8)
Tinea cruris	3 (1.1)
Furunculosis	3 (1.1)
Cellulitis	2 (0.7)
Ecthyma	2 (0.7)
Impetigo	1 (0.4)
Tinea manuum	1 (0.4)
Skin manifestation of diabetic complication	
Diabetic foot	6 (2.2)
Trophic ulcers	1 (0.4)
Other cutaneous lesions	
Eczema*	39 (14.4)
Xerosis	12 (4.4)
Callus	5 (1.8)
Skin Tag	5 (1.8)
Corn	3 (1.1)
Lipoma	2 (0.7)
Psoriasis	2 (0.7)
Xanthelasma	1 (0.4)
Tophi	(0.4)

*The term eczema here is inclusive of both endogenous and exogenous types of eczema

as cellulitis. Fungal infections should be identified early and treated.

We did not determine the onset of lesions in relation to diabetes duration. Skin manifestation like acanthosis nigricans precede diabetes, screening for diabetes at regular intervals for early diagnosis would be beneficial [6]. Although acanthosis nigricans is popularly described as a common association with T2DM, only 0.4 % of our study participants had this manifestation. Prevalence acanthosis nigricans ranged from 1.88% to 4% [8, 18].

We identified the male gender and duration of T2DM of ≥ 5 years as risk factors for SDWSA. Diabetic dermopathy was significantly more frequent in males and those with longer duration of DM [19, 20]. Skin lesions were also more common among diabetic men [16]. Skin diseases affect men and women differently and this is attributed differences in skin thickness, pH, effect of sex hormone and immune system [21]. Our study did not show an association between BMI and risk for cutaneous manifestations of T2DM or SDWSA. This may be attributed to the cross-sectional nature of this study where at the point of data collection, cutaneous signs were not elicited as it may have resolved after treatment or yet to manifest in the future, which may be identified in a longitudinal study.

Although an association was expected between the presence of cutaneous manifestations of T2DM and poor glycemic control, this was not evident in our study. There are inconsistent observations on the association between cutaneous manifestations of T2DM with glycemic control with some showing positive association while some did not show any association [22–24]. The cause for cutaneous manifestations of T2DM is multifactorial and not purely due to hyperglycemia. The lack of standardization in the cut off values for good and poor glycemic control based on HbA_{1c} in earlier studies makes the comparison of outcome difficult. HbA_{1c} of more than 6.5% is considered as poor control while some consider 7% as poor control. HbA_{1c} test is performed 6 monthly for our local diabetic population. An average HbA_{1c} level over a longer duration would give a better evaluation of control compared to a single reading to assess the association.

As expected, patients with diabetic neuropathy and PVD have very high odds of having SMDC, such as diabetic foot and trophic ulcers in our study. These associations are well described [25, 26]. Peripheral vascular disease and diabetic neuropathy are indeed risks for developing diabetic foot and trophic ulcers due to poor sensation and blood circulation of the lower limbs. Diabetic foot ulcer is a strong predictor for major limb amputation [27]. Regular foot assess-

Table 3. Risk factors for cutaneous manifestation of T2DM

Variables	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Gender				
Male	1.97 (1.19–3.27)	**0.01***	1.89 (1.12–3.20)	**0.02***
Female	(1)		(1)	
Ethnicity				
Malay	(1)		(1)	
Non-Malay	0.64 (0.39–1.06)	0.08	0.65 (0.39–1.10	0.10
BMI				
Underweight/normal	(1)		(1)	
Overweight	1.07 (0.51–2.25)	0.85	0.86 (0.40–1.87)	0.71
Obese	1.63 (0.78–3.37)	0.19	1.352 (0.63–2.90)	0.44
Duration of DM				
< 5 years	(1)		(1)	
≥ 5 years	1.05 (0.55–2.01)	0.88	0.93 (0.47–1.85)	0.84
Glycemic control				
Good (HbA_{1c} ≤ 6.5%)	(1)		(1)	
Poor (HbA_{1c} > 6.5%)	1.21 (0.67–2.18)	0.53	1.09 (0.58–2.03)	0.79
Diabetic complication				
Yes	1.53 (0.93–2.51)	0.10	1.40 (0.82–2.38)	0.22
No	(1)		(1)	

*Indicate significant P < 0.05, (1) reference group, adjusted for gender, ethnicity, BMI group, duration of DM, glycemic control, nephropathy, retinopathy

Table 4. Risk factors for SDWSAD type of cutaneous manifestation of T2DM

Variables	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Gender				
Male	2.60 (1.53–4.42)	**0.00***	2.55 (1.46–4.43)	**0.00***
Female	(1)		(1)	
Ethnicity				
Malay	(1)		(1)	
Non-Malay	0.85 (0.51–1.41)	0.53	0.86 (0.49–1.48)	0.52
BMI				
Underweight/normal	(1)		(1)	
Overweight	1.68(0.74–3.82)	0.22	1.51(0.64–3.60)	0.35
Obese	1.32 (0.59–2.95)	0.51	1.14 (0.49–2.69)	0.76
Duration of DM				
< 5 years	(1)		(1)	
≥ 5 years	2.69 (1.20–6.03)	**0.02***	2.42 (1.03–5.70)	**0.04***
Glycemic control				
Good (HbA_{1c} ≤ 6.5%)	(1)		(1)	
Poor (HbA_{1c} > 6.5%)	2.16 (1.08–4.32)	**0.03***	1.97 (0.95–4.10)	0.07
Diabetic Complications				
Yes	1.39 (0.83–2.32)	0.21	0.94 (0.53–1.65)	0.83
No	(1)		(1)	

*Indicate P < 0.05, (1) — reference group, adjusted for gender, ethnicity, BMI, diabetes duration, glycemic control, DM complications

ment, foot self-care advice and training to prevent the development of SMDC are important in patients with T2DM complicated by with peripheral neuropathy and peripheral vascular disease. There was no association between diabetic dermopathy and retinopathy among the participants of this study although diabetic der-

Table 5. Risk factors for SMDC type of cutaneous manifestation of T2DM

Variables	Crude OR (95% CI)	P value	Adjusted OR (95% CI)	P value
Gender				
Male	0.54 (0.10–2.97)	0.48	0.19 (0.02–2.26)	0.19
Female	(1)		(1)	
BMI				
Underweight/normal	(1)		(1)	
Overweight/obesity	0.34 (0.06–1.89)	0.22	0.39 (0.04–3.74)	0.41
Duration of DM				
< 5 years	(1)		(1)	
≥ 5 years	1.08 (0.12–9.44)	0.10	0.13 (0.01–3.77)	0.24
Glycemic control				
Good (HbA_{1c} ≤ 6.5%)	(1)		(1)	
Poor (HbA_{1c} > 6.5%)	1.43 (0.16–12.50)	0.95	1.58 (0.11–23.63)	0.74
Neuropathy				
Yes	10.33 (1.83–58.15)	**0.01***	23.26 (1.19–454.2)	**0.04***
No	(1)		(1)	
Nephropathy				
Yes	2.73 (0.54–13.85)	0.23	1.89 (0.24–14.78)	0.55
No	(1)		(1)	
Retinopathy				
Yes	5.91 (1.06–33)	**0.04***	3.07 (0.34–27.72)	0.32
No	(1)		(1)	
Peripheral vascular disease				
Yes	32 (4.57–23)	**0.00***	102.36 (4.01–261)	**0.01***
No	(1)		(1)	

*Indicate P < 0.05, (1) — reference group, adjusted for gender, DMI, duration of DM, glycemic control, diabetic neuropathy, nephropathy, retinopathy, and peripheral vascular disease

mopathy is considered as a diabetic microangiopathy. Half of the patients with diabetic dermopathy were found to have retinopathy [28]. A prospective cohort study would yield more information on the association between diabetic dermopathy and retinopathy. Limitation of this study is that peripheral vascular disease was evaluated clinically and not confirmed using arterial-brachial pressure index (ABSI) or Doppler ultrasound which gives a more objective evaluation.

Conclusions

The prevalence of cutaneous manifestation among T2DM in this study was high, affecting almost two thirds of the participants. The commonest cutaneous manifestation was infection and diabetic dermopathy. Fungus was the most common cause for infection presenting as onychomycosis. Risk factors for cutaneous manifestation of T2DM are males and duration of diabetes of 5 years and more. Diabetic neuropathy and peripheral vascular disease are risks for SMDC diabetic foot and trophic ulcers. Our study did not demonstrate an association between glycemic control and cutaneous manifestations of T2DM. A prospective study looking at glycemic control over a longer duration would be useful to elicit the association. T2DM patients should be screened early for skin manifestations especially males, T2DM ≥ 5 years, those with diabetic neuropathy and peripheral vascular disease so that management can be instituted early to prevent complications.

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Conflict of interest

The authors have no competing interests to declare.

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