# The Correlation between Skin Lesions, Microalbuminuria and other Microvascular Complications in Type 2 Diabetic Patients

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## Abstract

**Background and Aims:** Patients with diabetes mellitus commonly suffer from a wide variety of cutaneous disorders. Clinical manifestations and complications of skin diseases are more common and severe in these patients. Some skin disorders are more prevalent in patients with microvascular complications. The aim of this study was to evaluate the correlation between skin lesions in type 2 diabetic patients and microvascular complications.

*Methods:* In this study, 1135 type-2 diabetic patients were included and examined by a dermatologist for diabetes mellitus related skin lesions, skin infections and cutaneous manifestations due to treatment. Smear, culture and biopsy of the lesions were done for definite diagnosis. Retinopathy, neuropathy and nephropathy were evaluated in all the patients.

**Results:** The mean age of study population was  $54\pm11$  years; 619 (55%) female and 516 (45%) male. Mean duration of disease was  $9\pm7$  years and HbA1c was  $7.8\pm1.6$ . Prevalence of skin lesions was 64% (95% CI: 61.2-66.8). Of all micro vascular complications, only neuropathy had a strong association with diabetes mellitus-related skin lesions with an odds ratio of 1.9 (95% CI: 1.5-2.5).

Only eight percent of the skin manifestations had developed in less than one year after diagnosis of diabetes mellitus. The prevalence of neuropathy and albuminuria was significantly higher in patients with tinea pedis. The prevalence of neuropathy was significantly higher in patients with facial erythema, pyoderma, tinea pedis, nail dermatophytosis, candidial paronychia and itching.

In patients with diabetic dermopathy and foot ulcer, the prevalence of retinopathy, neuropathy, albuminuria, mean age, duration of diabetes and percentage of insulin users were significantly higher than those without such lesions.

**Conclusions:** This study shows that skin lesions are common in patients with type-2 diabetes mellitus. Some of cutaneous manifestations are indicative of microvascular complications and patients with these skin manifestations should be evaluated for microvascular complications.

Keywords: Correlation, Skin Lesions, Type-2 Diabetes, Microvascular Complication

# Introduction

Diabetes mellitus (DM) is characterized by hyperglycemia resulting from secretion or function of Insulin. Type 2 of DM is the most common form (1). \*Correspondence: Amir Hoshang Ehsani, MD Razi hospital, Tehran University of Medical Sciences 10395-4763, Tehran- Iran Email: ehsanih@sina.tums.ac.ir Received: 20 Nov 2009 Revised: 2 Dec 2009 Accepted: 18 Dec 2009 This disease can affect any organ such as skin (2). Cutaneous manifestations of DM can be classified in four categories:

1) Skin manifestations related with DM:Necrobiosis lipoidica, Diabetic dermopathy, Diabetic bulla, Eruptive xanthoma, Perforating dermatoses, Acantosis Nigricans, Oral leukoplakia and Lichen planus

2 and 3) Infections: Bacterial and fungal

4) Skin manifestation due to diabetic complications: microangiopathy, macroangiopathy and neuropathy and skin Manifestations due to treatment of DM (3)

There is little information about the prevalence of skin lesions in patients with type 2 DM (4-7). In previous studies, a wide range of prevalence has been reported but number of evaluated patients was inadequate in most of these articles. None of them had considered the relationship of cutaneous manifestations with microvascular complications and other variables such as age, gender, HbA1c, duration of disease and type of treatment. This study was designed to assess dermatological manifestations in patients with type 2 DM and to determine the association between skin lesions and microvascular complications.

#### **Materials and Methods**

This was a cross-sectional study which was done between October and March in 2006 in Tehran, Iran. According to the prevalence of diabetic bulla (%5.6), which is one of the less common lesions in DM, the calculated sample size was 1135. The selection of type 2 diabetic patients was according to ADA criteria (8).

All the outpatients were consecutively enrolled through the Iran Diabetic Association and endocrine clinics affiliated to two Medical Universities in Tehran and were examined by a dermatologist to determine the presence of diabetes mellitus-related skin lesions, skin infections and skin lesions due to treatment. Other skin lesions were taken care only on the basis of patients' complaints.

Definite diagnosis of necrobiosis lipoidica, scleroedema, perforating dermatoses, granuloma annulare, xanthoma and diabetic bullae were made by skin biopsy. To confirm the cutaneous infections, skin smear and culture were taken. All patients were assessed for blood pressure, (twice after the subjects sit for 15 min), height (in a standing position without shoes, using tape meter with the shoulder in normal state), weight (while minimally dressed, without shoes, using digital scales and recorded to the nearest 100g), BMI (weight in kg divided by height in m2) and neurological examination (with Michigan neuropathy screening instrument while a Score above 2 indicated the presence of neuropathy) (9).

To assess retinopathy, all patients were referred to an ophthalmologist and the stage of eye involvement was determined, including PDR and NPDR. Ophthalmologic examination was done with indirect ophthalmoscopy with dilated pupils. To determine the prevalence of true albuminuria, we tried to remove other factors inducing transient albuminuria (UTI, severe hypertension, severe hyperglycemia, exercise and acute fever). If these factors could not be removed, patients were not assessed for albuminuria. The level of albumin, creatinine and albumin to creatinine ratio were measured in morning urine sample. Simultaneously, FBS and HbA1c were measured. Only the skin lesions with the duration of less than 3 months of the study time were accounted to find their association with HbA1c. All the information was registered in a questionnaire.

#### Laboratory Methods

All tests were done in a single laboratory; the tests were not repeated if the level of albuminuria and HbA1c were measured during the past year for albumin and last 3 months for HbA1C. Albumin to Creatinine ratio was measured with the unit of mg/gm by Turbitimer method, Bring Company. If it was above 30 mg/gm, it indicated the presence of

albuminuria. HbA1c was measured by the LPLC method.

In both mentioned methods interassay CV was 3% and intra assay CV was 2%.

#### **Statistics**

After coding, collected information in questionnaires was analyzed in computer software program SPSS-11. T-test was used to determine the difference between quantitative variables and results expressed as mean  $\pm$  standard deviation and chi-square test used for qualitative variables and results expressed as percentages. Logistic regression method was used to assess the role of different variables in inducing cutaneous lesions and in this model; dependent variable was diabetes mellitus-related skin lesions. P<0.05 was considered as significant.

#### Results

The average age of 1135 patients who attended in this study was  $54\pm11$  years old, 619 (55%) female and 516 (45%) male. Mean duration of disease was  $9\pm7$  years and mean HbAlc was  $7.8\pm1.6$ . Prevalence of skin lesions was 64%.

The prevalence of neuropathy, retinopathy and duration of DM in patients with skin lesions were higher than diabetic patients without them (Table 1).

**Table 1.** Basic characteristics of diabetic patients attending the study and comparison of these variables

 between patients with or without skin lesions

Variable	All patients	With skin lesion	Without skin lesion	P value
Age (year)	54±11	55±11 ¶	51±6	0.01
Gender				0.02
Female	619 (55)	353 (48)¶	266 (64)	
Male	516 (45)	370 (52)	146 (36)	
*duration of disease (year)	9±7	10±7¶	7±7	0.002
+family history of DM	827 (73)	535 (74)	292 (73)	-
BMI( Kg/m <sup>2</sup> )	27±4	28±3	27±3	-
±type of treatment				-
drugs	913 (82)	576 (81)	337 (84)	
Insulin	162 (14)	111 (15)	51 (12)	
Both	34 (3)	23 (3)	12 (3)	
HbA1c (percent)	7.8±1.6	7.8±1.6	7.7±1.7	-
Retinopathy	397 (35)	276 (38)¶	121 (29)	0.01
Neuropathy	643 (57)	462 (64)¶	181 (44)	0.001
Albuminuria	293 (27)	177 (26)	116 (24)	-
Total	1135	723 (64)**	412 (36)	-

\* Duration of disease: Time from diagnosis.

+ Family history: parents, siblings, and offspring.

± 21 patient did not use any medication.

¶ P<0.05 In comparison with patients without skin lesions except gender that is comparison between females and males with skin lesions.

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Duration of		Skin Lesions		
disease (years)	Diabetic Dermopathy	Acanthosis Nigricans	Total skin lesions	P value
<1	23 (6%) *†	146 (49%)	140 (8%)	0.001
1-5	74 (20%)	54 (18%)	438 (24%)	
5-10	105 (29%)	48 (16%)	595 (32%)	
10-15	72 (20%)	24 (8%)	341 (19%)	
>15	93 (25%)	28 (9%)	319 (17%)	
SUM.	367	300	1833	

#### Table 2. Presentation time of the two more common skin lesions according to duration of diabetes

\* The numbers in parenthesis show percent.

† P<0.05 in comparison with acanthosis nigricans during less than one year of diabet diagnosis.

**Table 3.** Retinopathy, neuropathy and albuminuria prevalence in diabetic related skin lesions and comparison between affected and unaffected patients

	Rethinopathy			Neuro	pathy		Albuminoria		
Skin Lesions	Affected patients	Unaffected patients	P value	Affected patients	Unaffected patients	P value	Affected patients	Unaffected patients	P value
Diabetic Dermopathy	183 (50)*†	214 (28)	0.04	273 (75) <sup>†</sup>	370 (49)	0.002	0.002	0.002	0.01
Acantosis nigricans	100 (33)	297 (35)	-	120 (40)	523 (62)	-	-	-	-
Diabetic foot	52 (67) <sup>†</sup>	345 (33)	0.02	70 (91)†	573 (54)	0.005	0.005	0.005	0.02
Granloma Annulare	14 (40)	383 (35)	-	19 (54)	624 (57)	-	-	-	-
Face Erythema	6	391 (35)	-	15 (83)†	628 (57)	0.01	0.01	0.01	-
Diabetic bulla	4	393 (35)	-	7	636 (56)	-	-	-	-
Perforating dermatosis	3	394 (35)	-	3	64 (57)	-	-	-	-
Scleroderma	3	393 (35)	-	3	640 (57)	-	-	-	-
Necrobiosis lypoidica	1	396 (25)	-	3	640 (57)	-	-	-	-
Xanthoma	1	396 (35)	-	1	642 (57)	-	-	-	-

\* The numbers in parentheses show percent.

+ p < 0.05 in comparison with unaffected patients.

Percent has not been written in cases with less than 10 patients.

- Albuminuria was not measured in one patient with necrobiosis lipoidica, three patients with granuloma annularis and 15 patients with diabetic foot ulceration.

International Journal of Nephrology & Urology, 2010;2(4):553-560

Only about 8% of lesions appeared during one year of DM diagnosis. In 49% of patients with acanthosis nigricans, the lesions appeared during first year of DM diagnosis in contrast with diabetic dermopathy which its incidence was 6% during first year of DM diagnosis (Table 2).

The prevalence of neuropathy and albuminuria

was significantly higher in patients with diabetic foot ulcer, dermopathy and tinea pedis. The prevalence of neuropathy was significantly higher in patients with facial erythema, pyoderma, tinea pedis, nail dermatophytosis, candidial paronychia and itching (Table 3, 4 and 5).

	Retin	opathy		Neur	opathy		Albur	ninuria	
Skin Lesions	Affected	Unaffected	P value	Affected	Unaffected	P value	Affected	Unaffected	P value
	patients	patients		patients	patients		patients	patients	
Tinea Pedis	71 (52)*†	326 (33)	0.04	98 (73) <sup>†</sup>	545 (55)	0.03	47 (36) *	264 (26)	0.02
Erythracema	53 (39)	344 (35)	ı	87 (64)	556 (56)	ı	36 (28)	257 (27)	·
Tinea versicolor	27 (21)	370 (37)	I	68 (52) <sup>†</sup>	575 (57)	0.04	9†	284 (28)	0.03
Candidial Paronychia	22 (32)	375 (36)	ı	70 (69)	573 (55)	0.04	21 (21)	272 (26)	
Onychomycosis	39 (43)	358 (34)	ı	66 (73) <sup>†</sup>	571 (55)	0.03	30 (33)	263 (25)	ı
pyoderma	23 (30)	374 (35)	ı	52 (68) <sup>†</sup>	591 (56)	0.03	17 (24)	276 (28)	ı
Candidial Intertrigo	37 (61) *	360 (34)	0.03	42 (69)	601 (56)	ı	11 (22)	282 (28)	ı
*The numbers in par $\dot{\tau} p < 0.05$ in compal Percent has not been	entheses sh rison with 1 written in (	iow percent. unaffected pi cases with le	atients. sss than 1	0 patients.	;				
- In seven patients	with eryun measured.	acema, eign.	t patient	s with tine	a pedis and	ten pau	ents with	candidial II	itertrigo,

	Rethi	nopathy		Neuropathy			Albu	ninuria	
Skin Lesions	Affected	Unaffected	P value	Affected	Unaffected	P value	Affected	Unaffected	P value
	patients	patients		patients	patients		patients	patients	
Pruritus	31 (32)*	366 (35)	0.04	68 (70) <sup>†</sup>	575 (56)	0.001	19 (20)†	274 (28)	0.04
Pigmented									
purpuric	15 (30)	382 (35)	-	25 (50)	618 (58)	-	10 (20)	283 (26)	-
dermatosis									
<b>Contact Dermatitis</b>	8 <sup>†</sup>	389 (36)	0.04	30 (63)†	613 (57)	0.04	4†	289 (28)	0.04
Lichen Planus	8	389 (36)	-	14 (61)	629 (57)	-	4	289 (28)	-
Vitiligo	8	359 (32)	-	$4^{\dagger}$	639 (57)	0.04	$2^{\dagger}$	29 (26)	0.03
Psoriasis	$1^{\dagger}$	396 (36)	0.04	13 (65)	630 (56)	-	2 (10)*	291 (26)	0.04
Atopic Dermatitis	-	397 (35)	-	2	641 (57)	-	1	292 (27)	-

Table 5. Retinopathy, neuropathy and albuminuria pr	evalence in miscellaneous skin disorders and
comparison between affected and unaffected patien	ts

\*The numbers in parentheses show percent.

+ p < 0.05 in comparison with unaffected patients.

Percent has not been written in cases with less than 10 patients.

- Albuminuria wasn't measured in 7 patients with vitiligo, 5 patients with proritus, 4 patients with lichen planus and 2 patients with contact dermatitis.

Lipohypertrophy and lipoatrophy was seen in 4 (0.3%) and 2 (0.1%) respectively and all of them had neuropathy, retinopathy and albuminuria.

Logistic regression was used to assess the effect of mean age, HbA1c, duration of disease, sex, BMI, type of treatment, neuropathy, retinopathy and albuminuiria in diabetes mellitus-related skin lesions. Age, duration of disease and neuropathy were entered in the model. Only neuropathy with odds ratio of 1.9 (CI 95%: 1.5-2.5) had a strong association with diabetes mellitus-related skin lesions development.

## Discussion

This study demonstrated that two third of type 2 diabetic patients had skin lesions. Retinopathy and neuropathy were more prevalent in patients with skin lesions. Age, duration of disease and neuropathy were independent variables in association with diabetes mellitus-related skin lesions. By using logistic regression method, odds ratio of these variables were 1.01 (1.01-1.03), 1.04 (1.01-1.06) and 1.9 (1.5-2.5) respectively.

Mean age, level of HbA1c, duration of disease and presence of neuropathy, retinopathy and albuminuria were significantly higher in patients with dermopathy. These findings are compatible with previous articles (10, 11). For example Shemer et al reported the prevalence of diabetic dermopathy in 63%, 62%, and 63% of diabetic patients who also had retinopathy, neuropathy and nephropathy respectively. According to these results, it seems that evaluation of patients with dermopathy for microvascular complications is logical and if it is necessary, therapeutic strategies must be undertaken as soon as possible.

Neuropathy in half of the patients with cutaneous infections is significantly higher than the others without cutaneous infections. This finding can be explained by the fact that neuropathy may have a role in inducing skin xerosis, trauma, and fissures and increases the risk of infections. Mean age in half of the patients with these lesions was higher than those without skin infections. Bouguerra et al reported that patients' age and duration of DM are the major risk factors for cutaneous mycosis (12). Most of these lesions had a chronic course (about more than 3 months before our survey). But in a group of patients affected by candidial intertrigo during previous 3 months, level of HbA1c was significantly higher than the others without intertrigo. It is mentioned in Rayfield's study that poor control of blood sugar (BS) may result in immune dysfunction and so cutaneous and soft tissue infections may happen consequently (13).

According to these findings, strict control of BS levels and precise education on foot hygiene is necessary in patients with these infections because of the risk of severe foot ulceration, gangrene and limb amputation. Some of these lesions may appear before DM diagnosis.

Mean age, level of HbA1c, duration of illness, frequency of insulin administration and presence of retinopathy, neuropathy and albuminuria were more common in patients suffering from diabetic foot ulceration and these findings were compatible with previous studies (14, 15).

Miller has reported that the prevalence of accompanying neuropathy and peripheral vessel disease combination in diabetic foot ulcer is about 15-20% (14) which means that all the diabetic patients with foot ulcer should be evaluated for microvascular complications, BS control and education in treatment and prevention of diabetic foot ulcer.

All patients with lipohypertrophy and lipohypotrophy had been complicated with neuropathy, retinopathy and albuminuria, due to long standing DM in insulin users and high prevalence of microvascular complications in them.

From microvascular complications, only neuropathy increased diabetes mellitus related skin lesions development to 1.5-2.5 folds. The presence

of neuropathy may increase frequency of multiple trauma, skin xerosis and consequent itching that all result in microorganism penetration via skin in neuropathic patients. Also, neuropathy is a manifestation of microangiopathy that contributes in pathogenesis of some cutaneous lesions.

This study has some limitations: first, in some of the female subjects due to religious beliefs, examination of skin at some parts was not possible such as groin, axilla and sub mammary folds which may have disturbed the estimation of cutaneous lesions prevalence.

Second, other etiologies of neuropathy were ruled out only by taking history; due to impossibility of doing complete para clinical examinations in all patients. Third, about 40% of patients were visited in dermatology clinics and it may affect the prevalence of skin lesions. Fourth, because of the variability in urinary albumin excretion, two of three urine specimens should be abnormal before considering a patient to have albuminuria, but in this study we measured albuminuria once in every patient.

#### Conclusions

Skin lesions are common in type 2 diabetes. Proper skin care and long term control of blood glucose levels may reduce the risk of some of skin disorders in diabetic subjects. Some skin lesions are indicative of microvasular involvement and it's logical to evaluate them for relevant complications.

#### Acknowledgements

The authors wish to thank Dr. Rajab and other members of Iranian Diabetes Association and also the colleagues in Endocrinology Research Center of Shahid Beheshti University of Medical Sciences for their contributions to this research. 560 Mahbobeh- Sadat Hosseini et al

## **Conflict of Interest**

None declared.

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