

Diabetes induced Dermatological manifestations and their association with Vascular complications

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Author's Contribution

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Introduction

Diabetes Mellitus (DM) is a chronic non communicable disease that has evolved as a threat to the world's population due to its continually rising incidences. There were about 422 million people with diabetes globally in 2014, and the figure is expected to rise for low- and middle-income countries.¹ T2DM contributes to 90-95% of diabetes-related patients, and complications of this disease are life threatening, including cardiovascular disease, neuropathy, retinopathy, nephropathy, and dermatological disorders.^{2,3} However, these skin lesions that are commonly ignored have very significant roles in indicating complication of internal organs and directing prognostic standards of the disease.⁴

Diabetes related skin diseases which are also known as diabetes induced dermatological manifestations (DDMs) includes diabetic dermopathy (DD) acanthosis nigricans, necrobiosis lipoidica diabetorum (NL), and bullosis diabetorum (BD), and so on. It is also possible these

ABSTRACT

Background: Diabetes related skin diseases, microvascular complications or metabolic alterations are affecting a majority of diabetic individuals. The purpose of this study was to identify the proportion of patients who presented with dermatological manifestations and to determine associated macrovascular and microvascular complications such as CAD, LEAD and Diabetic retinopathy.

Methods: The present study was a cross-sectional descriptive survey with 355 T2DM. Participants were divided into two groups: to compare the incidence of skin manifestations and their association with cardiovascular complications between the patients with dermatological manifestations (n = 136) and those without (n = 219). Demographic data and clinical data regarding HbA1c, diabetes duration, and treatment method of patients with type 2 diabetes were also assessed. Skin inspection detected findings such as diabetic dermopathy, presence of Huntley's papules, and necrobiosis lipoidica diabetorum. Vascular complications were ascertained clinically and by imaging. The data was analyzed by using descriptive and inferential tools chi-square test, independent sample t-test as well as logistic regression.

Results: Diabetes induced dermatological manifestations (DDMs) were observed in 38, 3% of the patients with diabetic dermopathy as the most frequent condition in this study with Huntley's papules and necrobiosis lipoidica diabetorum following the same trend. The number of vascular complications were significantly higher in patients with DDMs compared to those without DDMs patients. CAD was detected in 28.8% of the patients with DDMs as compared to 18.2% without DDMs (p = 0.008). LEAD was detected in 35.5% of patients with DDMs compared to 23.5% of those without DDMs; p < 0.001. Choroidal detachment and retinopathy of 10.5% were more common in patients with DDMs compared to those without 4.0% (p = 0.003). Necrobiosis lipoidica diabetorum was strongly associated with diabetic retinopathy and nephropathy, with an odds ratio (OR) of 5.11 (p < 0.001). Multivariable analysis confirmed that the presence of DDMs was an independent predictor of vascular complications with OR: 2.35 (p < 0.001).

Conclusions: The three DDMs; diabetic dermopathy, Huntley's papules, and necrobiosis lipoidica diabetorum are strongly linked with vascular complications in T2DM patients. Dermatological screening should be incorporated into the usual diabetes care to enable early assessment of patients with increased potential for developing vascular complications that affects their prognosis.

Keywords: Diabetes mellitus, dermatological manifestations, vascular complications, diabetic dermopathy, necrobiosis lipoidica diabetorum, coronary artery disease, diabetic retinopathy.

skin manifestations to be due to poor glycemic control, microvascular complications or metabolic alterations that are documented to affect the majority of diabetic individuals.⁷ For example, diabetic dermopathy, which presents itself as brown, scaly skin patches, is probably the most frequent cause of dermatological symptoms and is associated with microvascular lesion and diabetic neuropathy.⁸ Likewise, necrobiosis lipoidica, an even more serious cutaneous complication, is strongly related to diabetic retinopathy and nephropathy.⁹

The presence of these dermatological conditions cannot be looked at as just a skin problem hides deeper actual vascular complications. Several studies have proposed that DDMs could be associated with both macrovascular and microvascular diseases, including CAD, PAD and diabetic retinopathy.¹⁰ Shamsi F, et al. (2020) during their research detected

that patients with necrobiosis lipoidica had a higher risk of having retinopathy and nephropathy, hence early dermatological involvement in diabetic patients.¹¹ Moreover, diabetics with several skin disorders were found to have more frequent lower extremity arterial disease (LEAD), and cerebrovascular diseases and therefore skin signs may be used to identify severe vascular complications patients.¹²

Nevertheless, despite an increasing awareness of DDMs in diabetic management, the relationship between many of these skin lesions and particular vascular complications is still poorly defined. Several studies have focused on documenting the clinical implications of skin disease in diabetes, but the direct link between dermatological changes and vascular outcomes remains uncertain and warrants further extensive investigation of clinical implications and intervention measures for the disease management. Thus, it seems reasonable to assume that early recognition of DDMs and their relation to the presence of vascular involvement may open a more extensive approach to the management of diabetes, which might help to avoid further development of severe-end complications.

The purpose of this research is to establish the rate of skin disorders in patients with T2DM and examine the relationship between dermatological lesions and macro- and microvascular complications.

Methodology

This cross-sectional study was conducted after taking ethical approval from institutional Ethical Review board. All the diagnosed patients of diabetes mellitus visiting to the OPD of General Medicine department of KRL hospital and HBS medical college Islamabad, and fulfilling the inclusion exclusion criteria were enrolled for this study. This study was conducted over a period of one year from July 2023 up to July 2024.

A total of 355 patients were selected by nonprobability consecutive sampling technique for this study. The sample size was calculated by using WHO sample size calculator using confidence level of 95%, Anticipated population proportion (rate of dermatological manifestations in diabetic patients) of 36.15%, and absolute precision of 5%. All the patients were briefly described about the purpose of the study and informed written consent was taken from all participants at the time of enrolment in the study. All personal information was kept confidential, and data were anonymized to protect participants' privacy. The inclusion criteria comprised of adults of both gender and aged 18 years and older who had been diagnosed with T2DM. Patients were excluded if they were not attending a scheduled diabetes follow-up visit, had other chronic conditions

affecting the skin, or were unable to provide informed consent.

Data collection was performed through a standardized questionnaire, gathering demographic information such as age, sex, duration of diabetes, HbA1c levels, and current medications. A complete clinical examination was conducted by trained physicians to identify the presence of diabetes-induced dermatological manifestations, including diabetic dermopathy (DD), Huntley's papules (HP), necrobiosis lipoidica diabetorum (NL), acanthosis nigricans, cheiroarthropathy, scleredema adutorum of Buschke, bullosis diabetorum, xerosis, and granuloma annulare. Vascular complications were determined based on clinical diagnosis, confirmed by specialist consultant or imaging, and included coronary artery disease (CAD), lower extremity arterial disease (LEAD), peripheral artery disease (PAD), cerebrovascular disease (stroke), retinopathy, and nephropathy.

Statistical analysis was performed using Statistical Package for Social Science (SPSS v. 25). Descriptive statistics summarized the demographic and clinical characteristics, presenting continuous variables as means and standard deviations and categorical variables as frequencies and percentages. The prevalence of dermatological manifestations was calculated for the total sample and stratified by the presence of vascular complications. Chi-square tests compared the prevalence of dermatological manifestations between patients with and without vascular complications, while independent t-tests or Mann-Whitney U tests were used for continuous variables based on data distribution. Multivariable logistic regression was employed to assess the association between dermatological manifestations and vascular complications, adjusting for potential confounders like age, diabetes duration, and HbA1c levels. A p-value of less than 0.05 was considered statistically significant.

Results

Table 1 compares the demographic and clinical characteristics of 355 diabetic patients, divided into those with (n = 136) and without (n = 219) dermatological manifestations. The group with dermatological manifestations was slightly older (52.1 ± 10.8 years vs. 50.5 ± 11.9 years, $p = 0.045$) and had a longer duration of diabetes (12.3 ± 8.1 years vs. 10.2 ± 7.3 years, $p = 0.018$). They also had higher mean HbA1c levels (7.5% vs. 7.2%, $p = 0.012$) and a higher percentage of patients with diabetes duration ≥ 10 years (55.8% vs. 47.1%, $p = 0.021$). While optimal glycemic control (HbA1c $< 7\%$) was more common in the non-dermatological group

(70.2% vs. 65.5%, $p = 0.067$), no significant differences were found in insulin therapy use (34.9% vs. 30.0%, $p = 0.142$) or oral medication therapy (62.5% vs. 59.1%, $p = 0.244$).

Table 1: Demographic and Clinical Characteristics

Characteristic	Patients With Dermatological Manifestations (n = 136)	Patients Without Dermatological Manifestations (n = 219)	p-value
Mean age (years)	52.1 ± 10.8	50.5 ± 11.9	0.045*
Male-to-female ratio	1.5:1	1.3:1	0.063
HbA1c (%)	7.5 ± 0.9	7.2 ± 0.8	0.012*
Duration of diabetes (years)	12.3 ± 8.1	10.2 ± 7.3	0.018*
Diabetes duration ≥10 years	76 (55.8%)	103 (47.1%)	0.021*
Optimal glycemic control (HbA1c <7%)	89 (65.5%)	154 (70.2%)	0.067
Insulin therapy use	47 (34.9%)	66 (30.0%)	0.142
Oral medication therapy	85 (62.5%)	129 (59.1%)	0.244

Table 2 compares the prevalence of various dermatological manifestations in diabetic patients with and without vascular complications. Diabetic dermopathy (DD) was significantly more common in patients with vascular complications, with a prevalence of 21.5% compared to 12.8% in those without vascular complications ($p < 0.001$). Huntley's papules (HP) also showed a higher prevalence in the vascular complications group (10.5% vs. 6.4%, $p = 0.028$), as did necrobiosis lipoidica diabetorum (5.8% vs. 2.1%, $p = 0.007$) and acanthosis nigricans (4.4% vs. 2.6%, $p = 0.042$). Cheiroarthropathy (3.6% vs. 2.1%, $p = 0.089$) and scleredema adutorum of Buschke (2.9% vs. 1.4%, $p = 0.054$) were more prevalent in patients with vascular complications, although these differences were not statistically significant. Bullosis diabetorum (2.3% vs. 1.2%, $p = 0.078$) also showed a slightly higher prevalence in those with vascular complications, but the difference was marginal. There was no significant difference in the prevalence of xerosis (dry skin) or granuloma annulare between the two groups ($p = 0.366$ and $p = 0.158$, respectively).

Table 3 examines the association between dermatological manifestations and vascular complications in diabetic patients. Patients with dermatological manifestations were significantly more likely to have coronary artery disease (CAD), with a prevalence of 28.8% compared to 18.2% in those without dermatological manifestations (OR: 1.83, 95% CI: 1.21–2.77, $p = 0.008$). Similarly, lower extremity arterial disease (LEAD) was more common in patients with dermatological manifestations (35.5% vs. 23.5%,

OR: 1.91, $p < 0.001$). There was a strong association between necrobiosis lipoidica and both retinopathy and nephropathy (12.5% vs. 2.7%, OR: 5.11, $p < 0.001$). Peripheral artery disease (PAD) was also more prevalent in patients with dermatological manifestations (34.2% vs. 20.9%, OR: 1.80, $p = 0.003$). While stroke (cerebrovascular disease) was slightly more common in the dermatological group (7.9% vs. 4.5%), this difference was not statistically significant (OR: 1.92, 95% CI: 0.76–4.88, $p = 0.182$). Diabetic retinopathy showed a significant association with dermatological manifestations, with 10.5% of patients with dermatological signs affected compared to 4.0% without (OR: 3.19, 95% CI: 1.56–6.52, $p = 0.003$).

Table 2: Prevalence of Dermatological Manifestations

Dermatological Condition	Prevalence in Patients with Vascular Complications (n = 136)	Prevalence in Patients Without Vascular Complications (n = 219)	p-value
Diabetic dermopathy (DD)	29 (21.5%)	28 (12.8%)	0.001*
Huntley's papules (HP)	14 (10.5%)	14 (6.4%)	0.028*
Necrobiosis lipoidica diabetorum	8 (5.8%)	5 (2.1%)	0.007*
Acanthosis nigricans	6 (4.4%)	6 (2.6%)	0.042*
Cheiroarthropathy	5 (3.6%)	5 (2.1%)	0.089
Scleredema adutorum of Buschke	4 (2.9%)	2 (1.4%)	0.054
Bullosis diabetorum	3 (2.3%)	2 (1.2%)	0.078
Xerosis (dry skin)	17 (12.7%)	24 (11.3%)	0.366
Granuloma annulare	4 (3.1%)	9 (4.3%)	0.158

Table 3: Association Between Dermatological Manifestations and Vascular Complications

Complication	With Dermatological Manifestations (n = 136)	Without Dermatological Manifestations (n = 219)	OR (95% CI)	p-value
Coronary artery disease (CAD)	39 (28.8%)	40 (18.2%)	1.83 (1.21–2.77)	0.008*
Lower extremity arterial disease (LEAD)	48 (35.5%)	51 (23.5%)	1.91 (1.29–2.82)	0.003*
Retinopathy and nephropathy (NL)	17 (12.5%)	6 (2.7%)	5.11 (2.15–12.11)	0.001*
Peripheral artery disease (PAD)	47 (34.2%)	46 (20.9%)	1.80 (1.22–2.67)	0.003*

Stroke (Cerebrovascular disease)	11 (7.9%)	10 (4.5%)	1.92 (0.76–4.88)	0.182
Diabetic retinopathy	14 (10.5%)	9 (4.0%)	3.19 (1.56–6.52)	0.003*

Table 4 explores factors associated with dermatological manifestations in diabetic patients. The results show that a longer duration of diabetes (≥ 10 years) was significantly associated with dermatological manifestations, with 55.8% of patients in this group affected, compared to 47.1% in those without dermatological manifestations ($p = 0.021$). Similarly, a higher proportion of patients with dermatological manifestations had HbA1c levels $>7\%$ (71.3% vs. 63.1%, $p = 0.018$) and were older than 50 years (58.2% vs. 48.6%, $p = 0.016$). There was no significant difference in terms of sex (male: 61.2% vs. 54.0%, $p = 0.097$), obesity (BMI >30 : 41.5% vs. 36.1%, $p = 0.242$), or hypertension (35.5% vs. 28.7%, $p = 0.067$) between the two groups. Insulin therapy use and oral medication therapy were also similar between patients with and without dermatological manifestations ($p = 0.142$ and $p = 0.244$, respectively).

Table 4: Factors Associated with Dermatological Manifestations			
Factor	Patients With Dermatological Manifestations (n = 136)	Patients Without Dermatological Manifestations (n = 219)	p-value
Diabetes duration ≥ 10 years	76 (55.8%)	103 (47.1%)	0.021
HbA1c $>7\%$	97 (71.3%)	138 (63.1%)	0.018
Age >50 years	79 (58.2%)	107 (48.6%)	0.016
Male sex	83 (61.2%)	118 (54.0%)	0.097
Obesity (BMI >30)	56 (41.5%)	79 (36.1%)	0.242
Hypertension	48 (35.5%)	63 (28.7%)	0.067
Insulin therapy use	47 (34.9%)	66 (30.0%)	0.142
Oral medication therapy	85 (62.5%)	129 (59.1%)	0.244

Discussion

In people who have Type 2 diabetes mellitus (T2DM), the relationship between vascular problems and diabetes-induced dermatological manifestations (DDMs) is attracting more attention as a possible indicator for the early identification of systemic involvement. This present study aimed to investigate the prevalence of DDMs and their relationship with both macrovascular and microvascular complications. The findings suggest that the presence of certain dermatological conditions in T2DM patients, particularly diabetic dermopathy, Huntley's papules, and necrobiosis lipoidica diabetorum, is significantly associated with vascular

complications, including coronary artery disease (CAD), lower extremity arterial disease (LEAD), and diabetic retinopathy.

A number of authors have pointed to the ability of DDMs to predict the presence of vascular disease. When it comes to particular microvascular consequences, macrovascular conditions like CAD and LEAD frequently coexist with diabetic dermopathy. These results support Quatresooz et al., who observed that diabetic dermopathy is positively related to microvascular disease.¹⁴ In their study diabetic dermopathy was manifested mainly in patients with poorly controlled diabetes mellitus and involvement of blood vessels indicating that cutaneous changes may be the first manifestation of systemic involvement. Furthermore, Huntley's papules and necrobiosis lipoidica diabetorum were more frequent in our study sample, which, according to Shamsi et al.¹⁵ can be used for early recognition of diabetic retinopathy and nephropathy.

Furthermore, reinforcing the findings of the literature research, there is a significant connection between NL (necrobiosis lipoidica diabetorum) and microvascular complications including retinopathy and nephropathy. According to the study conducted by Baghaei et al., NL was a determinant factor of diabetic retinopathy and supports the use of dermatological check as being an important aspect of diabetic management.¹⁶ Thus, acanthosis nigricans and cheiroarthropathy patients also had higher macroangiopathy frequencies, which confirms that dermatological symptoms indicate diabetic macroangiopathy.^{17,18}

We also found that patients with longer duration of diabetes and poor glycemic control defined by HbA1c $>7\%$ are more likely to have DDMs. The result is in concordant with Samanta, et al where they concluded that the duration of the disease and control of blood sugar were significantly associated with the presence of DDMs.¹⁹ Such conditions are most probably due to chronicity of hyperglycemia which subsequently causes microvascular damage in diabetic patients, a pathological feature for long-standing diabetes.²⁰

Surprisingly, gene frequencies for xerosis and granuloma annulare failed to demonstrate any correlation with vascular complications but diabetic dermopathy (common manifestation) with HP and NL were closely related to adverse vascular outcomes. This could mean that specific and severe dermatological symptoms may contain more diagnostic information useful for predicting patients at risk for severe complications.²¹

Overall, it can be concluded that DDMs can identify the clinical severity of Visual impairment (VI) in T2DM patients and may be useful tools for patient

management. These dermatological conditions should be included in regular diabetic management as this may increase chances of early identification of vascular complications and improved patient's prognosis. The future work should continue on the clarification of the mechanism of how DDMs affect vascular diseases and the value of dermatological examination as a part of the diabetes care program.

Conclusion

A range of dermatological conditions: diabetic dermopathy, Huntley's papules and necrobiosis lipoidica diabetorum were associated with both macrovascular and microvascular complications such as CAD, LEAD and Diabetic retinopathy. This study reveals that DDMs are related to vascular complications among patients with T2DM. According to these findings, DDMs may be a valuable source of clinical data that might be used to identify patients who are more likely to experience

vascular involvement. Patients may benefit from improved detection and treatment of peripheral vascular problems if dermatological examinations are incorporated into diabetes care.

Strengths and Weaknesses

A major advantage of this study is that in addition to testing the frequency of DDMs, it investigates their relationship with both macrovascular and microvascular comorbidities in T2DM patients. A major limitation of the study is the cross-sectional approach, which makes it difficult to conceptualize causality between DDMs and vascular complications. However, further longitudinal work in multiple environments could further strengthen rating regarding the prognostic capabilities of DDMs in diabetes mellitus.

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