Cutaneous Manifestations in Diabetic Patients and its Correlation with HbA1c Level

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Abstract	Original Research Article

Introduction: Cutaneous manifestations of DM are very important to the clinician as some of them can prompt the physician to the early detection of diabetes and also reflect the glucose level and lipid metabolism over period of time. Long standing Diabetes Mellitus (DM) leads to permanent and irreversible functional damage in cells of the body, which may be a cause for various complications. Skin being the largest organ of the body, is readily available for examination and study in case of cutaneous disorders of diabetes. *Objective:* To see the association of skin manifestations with HbA1c in diabetes patients. *Material and Methods*: 300 known case of diabetic patient were taken and after taking the informed consent, demographic details, duration of diabetes, mode of treatment for diabetes, and glycemic profile were documented. Complete history and examination of all the patients with regards to onset of cutaneous manifestations was taken. *Result:* 300 patients (45.7% male and 54.3% female), mean age was 53+10.2 years and mean duration of diabetes 7.1+4 years. Mean HbA1c was 8.7+2.7 with 68.7% patients belongs to uncontrolled glycemic group. Most frequently observed skin disease was Bacterial infections (24%), Fungal infections (22.7%), Acanthosis Nigricans (20.4%), Diabetic foot (13.7%), Nail changes (6.6%), Acrochordons (12%), Necrobiosis Lipoidica (7.8%), Viral infections (4.7%), Pruritus (9%) and Xanthelasma (6.2%). There was significant association of uncontrolled diabetes with bacterial (p = 0.013) fungal (p = 0.005) and viral infection (0.045). Females especially had a higher frequency of Acanthosis Nigricans (p = 0.048) and Acrochordons (0.037). *Conclusion:* Patients with type 2 DM have high frequency of skin infections especially Bacterial and Fungal. Other manifestations like Acanthosis Nigricans and Diabetic foot are comparatively less common.
Keywords: Cutaneous Manifestations, Diabetic Patients, HbA1c Level.

INTRODUCTION

In India Diabetes Mellitus (DM) continues to be a major public health problem, and India is having the highest number of diabetics in world [1].

According to International Diabetes Federation (IDF) 2018 the total number of diabetic patients are approx 40.9 million in India and this may rise in the future to 70 million by the year 2025. The prevalence of a cutaneous disorder appears to be similar between people affected with Type 1 DM and Type 2 DM, but Type 2 DM patients develop more skin infections[2-5].

Abnormalities of insulin and elevated blood glucose level leads to involvement of multiple organ systems like CVS, CNS, eyes, renal and skin[6]. According to a study, more than one third of diabetic patients have one or the other type of dermatological manifestations during the course of their disease [7].

Multiple factors play a role in the manifestations of cutaneous signs of diabetes mellitus. Abnormalities in the metabolism of carbohydrates, alteration of metabolic pathways, vascular involvement in the form of atherosclerosis, microangiopathy and neuronal involvement in the form of sensory, motor and autonomic neuropathies and impaired host mechanisms, all play a role in pathogenesis of Diabetic dermopathy[8].

Cutaneous manifestations of DM are very important to the clinician as some of them can prompt the physician to the early detection of diabetes and also reflect the glucose level and lipid metabolism over

period of time. Long standing DM leads to permanent and irreversible functional damage in cells of the body which may be a cause for various complications. Skin being the largest organ of the body, is readily available for examination and study in case of cutaneous disorders of diabetes [9].

Skin changes mostly appear later to DM but may be the first clinical presenting sign or even precede the diagnosis by many years. The main mechanism leading to these changes is thought to be non-enzymatic glycosylation. This mechanism occurs to a lesser extent at normal blood sugar level and is apparently accelerated in patients with increased blood glucose levels [10].

METHOD AND MATERIAL

This cross sectional analytical study was carried out in the Department of Medicine, Shyam Shah Medical College and Sanjay Gandhi Memorial Hospital Rewa, spanning from April 2018 to June 2019 over a period of fifteen months. The study was conducted after a formal approval from the ethical research committee.

Total 300 Adult subjects, already diagnosed as type 2 DM presenting with cutaneous manifestations were included in the study. An informed consent was obtained from all the enrolled subjects. The demographic details of all subjects were also documented. A detailed history was obtained from the enrolled patients including duration of diabetes and mode of treatment for diabetes (i.e. diet only, oral hypoglycemic, insulin therapy or combination therapy).

After a detailed general, systemic and cutaneous examination, the clinical diagnosis of dermatological findings was established. Their fasting blood sugar, random blood sugar and HbA1c were advised to assess the glycemic control. HbA1c was measured by High Performance Liquid Chromatography. Plasma glucose estimation (FBS and PPBS) was carried out by the glucose oxidase method in the auto analyzer. The patients were grouped as controlled glycemic group and uncontrolled glycemic group based on their HbA1c levels. Uncontrolled glycemic group has HbA1c > 7 as per American Diabetic Association (ADA) criteria.

Other relevant laboratory investigations were advised including complete blood picture, renal function test, liver function tests, lipid profile, urine examination and pus for culture and sensitivity. Any special tests like Wood's lamp examination, fungal scrapings, skin biopsy, Tzanck smear, nail biopsy and nail clippings were performed in doubtful cases.

SELECTION CRITERIA
Inclusion criteria
- All patients with diagnosed diabetes fulfilling the revised American Diabetes Association (ADA) criteria.
- Age >18 Years

Exclusion criteria
- Patients having skin changes secondary to pregnancy and other systemic illness and iatrogenic factor were excluded.

STATISTICAL ANALYSIS

All the findings were recorded on a specially designed proforma. Data were compiled, tabulated and analyzed by SPSS (Statistical package for social sciences version 17. Mean and standard deviation were used to represent quantitative variables like age, duration of diabetes, fasting blood sugars, random blood sugars and HbA1c. Descriptive variables like presence of various skin changes were presented as frequencies and percentages. Chi-square test was used to determine association of various skin lesions with glycemic control and gender. P value < 0.05 is considered as significant.

RESULTS

Among the 300 diabetic patients enrolled in the study, we divided them into two groups, controlled glycemic group and uncontrolled glycemic group based on their HbA1c values. Controlled glycemic group (HbA1c≤7) contains 94 patients and uncontrolled glycemic group (HbA1c>7) contains 206 patients. Table 1 shows the mean and standard deviation values of age, body mass index (BMI), duration of diabetes, fasting and postprandial blood sugar, gender distribution, and also the presence and absence of hypertension in controlled and uncontrolled glycemic group patients. Mean age in controlled glycemic group was 49.89±10.25 and in uncontrolled glycemic group was 52.98±10.22 (p value=0.016).In controlled glycemic group 45 patients were male and 49 patients were female and in uncontrolled glycemic group 92 patients were male and 114 patients were female (p value=0.60). In controlled glycemic group mean BMI was 25.24±4.01 and in uncontrolled glycemic group mean BMI was 24.99±2.84 (p value=0.9122). In controlled glycemic group mean duration of diabetes was 6.81±3.72 and in uncontrolled glycemic group mean duration of diabetes was 7.18±3.52 (p value=0.418). In controlled glycemic group mean fasting blood sugar was 118.8±20.24 and in uncontrolled glycemic group mean fasting blood sugar was 158.7±31.27(p value<0.001). In controlled glycemic group mean post prandial blood sugar was 159.7±37.08 and in uncontrolled glycemic group mean post prandial blood sugar was 237.3±53.07(p value<0.001).In controlled glycemic group incidence of hypertension 21.28% and in uncontrolled glycemic group incidence of hypertension was 32.04% (p value=0.056).

Table-1: Demographic and Biochemical Parameters in controlled glycemic group and uncontrolled glycemic groups

S.N	PARAMETERS	CONTROLLED GLYCEMIC GROUP (HbA1c≤7) (n=94)	UNCONTROLLED GLYCEMIC GROUP (HbA1c >7) (n=206)	P VALUE
1.	Age distribution (years)	49.89±10.25	52.98±10.22	0.016
2.	Gender (F/M)	49/45	114/92	0.600
3.	BMI(Kg/m^2)	25.24±4.01	24.99±2.84	0.586
4.	Duration of diabetes (years)	6.81±3.72	7.18±3.52	0.418
5.	FBS (mg/dl)	118.8±20.24	158.7±31.27	0.0001
6.	PPBS (mg/dl)	159.7±37.08	237.3±53.07	0.0001
7.	Hypertension(yes/no)	20/74	66/140	0.056

Among the enrolled subjects, the most frequently seen skin diseases were Bacterial infections in 73(24%) patients, followed by Fungal infections 68(22.7%), Acanthosis Nigricans 61(20.4%), Diabetic foot 41(13.7%) and Acrochordons 37 (12.3%) patients.

Other diseases seen with a lesser frequency in the descending order included Eczema, Pruritus, Psoriasis, Xanthelasma, Hyperkeratosis of skin, Viral infections And Acquired Ichthyosis (Table 2).

Table-2: Prevalence of Skin lesions in diabetes

Skin lesions in diabetes	No. of cases (%)	Controlled glycemic group (%)	Uncontrolled glycemic group (%)	P value
Infectious				
Bacterial infection	72 (24)	14 (14.89)	58 (28.15)	**0.013**[*]
Fungal infection	68 (22.7)	12 (12.77)	56 (27.18)	**0.005**[*]
Viral infection	14 (4.7)	01 (1.06)	13 (6.31)	**0.045**[*]
Non infectious				
Acanthosis nigricans	61 (20.4)	24 (25.53)	37 (17.96)	0.130
Acrochordons	37 (12.3)	12 (12.7)	25 (12.1)	0.877
Pruritus	27 (9.0)	11 (11.7)	16 (7.77)	0.268
Eczema	28 (9.33)	06 (6.38)	22 (10.68)	0.235
Psoriasis	23 (7.67)	10 (10.64)	13 (6.31)	0.191
Xanthelasma	19(6.34)	5(5.32)	14(6.8)	0.626
Hyperkeratosis of skin	13 (4.34)	02(2.13)	11 (5.34)	0.205
Acquired ichthyosis	10 (3.34)	02 (2.13)	08 (3.88)	0.432
Erythema abigne	06 (2.00)	02 (1.88)	4 (4.12)	0.173
Vitiligo	06 (2.00)	01 (1.06)	05 (2.43)	0.434
Cutaneous angioma	01 (0.34)	01 (1.06)	00 (0.0)	0.089

This table shows that, 58(28.15%) cases of uncontrolled glycemic group had bacterial infections compared to 14 (14.89%) from controlled glycemic control (p =0.037). Among patients with fungal infections, 56(27.2%) belongs to Uncontrolled glycemic group and 12 (12.7%) to controlled glycemic group (P value=0.005). Cases of viral infections were very less in number but this also have significant p value. In controlled glycemic group only 1 (1.06%) patient had fungal infection compare to 13(6.32%) from uncontrolled glycemic group (p value=0.045).

Table-3: Prevalence of Skin lesions in diabetes

Skin lesions in diabetes	No. of cases (%)	Male (%)	Female (%)	P value
Infectious				
Bacterial infections	72 (24)	32 (23.35)	40 (24.53)	0.811
Fungal infections	68 (22.7)	30 (21.89)	38 (23.31)	0.770
Viral infections	14 (4.7)	04 (2.91)	10 (6.13)	0.188
Non infectious				
Acanthosis nigricans	61 (20.4)	21 (15.32)	40 (24.54)	**0.048**[*]
Acrochordons	37 (12.3)	11 (8.03)	26 (15.95)	**0.037**[*]
Pruritus	27 (9.0)	13 (9.49)	14 (8.59)	0.786
Eczema	28 (9.34)	15 (10.95)	13 (7.98)	0.377
Psoriasis	23 (7.67)	08 (5.84)	15 (9.20)	0.275
Xanthelasma	19 (6.34)	10 (7.3%)	9 (5.52%)	0.528
Hyperkeratosis of skin	13 (4.34)	09 (6.57)	04 (2.45)	0.081
Acquired ichthyosis	10 (3.34)	07 (5.11)	03 (1.84)	0.116
Erythema abigne	06 (2.0)	05 (3.68)	01 (0.61)	0.060
Vitiligo	06 (2.0)	05 (3.68)	01 (0.61)	0.060
Cutaneous angioma	01 (0.34)	01 (0.73)	00 (0.0)	0.187

In view of gender (Table 3), there were 40 females (24.5%) with Acanthosis Nigricans as compared to 21 males (15.3%), (p = 0.048). for Acrochordons female were 26 (15.9%) and 11(8.03%) were male. This is also statistically significant (p value=0.037) Gender preponderance was not found to be associated with other Dermatoses.

Acrochordons

Onychomycosis

Erythema ab igne

Diabetic dermopathy

Psoriasis

DISCUSSION

In this current study mean age of presentation of diabetes patients is 52.01 years with SD of 10.31 years. This seems to be similar to the report from Ahmed *et al*.[11], where the mean age of diabetic patients was 54 years. Likewise, Basit *et al*. [12] also reported a comparable mean age of presentation [11].

Majority of patients enrolled in our study were females. Dermatological manifestations were seen more commonly in women in our study indicates greater disease burden and health awareness among females.11On the contrary, some regional studies have shown a preponderance of males.

In our study the mean duration of diabetes is 7.06 years; majority of patients (45.34%) had diabetes for 6-10 years. Majority of patients (68.7%) had uncontrolled diabetes with mean fasting blood sugars

158 mg/dl and a mean HbA1c value of 9.8%. Bhat *et al*. [13] have reported similar figures for uncontrolled diabetes and associated dermatological features. Ahmed *et al*.[11] have reported a higher frequency (93%) of uncontrolled diabetes in a similar series of patients. However, the results can vary from one study to another depending upon the study design and setting. This in turn may be correlated with medical facilities, hygiene, literacy level and lack of awareness about the disease. Therefore, uncontrolled DM increases the risk of development of various complications like dermatological manifestations and progression of the disease [14, 15].

Corelation of Infectious lesion and HbA1c level

Cutaneous infections were the most common group of Dermatoses (53%) seen in our study comprising bacterial infections, fungal infections and viral infections. Bacterial infections were the more common infectious skin lesion in our study. The overall

frequency of skin infections in patients with DM varies between in 20-50% [15]. In our study Bacterial infectious lesions are present in 14.89% of controoled glycemic group patients and 28.15% of uncontrolled glycemic group patients, which is comparable to study of Majeed M *et al*. [16]. There is statistical significant association of infectious skin lesion with uncontrolled glycemic group as in study of majeed M *et al*. [16]. Basit *et al*. [12] have reported a higher frequency of infections in males in a similar set of patients. Vahora *et al*. [15] have reported a similar frequency of Bacterial infections in such patients.

Ahmed *et al*. [11] also reported Bacterial infections to be more common in their study. In our study frequency of fungal infections in uncontrolled diabetic group is almost similar to Bacterial infection but viral infection is relatively less common due to less number of cases. Ahmed *et al*. [11] also claimed a lower frequency of Fungal and Viral infections.

Diabetic foot
In our study, 13.7% of the enrolled patients had diabetic foot. Diabetic foot ulcers are usually related to different mechanisms like impaired immunity, neuropathy, peripheral arterial disease, venous insufficiency and lymphedema. Diabetic foot has been reported with a variable frequency in different studies ranging between 10 and 50% [11, 15, 17]. Mansour *et al*.[18] have reported foot abnormalities to be more common in male diabetics and Other studies have also confirmed the same association[19]. But our study does not show any gender prevalence in diabetic foot.

In our study diabetic foot is present in 07.45% of controlled glycemic group and 16.5 % in uncontrolled glycemic group. In the study of Majeet M *et al*. [16] diabetic foot is present in 12% of controlled glycemic group and 18 % in uncontrolled glycemic group which is quite comparable with our study.

Fungal infection
The prevalence of Fungal infection is (22.7%) in our study. The incidence of fungal infection in controlled glycemic group is 12.77% and in uncontrolled glycemic group is 27.18%. In the study of Baloch GH *et al*. [20] incidence of Fungal infection in controlled glycemic group is 9% and in uncontrolled glycemic group is 28%.Which is near similar to current study and statistically significant.

In this study fungal infection most common lesion is Tenia Carporis followed by Tenia Pedis. In study of Baloch *et al*. [20] Tenia Pedis was the commonest clinical type.

Viral infections
The prevalence was 4.7% in our study group which was close to the previous study prevalence of Baloch *et al*.[20].

In this study incidence of Viral infection in controlled glycemic group is 1.06% and in uncontrolled glycemic group is 6.31% which is different in Baloch *et al*.[20] study but in both study p value is <0.05 and statistically significant.

Corelation of non-Infectious lesion and HbA1c level
Acanthosis Nigricans
Noninfectious lesion has no correlation with glycemic control. Acanthosis Nigricans (20.4%) is most common noninfectious Dermatoses associated with type 2 DM in the current study. The frequency was found to be higher in females (p value 0.048). The noninfectious dermatological feature had a lesser frequency than infections and can be accounted for by the fact that it is not due to uncontrolled diabetes but due to insulin resistance. The high levels of insulin act on the insulin-like growth factor receptors and lead to formation of the Acanthosis Nigricans. Different domestic and international studies have also confirmed this association in the past [15, 17, 22].

Acrochordons
Acrochordons were seen in 12.3% of our patients. Similar association of Acrochordons with type 2 DM has been reported by Vahora R *et al*. [15]. In this study Acrochordons is also seen more frequently in female cases (p value 0.037).

In female patient it is seen in 15.95% cases and in male patients seen in 8.03% cases which are statistically significant.

Pruritus
Pruritus is well known to have an association with diabetes mellitus as reported in the past literature [11, 20, 23]. Al-Mutairi *et al*.[24] have reported the frequency to be 47% in a similar series of patients. This is much higher in frequency as compared to our study (9.0%).

In this study Pruritus is prsesnt in 11(11.7%) cases of controlled glycemic group and 16 (7.77%) cases of uncontrolled glycemic group which is similar to previous study by Baloch GH *et al*.[20]. In both study pruritus is having statistically non-significant correlation with HbA1c level.

Xanthelasma
In this study Xanthelesma is present in 19(6.34%) of total cases studied and was seen in 5(5.32%) cases of controlled glycemic group and 14(6.8%) cases of uncontrolled glycemic group with p value 0.626 which is statistically insignificant. In other study similar results were found by Majeed M *et al*. [16]. Other Non-infectious lesions also do not have any correlation with HbA1c level [15].

CONCLUSSION

We can conclude that glycemic control of diabetic patients has direct correlation with various infectious cutaneous manifestations like bacterial, fungal and viral infections and these are more in uncontrolled diabetics while noninfectious cutaneous manifestations have no relation with HbA1c level. In non-infectious skin lesion, prevalence of Acanthosis Nigricans and Acrochordons were more in female diabetic as compare to male diabetics.

LIMITATIONS

The major limitation of the study was that it was conducted in small population that may not represent the entire population. The study was conducted from that population attending the hospital and thus may reflect high prevalence of complications observed in this study. The follow up of the cases was not possible to determine the prognostic significance of our findings.

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