

Impact of Glycaemic Control on the Pattern of Cutaneous Disorders in Diabetes Mellitus- A Hospital Based Case Control Study

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ABSTRACT

Introduction: The skin is the largest and the most visible organ of the body. It is a well known fact that it is referred to as window or mirror to the internal health of the body. Abnormalities of insulin and elevated blood glucose levels lead to metabolic, vascular, neurological and immunological abnormalities. Affected organs include the cardiovascular, renal, nervous system, eyes and the skin. The skin manifestations can be the first presenting sign of diabetes but more often appear in known diabetic patients during the course of the disease.

Aim: To study the clinical profile of cutaneous lesions in diabetic patients and to compare the pattern of these dermatoses with HbA1C levels (glycosylated haemoglobin).

Materials and Methods: Three hundred consecutive diabetic patients with cutaneous manifestations who attended dermatology OPD at Rajah Muthiah Medical College, Chidambaram from November 2013 to October 2015, constituted the study group. Hundred age and sex matched

non diabetic patients who attended our OPD, constituted the control group. They were subjected to relevant investigations. Fasting blood sugar, post prandial blood sugar, glycosylated haemoglobin levels and renal function test were done for all patients. Potassium hydroxide mount and gram stain were done for relevant cases. Chi-square test was used for statistical analysis using software SPSS version 21.

Results: The most common dermatological manifestation among diabetics was cutaneous infections, seen in 126 (42%) patients. Among the infections, fungal infections predominated in 89 (29.7%) patients, followed by bacterial infections in 31(10.3%) patients. There was a statistically significant correlation between infections and uncontrolled diabetes (HbA1C >7).

Conclusion: Skin is involved quite often in diabetics, some of which can be a consequence or can be a clue for the diagnosis of underlying diabetes. Diabetic control is very important in reducing the morbidity and mortality of the diabetic patients.

Keywords: Dermatoses in diabetes, Diabetic bulla, Fungal infections

INTRODUCTION

Diabetes mellitus, the most common endocrine disorder causes significant impairment of the various organ systems of the body including skin. The prevalence of dermatological disorders seen in diabetic patients is around 32% [1]. Prolonged hyperglycaemia results in production of advanced glycosylated end products which in turn is responsible for most of the complications of diabetes. The pathogenic mechanisms like abnormal carbohydrate metabolism, atherosclerosis, microangiopathy, neuron degeneration and impaired host mechanisms can be the causes of various dermatoses in diabetes [2].

Cutaneous manifestations of diabetes mellitus usually appear subsequent to the development of the disease, but sometimes it may be the first presenting sign and in some cases they may even precede the onset of primary disease by many years [3]. Therefore, early recognition of these manifestations will help to achieve good glycaemic control and prevent morbidities. Many similar studies had been conducted throughout the country [1,2]. Studies done by Raghu TY et al., and Rao GS et al., showed infections as the major cutaneous manifestations among diabetics and fungal infections accounted for the majority of infections [1,2], but only very few studies exist from Tamil Nadu and Pondicherry [3]. This made us to conduct this study. The aim of this work is to analyse the pattern of various cutaneous lesions among diabetic patients and to compare it with HbA1C levels.

MATERIALS AND METHODS

A prospective case control study was conducted at RMMCH for a period of two years from November 2013 to October 2015. RMMCH

is a teaching medical institution situated in a rural town catering to the needs of 4,69,416 population. A total number of 300 diabetic patients with various dermatoses were enrolled as study group. Sample size was not calculated. It was just fixed based on the previous studies [4,5]. Hundred non diabetic patients with various dermatoses, constituted the control group. All confirmed cases of diabetes with cutaneous manifestations irrespective of age, sex, associated diseases and those who were willing to participate in the study were included in the study group and all non diabetics with cutaneous manifestations were taken as control group.

Patients who did not give consent and gestational diabetes patients were excluded from the study. The ethical clearance was sought from the institutional ethical committee before starting the study. Informed consent has been obtained from all patients. All relevant details were entered in the case report form and associated comorbid conditions were also noted. All patients underwent a detailed dermatological examination. Various investigations like fasting blood sugar, post prandial blood sugar, glycosylated haemoglobin (HbA1C) levels, renal function test, lipid profile and urine analysis were done for all patients. Gram stain, KOH mounts and skin biopsy were done in relevant cases to confirm the dermatological diagnosis. The classification of cutaneous manifestations in diabetes proposed by Sreedevi C had been adapted for this study [Table/Fig-1] [6].

STATISTICAL ANALYSIS

Descriptive statistical analysis was done using software SPSS version 21. Chi-square test was used for the comparison. Level of significance was fixed as 5% (p-value <0.05).

Serial No	Classification	Dermatoses
1	Strongly associated but not specific for diabetes (disease markers)	Diabetic bullae Necrobiosis lipoidica diabetorum Diabetic dermopathy Granuloma annulare Scleroderma like syndrome Pruritus
2	Due to diabetic complications	Diabetic foot Cutaneous infections Xanthomatosis Xanthelasma Phycomycetes Malignant otitis media
3	Due to neurovascular complications	Microangiopathy Macroangiopathy Diabetic neuropathy
4	Due to diabetes treatment	With Oral hypoglycaemic drugs With Insulin
5	Endocrine syndromes with diabetes mellitus	Migratory necrolytic erythema
6	Commonly associated with diabetes mellitus	Psoriasis Lichen planus Vitiligo Perforating dermatoses Eruptive xanthomas Bullous pemphigoid Dermatitis herpetiformis Kaposi sarcoma

[Table/Fig-1]: Classification of cutaneous manifestations in diabetes [6].

RESULTS

The demographic details of the patients in both the groups are shown in [Table/Fig-2].

[Table/Fig-3] showed the pattern of cutaneous manifestations of diabetic patients which revealed that infections were the commonest, as seen in 126 (42%) patients. [Table/Fig-4] showed the pattern of infections among study group and control group which revealed that infections were less in the control group. In [Table/Fig-5] the frequency of infections had been compared with HbA1C levels in the study group. It revealed that all the nine patients with multiple infections had uncontrolled diabetes.

[Table/Fig-6] compared the pattern of bacterial infections in study group patients and HbA1C levels. Furuncle was seen in 10 patients and out of which 9 patients had uncontrolled diabetes. Carbuncle was diagnosed in one patient with uncontrolled diabetes. [Table/Fig-7] revealed the pattern of fungal infections among study group compared with HbA1C levels. Interestingly a life threatening infection, mucor mycosis was diagnosed in two patients who had uncontrolled diabetes. [Table/Fig-8] showed the detailed pattern of number of infections among study group on comparison with HbA1C levels. All seven patients with two fungal infection had uncontrolled diabetes. [Table/Fig-9] compared the pattern of viral infections among study group with HbA1C levels. Out of eight patients with viral infections six patients had uncontrolled diabetes.

Pattern of dermatoses commonly associated with diabetes had been depicted in [Table/Fig-10]. Less common dermatoses were represented in [Table/Fig-11]. Pattern of the neuropathic and ischemic skin diseases is depicted in [Table/Fig-12].

The pattern of most closely associated dermatoses had been shown in [Table/Fig-13]. The patient who presented with diabetic bulla had uncontrolled diabetes i.e., HbA1C >7.

[Table/Fig-14] analysed the relation between cutaneous manifestations and control of diabetes. In this study group of 300 patients, we noticed 333 cutaneous manifestations and of which 198 manifestations occurred in uncontrolled diabetes i.e., HbA1C >7. Among diabetics out of all the groups, only infections had statistically significant association with control of diabetes i.e., p-value <0.05 which means infections were more common in uncontrolled diabetes (HbA1C >7).

Factor	Study group (N-300)		Control group (N-100)	
	No	%	No	%
Age				
<20 yrs	1	0.33	0	0
21-30 yrs	4	1.33	5	5
31-40 yrs	22	7.33	27	27
41-50 yrs	84	28.00	27	27
51-60 yrs	100	33.33	26	26
61-70 yrs	57	19.00	7	7
>70 yrs	32	10.67	8	8
Sex				
Male	175	58.3	53	53.0
Female	125	41.7	47	47.0
Duration of Diabetes				
<1 yrs	70	23.3	-	-
1-5 yrs	101	33.7	-	-
6-10 yrs	52	17.3	-	-
>10 yrs	77	25.7	-	-
Type of DM				
Type I	3	1.0	-	-
Type II	297	99.0	-	-
Family History DM				
No	153	51.0	63	63.0
Yes	147	49.0	37	37.0
Associated Co-morbidity				
Absent	124	41.3	80	80
Present	176	58.7	20	20
Pattern Co-morbidity				
Hypertension	130	43.3	15	15.0
Dyslipidemia	83	27.7	5	5.0
Coronary artery disease	33	11.0	1	1.0
Bronchial asthma	16	5.3	1	1.0
Hypothyroidism	16	5.3	1	1.0
Tuberculosis	3	1.0	0	-
Dermatoses				
Infectious	126	42	13	13.0
Non infectious	174	58	87	87.0
No of Dermatoses				
Single	246	82.00	97	97.0
Multiple	54	18.00	3	3.0
HbA1C				
<6.4	59	19.7	100	100
6.5-7	70	23.3	0	-
7.1-8	103	34.3	0	-
>8	68	22.7	0	-

[Table/Fig-2]: Demographic details.

Dermatoses	No. of patients	Percentage
Infections	126	42.0%
Commonly associated dermatoses in diabetes mellitus	103	34.3%
Less common dermatoses	55	18.3%
Neuropathic and ischaemic	27	9%
Most closely associated dermatoses in diabetes mellitus	21	7%
Reaction to diabetes treatment	1	0.3%

[Table/Fig-3]: Pattern of cutaneous manifestations in study group.

Infections	Study group (N=300)		Control group (N=100)	
	Number of patients	Percentage	Number of patients	Percentage
Fungal alone	87	29	8	8
Bacterial alone	29	9.7	5	5
Viral	8	2.6	0	0
Fungal and bacterial	2	0.7	0	0

[Table/Fig-4]: Pattern of infections in study group and control group.
In study group-Total no of patients with fungal infections: 89; Total no of patients with bacterial infections: 31; N=300 represents total number of patients in study group; N=100 represents total number of patients in control group

No. of infections	HbA1C				Total	
	<7		>7			
	N	%	N	%	N	%
Single infection	26.0	22.2	91.0	77.8	117.0	100.0
Multiple infections	0	0	9	100	9	100

[Table/Fig-5]: Comparison of number of infections in study group and HbA1C levels.

Bacterial infection	HbA1C				Total No-31	
	<7		>7			
	No	%	No	%	No	%
Acute paronychia	1	100.0	0	0.0	1	100
Carbuncle	0	0.0	1	100.0	1	100
Cellulitis	1	14.3	6	85.7	7	100
Folliculitis	1	33.3	2	66.7	3	100
Furruncle	1	10.0	9	90.0	10	100
Hansens disease	1	100.0	0	0.0	1	100
Hidradenitis suppurativa	1	100.0	0	0.0	1	100
Infective eczematoid dermatitis	0	0.0	1	100.0	1	100
Pitted keratolysis	0	0.0	1	100.0	1	100
Pyoderma	1	20.0	4	80.0	5	100

[Table/Fig-6]: Pattern of bacterial infections in study group vs HbA1C.

Fungal infection	HbA1C				No of infections N=96	
	<7		>7			
	N	%	N	%	N	%
Candidal balanoposthitis	0	0	15	100	15	100
Candidal intertrigo	0	0.0	5	100.0	5	100
Dermatophyte	13	22.8	44	77.2	57	100
Mucor mycosis	0	0.0	2	100.0	2	100
Oral candidiasis	0	0.0	2	100.0	2	100
Pityriasis versicolor	4	28.6	10	71.4	14	100
Vulvo vaginal candidiasis	0	0.0	1	100.0	1	100

[Table/Fig-7]: Comparison of fungal infections in study group Vs HbA1C value.
Out of 89 patients having fungal infections 7 patients had two fungal infections. So total number of fungal infections comes to 96

Infections	HbA1C		Total
	<7	>7	
	Number of patients	Number of patients	Number of patients
Single bacterial	7	22	29
Bacterial and fungal	0	2	2
Single fungal	17	63	80
Two fungal	0	7	7
Single viral	2	6	8

[Table/Fig-8]: Comparison of number of infection in study group with HbA1C levels.

Viral infection	HbA1C				Total No: 8	
	<7		>7			
	N	%	N	%	N	%
Herpes zoster	1	25.0	3	75.0	4	100
Warts	1	25.0	3	75.0	4	100

[Table/Fig-9]: Comparison of viral infections in study group Vs HbA1C levels.

Dermatoses	No of patients
Acquired perforating disorders	4
Amyloidosis	8
Bullous pemphigoid	3
Eruptive xanthoma	1
Lichen planus	11
Psoriasis	45
SLE	1
Urticaria	25
Vitiligo	7
Xanthelasma	1

[Table/Fig-10]: Pattern of dermatoses commonly associated with diabetes.
When the same patient had two dermatoses under the same group, that patient had been counted for both of those dermatoses. This is the reason for the discrepancy in numbers between this table and [Table/Fig-3].

Dermatoses	No of patients N=55
Bullous leucocytoclastic vasculitis	1
Contact dermatitis	10
Eczemas	14
Leiomyoma cutis	2
Polymorphic light eruption	5
Scabies	7
Others	16

[Table/Fig-11]: Pattern of less common dermatoses in study group.
16 patients had other dermatoses like keloid (4), melasma (3), erythroderma (3), alopecia areata (3) and androgenetic alopecia (3)

Dermatoses	No of patients
Asteatotic eczema	11
Diabetic foot ulcers	11
Fissure feet	1
Notalgia paresthetica	1
Peripheral neuropathy	5

[Table/Fig-12]: Pattern of Neuropathic and ischemic skin diseases in study group.
When the same patient had two dermatoses under the same group, that patient had been counted for both the dermatoses

Dermatoses	No of patients
Acanthosis nigricans	2
Acquired ichthyosis	3
Diabetic bulla	1
Diabetic hand syndrome	2
Granuloma annulare	2
Pruritus	11
Skin tags	4

[Table/Fig-13]: Pattern of most closely associated dermatoses in study group.
When the same patient had two dermatoses under the same group, that patient had been counted under both the dermatoses

Group	HbA1C		Total	p-value
	<7	>7		
Most closely associated dermatoses	11	10	21	0.368
Infections	26	100	126	0.021
Neuropathic and ischaemic	13	14	27	0.571
Reaction to diabetes treatment	0	1	1	0.384
Commonly associated dermatoses in DM	47	56	103	0.506
Less common dermatoses	38	17	55	0.029
Total	135	198	333	

[Table/Fig-14]: Comparison of cutaneous manifestations among study group in relation to control of diabetes.

Chi-square test was used for the comparison to calculate p-value. Level of significance was fixed as 5% (p-value <0.05)

Clinical pictures of few dermatoses like dermatophytosis, candidal balanoposthitis, carbuncle, mucor mycosis, diabetic bulla, eruptive xanthoma and insulin lipodystrophy were shown in [Table/Fig-15-21] respectively.



[Table/Fig-15]: Dermatophytosis. Well defined hyperpigmented patch with central clearing and erythematous papules in the margins in axilla suggestive of dermatophytosis. **[Table/Fig-16]:** Candidal balanoposthitis. Multiple fissures over the prepuce suggestive of candidal balanoposthitis.



[Table/Fig-17]: Carbuncle. Carbuncle over the nape of the neck. **[Table/Fig-18]:** Mucor mycosis. Well defined necrotic plaque with blackish eschar seen over medial canthi, bridge of the nose and left infra orbital region in mucor mycosis.



[Table/Fig-19]: Diabetic bulla. Multiple tense bulla present over the shin suggestive of diabetic bulla. **[Table/Fig-20]:** Eruptive Xanthoma. Multiple skin coloured to yellowish papules over extensor aspect of elbow suggestive of eruptive xanthoma.

DISCUSSION

Diabetes-associated skin conditions can be a direct result of the metabolic changes such as hyperglycaemia, or to progressive damage to the vascular, neurological or immune system [3]. Age group in diabetic patients correlated with a study conducted by Timshina DK et al., from a neighbouring town [3]. In contrast Bhat YJ et al., reported the common age group as 41-50 years [7]. Positive family history was noticed in more number of patients when compared to that of control group. This signifies the importance of



[Table/Fig-21]: Insulin lipodystrophy. Multiple atrophic plaques present at the sites of insulin injection suggestive of insulin lipo dystrophy.

regular screening for diabetes among patients with family history of diabetes. Associated co-morbidities were seen in more number of diabetic patients when compared to that of control group. Study done by Bhat YJ et al., showed similar pattern of co-morbidity like this study whereas study by Raghunatha S et al., revealed a lesser incidence of co-morbid conditions which could have been due to difference in population [7,8]. Hypertension was the commonest co-morbid condition associated with this study group patients. The relationship between hypertension and diabetes was explained by Mahajan S et al., where he hypothesized that hypertension was found to accelerate the process of micro-angiopathy among diabetics [9]. In this study we observed that 57% of the patients had uncontrolled diabetes. This could be due to the lack of awareness about the disease and its complications which could be attributed to lack of primary level education in 58% of patients. In contrast to this study, Rajendra KJ et al., and Mashkoo AW et al., observed less number of patients with uncontrolled diabetes [10,11]. The diabetic patients were selected from medicine and endocrinology departments respectively for these studies. Hence, all the patients were given adequate counseling regarding the importance of glycaemic control and all were under regular follow-up, which could be the reason for less number of patients with uncontrolled diabetes in these studies.

Infections were the commonest dermatoses among the study population which had a statistically significant association with the glycosylated haemoglobin levels. That means HbA1C levels (HbA1C >7) had a direct correlation to the incidence of infections whereas no significant association between glucose levels and occurrence of skin manifestations was observed in studies conducted by Rajendra KJ et al., Nandhini C et al., and Fady SY et al., [10,12,13]. Similarly on comparing the frequency of infections with HbA1C levels showed that all the patients with multiple infections had uncontrolled diabetes. Studies done by Vahora R et al., Mahajan S et al., and Al-Mutairi N et al., also showed infections as the major manifestation, similar to this study [4,9,14]. Raghu TY et al., Timshina DK et al., Bhat YJ et al., Raghunatha S et al., Al-Mutairi N et al., and Abhishek G et al., showed that fungal infections were the commonest which was similar to this study [1,3,7,8,14,15]. Khurshid A et al., and Rajendra KJ et al., reported bacterial infections more commonly than fungal infections, which were seen in 160(64.5%) and in 67 (19%) patients [5,10]. The causes of infections in diabetes were due to the following factors: a) Hyperosmolality of the hyperglycaemic serum which causes diminished chemotaxis; b) Impaired release of cytokines as a consequence of lack of insulin; c) Impaired phagocytosis, which may be due to diminished leukocyte response and associated neuropathy [1]. Infections were mostly prevalent during early diabetes because the decrease in the host defense mechanism and impaired phagocytosis were noticed immediately in diabetics and these changes do not require much longer time to develop unlike microangiopathy [2].

More number of patients were observed with psoriasis, urticaria, lichen planus, cutaneous amyloidosis, vitiligo acquired perforating disorders, bullous pemphigoid and xanthelasma. There was one patient with eruptive xanthoma with hypertriglyceridemia who was diagnosed to have diabetes based only on clinical presentation. Psoriasis had been significantly associated with diabetes [4, 16, 17]. An association between psoriasis and increased cardiovascular risk and metabolic syndrome has been reported. Hence, while treating a patient with psoriasis, screening for metabolic syndrome and cardiovascular risk factors are advised [4]. Vitiligo can occur in diabetes as a part of multiple auto immune dysfunction. Bhat YJ et al., Raghunatha S et al., Mahajan S et al., Al-Mutairi N et al., Neerja P, Mahmood F et al., observed lesser number of patients under the category of dermatoses commonly associated with diabetes [7-9,14,18,19]. Among 27 patients with neuropathic and ischaemic dermatoses, diabetic foot ulcers and asteatotic eczema were more common in uncontrolled diabetes but the association was not statistically significant. Girisha BS observed 12 patients having diabetic foot ulcer similar to this study [20]. Comparison of important dermatoses in this study with other studies has been shown in [Table/Fig-22] [2,6,8,11,13,15,18,20-22]. Only 21 patients had dermatoses closely associated with diabetes. Only one case of bullous diabeticorum this observed. Studies done by Rao GS et al., and Girisha BS et al., showed similar number of patients having diabetic bulla, seen in two and one patient respectively [2,20]. Again these manifestations also were not significantly associated with blood sugar control. One patient had insulin lipodystrophy in this study. Use of human insulin may be the reason for absence of insulin reaction in this study [8].

Dermatoses	Present study	Studies with similar frequencies	Studies with different frequencies
Fungal infections	89	106 [20] 69 [6]	24 [18] 31 [15]
Bacterial infections	31	20 [18] 34 [6]	67 [15] 80 [11]
Diabetic bulla	1	2 [20] 1 [2]	6 [22]
Eruptive Xanthoma	1	1 [22] 2 [21]	-
Perforating disorders	4	2 [21] 4 [20]	8 [13]
Insulin lipodystrophy	1	1 [22]	4 [8]

[Table/Fig-22]: Comparison of the important dermatoses in present study with other studies [2,6,8,11,13,15,18,20-22].

LIMITATION

This study was a hospital based study and was also conducted for a limited period of time with less number of patients. Therefore, we would like to look forward for larger group studies in general population to validate these findings.

CONCLUSION

In conclusion, we have observed that infections were the most common cutaneous manifestation, which occurred in diabetics with high HbA1C levels (>7) i.e., in uncontrolled diabetes. A good glycaemic control will definitely reduce the incidence and severity of various cutaneous manifestations of diabetes. Therefore health education regarding diabetic control can benefit the patients. Thus, role of a dermatologist is essential for early detection of potentially grave conditions and to provide prompt care for the patients thereby improving the quality of life of diabetic patients.

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