

An Observational Study to Analyze the Pattern of Mucocutaneous Manifestations in Diabetic Patients.

Authors - Dr. Sanjeev Gupta* . M.D., DNB, MNAMS, Dr Sunita Gupta** MD, Dr Nidhi Mittal* MBBS, Dr. Aneet Mahendra* M.D., Dr. Lakshmi Narayan Garg*** MS

Department of Dermatology* and Medicine** and oto rhinolaryngology***. Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala India.

Address for correspondence -Dr. Sanjeev Gupta, #B2, MM Medical College Residential Campus. Mullana Ambala India. Telephone No. + 91-9812017161. e mail- sanjeevguptadr@gmail.com

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INTRODUCTION - Diabetes mellitus is a chronic multisystem disorder. According to World Health Organisation (WHO), the term diabetes mellitus describes a metabolic disorder of multiple aetiology characterized by chronic hyperglycemia with disturbances of carbohydrates, fat and protein metabolism resulting from defects in insulin secretion, insulin action, or both. The clinical symptoms of DM include thirst, polyuria, blurring of vision, and weight loss. In severe form, a non-ketotic hyperosmolar state may develop and lead to stupor, coma and death in absence of effective treatment.¹

According to WHO estimates of diabetes 2011, 285 million people, corresponding to 6.4% of the world's adult population. The number is expected to grow to 438 million by 2030, corresponding to 7.8% of adult population. Out of which 70% of the current cases of diabetes occur in low and middle income countries. With an estimated 50.8 million people living with diabetes, India has the world's largest diabetes population, followed by China with 43.2 million.² Indians are genetically more susceptible to diabetes mellitus compared to other races. Indians settled abroad also show increased prevalence to DM indicating that genetic factors play a role in incidence of diabetes. India will have the largest number of diabetic subjects in the world by 2025 and one out of 5 diabetic subjects in the world will be an Indian. India is going to be the

“Diabetic capital of the world”.^{2,3} The rising prevalence of diabetes in developing countries is closely associated with industrialization and socioeconomic development. The major determinants for projected increase in the number of diabetes in these countries are population growth; age structure and urbanization. With the rise in the urban/rural population ratio in all regions and growing prevalence of obesity among urban dwellers, diabetes will increasingly concentrate in urban areas. Important differences are observed in the disease epidemiology of age structures of developed and developing countries. Previously, a disease of the middle age and elderly, type 2 diabetes has recently escalated in all age groups and is now being seen in the younger age group, including adolescents, especially in high risk population. This means that in developing countries the majority of diabetes patients acquire the condition during most productive years of life. This will have major implications in health care needs.²

MATERIAL AND METHODS- A total of hundred consecutive patients of Diabetes Mellitus (type 1 &2) attending the Department of Dermatology and Medicine at Maharishi Markandeshwar Institute of Medical Sciences and Research, Mullana, Ambala (Haryana) were enrolled in the study. Diabetic patients who were willing to participate of age more than 15 years were included. Patients of Gestational Diabetes Mellitus and who were on immunosuppressants were excluded. After a detailed history with special reference to age, sex, rural/urban background, socioeconomic status according to Uday Parekh Scale, BMI, BP, smoking, alcohol, duration of diabetes, type of diabetes, type of treatment taken, complications (if any) and family history of diabetes was taken from each patient and was recorded in the proforma attached. A complete general, physical, systemic and dermatological examination was done in each patient to detect the type and extent of cutaneous and systemic ailments present if any. Following routine investigations like Hemoglobin, Total leukocyte count, Differential cell count, Preprandial capillary plasma glucose, Peak postprandial capillary plasma glucose and complete urine examination were done in each patient. HbA1c was done in each patient.

Assessment of glycaemic control was done by measuring Preprandial capillary plasma glucose, Peak postprandial capillary plasma glucose and HbA1c. Diabetes was considered to be controlled when Preprandial capillary plasma glucose 3.9–7.2 mmol/L (70–130 mg/dL), Peak postprandial capillary plasma glucose <180 mg/dL and HbA1c < 7.0%. Body Mass Index (BMI)

was taken according to the International classification of adult underweight, overweight and obesity according to BMI.

BMI = Weight (Kg)/ Height (m²) - Underweight <18.50, Normal 18.50 - 24.99 ,
Overweight 25.00 , Pre obese 25.00-29.99, Obese ≥ 30.00

Results- Pattern of cutaneous manifestations among diabetes patients. Cutaneous infections was the commonest cutaneous manifestations present in 71% of patients, followed by condition associated with DM present in 67% of patients, miscellaneous complications were present in 45% of patients, while no patient had complications due to treatment of diabetic mellitus. Cutaneous infections/infestations were present in 71% of patients. Among them fungal infection was the commonest (48%). Out of the fungal infections, dermatophytosis was the most common fungal infection present in 36% of patients followed by candidiasis in 20% . Bacterial infections were present in 17% of total patients. Among them folliculitis and frunculosis were present in 7% patients each. Herpes simplex and herpes zoster were the commonest viral infections being present in 3% of patients each. No patient was reported to have parasitic infestation. Cutaneous conditions associated with DM were present in 67% of patients . Among the cutaneous conditions skin tag was the most common and present in 33 % , followed by chery angioma in 21%, xerosis in 19%, acanthosis nigricans in 18%, generalized pruitus 12%, xanthelasma palpebrarum in 8%, diabetic dermopathy in 7%, yellow discolouration of hand in 5%, diabetic thick skin in 2%, rubeosis faciei in 2% and granuloma annulare in 1%. Conditions related to the complications of DM was present in 19% of total diabetic patients. Out of complications neuropathy, nephropathy and retinopathy were present 6% patients each. CAD in 5%, diabetic ulcer in 3% and PVD in 1% of cases.

DISCUSSION - Cutaneous manifestations of diabetes mellitus generally appear subsequently to the development of the disease, but may be the first presenting sign, and in some cases they may even precede the primary disease manifestations by many years. Some diabetes associated skin conditions are a direct result of the metabolic changes such as hyperglycemia and hyperlipidemia, in addition to other contributing factors, which include progressive damage to the vascular, neurological or immune system⁴. In the present prospective study, one hundred patients were enrolled of age range 25-75 years and mean age 52 years with SD of 10.52 years.

Majority of the patients belonged to age group of 51-60 years (32%) and 41-50 years (27%). The cutaneous manifestations increases as the age advances. Similar observations were reported by various studies carried out by Mahajan *et al*⁵, Sawhney *et al*⁶, Nigam *et al*⁷, Nawaf *et al*⁸. The relative increased in the incidence of cutaneous involvement with age in diabetic patients may be attributed merely to the decreased resistance of body as well as long duration of diabetes.

Males (55%) outnumbered females (45%) in the present study which was in agreement with previous studies^{6,9,10,11}, while Mahajan *et al*⁵, Bhat *et al*¹², and Nigam *et al*⁷ reported that female diabetic patients had significantly higher incidence of cutaneous manifestations. The reason for less number of females could be lack of awareness and negligence on the part of female patients due to illiteracy and rural background. Ninety nine (99%) patients had type-2 DM/ NIDDM, while only one (1%) had type 1/ IDDM. It reflects the general distribution pattern of type 1 DM and type 2 DM in world population. In a study 97.5% of patients belong to type 2 and 2.5% to type 1 DM¹². In another study, 98.8% of patients belong to type 2 and 1.2% to type 1 DM¹³.

In the present study of cutaneous manifestations, majority of patients (50%) had duration of diabetes within 1-5 years and followed by 6- 10 years (21%) which is similar with other studies^{10,12,14}. This increased rate of infections in early part of diabetes onset may be due to decrease in the host defence mechanism and decreased phagocytic activity, which is noticed immediately in uncontrolled diabetes. Since glucose acts as a good culture medium for organisms and blood glucose takes time to attain normal levels, thus leading to increase chances of infections. While for other cutaneous complications of DM apart from infections, is due to deposition of PAS positive material with in lumina of the blood vessels which occurs slowly in the disease process. So as the duration of diabetes increases, there is nonenzymatic glycosylation of dermal collagen and mucopolysaccharides, leading to various manifestations¹². In our study, majority of the patients with cutaneous manifestations had uncontrolled diabetes (64%). Same findings were observed in other studies conducted by Ahmed *et al*¹⁴, Bhat *et al*¹², Sawhney *et al*⁶, Yosipovitch *et al*¹⁵, Nigam *et al*⁷. Uncontrolled diabetes increases the risk of development of microangiopathy related complications or sequelae. This could be due to lack of health related facilities in remote area or ignorance of patients about blood glucose measurements and low literacy rate.

Chances of diabetes increases if family history is positive. A strong family history of diabetes was positive in 33%. Out of the 100 patients screened, 30 patients (30%) had associated systemic co-morbidity such as hypertension. According to Mahajan et al⁵, 53.1% patients were hypertensive. Similar observations was reported by Bhat et al¹² (46.46%), Al- Mutairi et al¹¹ (44%) and Nigam et al⁷ (43%). Hypertension has been hypothesized to accelerate the process of microangiopathy in diabetics. In the present study, among the various dermatological manifestations, infections were the most common dermatoses (71 %), followed by conditions associated with DM (67%), followed by miscellaneous cutaneous findings (45%). Similar findings were reported by other studies^{5,7,10,12}. High incidence of infections can be due to the following factors: a) Hyperosmolality of the hyperglycemic serum which causes diminished chemotaxis. b) Impaired release of cytokines because of lack of insulin. c) Impaired phagocytosis which may be because of diminished leucocyte response caused by thickening of capillary valves. d) Microangiopathy, atherosclerosis, microaneurysms, increase mast cells in the upper dermis and elevated glucose levels may be additional factor¹⁶.

Fungal infections (50%) were the commonest infections followed by bacterial (19%) and viral (6%). This is in accordance with other studies by Mahajan et al⁵, (54.68%), Bhat et al¹² (34.34%), and Al- Mutairi et al¹¹(68%), Yosipovitch et al¹⁵ (32%) where fungal infections were more common. A large number of fungal infections seen in present study may be because, most of patients in our study belonged to lower socioeconomic group residing in rural areas where hot and humid conditions, poor hygiene, overcrowding and negligence were the prevailing factors which in turn predisposes the individuals to such infections. Among the 19 patients having bacterial infections, folliculitis and frunculosis were present in 8 patients each, carbuncle in 2 while cellulitis was present in 1. Similar findings were observed by Mutairi et al¹¹, folliculitis (14), frunculosis (1), carbuncle (2), cellulitis (4) were present out of total of 27 patients having bacterial infections . Among the viral infections, recurrent herpes simplex and herpes zoster was present in 3 patients each. Similar results were seen by Bhat et al¹² and Al- Mutairi et al¹¹. It is difficult to say whether it is an incidental observation or whether compromised resistance of the diabetic state is somehow responsible for precipitating the recurrences. Males outnumbered females in having infections in our study. It may be due to increased likelihood of exposure to the infectious organisms and humid climatic and working conditions. Among the cutaneous

conditions associated with diabetes, Skin tags were the commonest and was present in 33%. Kahana et al¹⁷, and Thappa¹⁸ had similar observations where skin tags was found in 26.3% and 62.85% respectively. So both the studies concluded that skin tags may serve as a marker for Diabetes mellitus.

Acanthosis nigricans was present in 18% of the patients, while Bhat et al¹², Mutairi et al¹¹, Mahajan et al⁵, and Ahmed et al¹⁴ reported a little low incidence of acanthosis nigricans in their study 5.3%, 4.7%, 3%, 2.8% respectively. Acanthosis nigricans and skin tags are the manifestations of insulin resistance, which may be present before the expression of DM. Increased levels of insulin act on insulin like growth factor receptors, resulting in development of acanthosis nigricans. So, the associations between multiple skin tags and DM has been reported. Skin tags have been regarded as a sign of impaired glucose tolerance and increased cardiovascular risk. In the present prospective study cherry angioma was present in 21%, while another study observed in 44.8% of diabetic patient¹⁹. Increased numbers have been recorded in diabetics which may not be correlated and may not be significant.

Xerosis was present in 19% in the present study, while it was present in 18.8% in another study. Xerosis may be due to reduced hydration of stratum corneum and decreased sebaceous gland activity in patients with diabetes, without impairment of stratum corneum barrier function²⁰. Generalized pruritus is commonly seen in patients with diabetes, but its relevance may or may not be correlated. Although pruritus vulvae and balanitis may be the presenting symptoms of diabetes. Autonomic neuropathy, advanced end glycosylation of stratum corneum proteins are the additional factors in addition xerosis may be responsible for pruritus. So, a high incidence of 18% cases having pruritus was seen in present study. Same observations were reported by Mahajan et al⁵, Nigam and Pande⁷. In the present prospective study xanthelasma palpebrarum was present in 8% of the patients, while Rao et al¹⁰ reported 2 cases (2%) of xanthelasma palpebrarum whereas Bhat et al¹² observed in 4 cases(4%). Microangiopathy also involves the skin. The different cutaneous changes because of microangiopathy were diabetic dermopathy and rubeosis faciei. Diabetic dermopathy affects 7-70% of the diabetics, and is more common in men over 50 years of age. The lesser incidence of these conditions in an Indian population can be attributed to dark skinned individuals⁵. In the present study diabetic dermopathy was present in 7%, while the other studies observed diabetic dermopathy varying between 3.5–59 %^{8,9,21}.

Similar low incidence was seen by Bhat et al¹² (11.3%), Mahajan et al⁵ (7%), Mutairi et al¹¹ (5.6%), Ahmed et al¹⁴ (4.2%), and Nigam and Pande⁷(3%). Rubeosis faciei was present in 2% of the patients. Rubeosis faciei has been reported in 3- 59 % of diabetics²². Increased viscosity of blood due to stiff red blood cell membranes result in engorgement of the post capillary venules in the papillary dermis, detected as erythema of the face. It is suggested that these skin changes may eventually be used as a reflection of the patients's current as well as past metabolic status²³. Yellow discolouration of skin is seen in diabetes sometimes, which may be due to probably responsible for yellowing of the skin and nails. Yellow discolouration of skin was present in 5% of the patients in the present study , while the other studies reported yellow skin varying from 2% - 5% 26. Similarly in diabetics, thick skin may be present due to collagen proliferation promoted by insulin excess. This observation was made in 2% of cases in present study.

Granuloma annulare is associated with Diabetes Mellitus, which was seen in 1% of cases. Similar observations were made by Ahmed et al²⁴ and Mahajan et al⁵. In the present prospective study, diabetic foot ulcer was present in 3% of the patients. Same findings were there in another study reported to be 2% and 4%²³.The causes of foot ulcer were infections, ill fitting foot wear, bare foot walking. This underlines the significance of health education regarding foot care in diabetic patients. Apart from infections and cutaneous conditions associated with diabetes, there can be some other miscellaneous cutaneous findings like discolouration of nail, decrease hair over lower legs, eczemas, psoriasis, lichen planus, alopecia, amyloidosis, urticaria, perforating dermatosis. In the present study discolouration of nail, decrease hair over lower legs, eczemas, psoriasis, pigmented purpuric dermatosis , lichen planus, seborrheic keratosis, alopecia, nevus, macular amyloidosis, vitiligo, prurigo nodularis, perforating dermatosis, syringoma, urticaria and acne keloidalis nuchae were present in 11%, 10%, 10%, 5%, 5%, 4%, 4%, 3%, 3%, 2%, 2%, 1%, 1%, 1%, 1% respectively. Some of the conditions like vitiligo, alopecia, lichen planus are known to occur in DM as a part of polyglandular autoimmune syndrome. Diabetes is also supposed to be autoimmune. So these autoimmune diseases can coexist together.

Treatment of DM is done with oral hypoglycemic drugs and insulin. So the side effects of different analogues of insulin like hypertrophy, atrophy, insulin site reaction can be seen. No drug reaction to insulin was as most of patients use insulin at different sites, also use of purified and recombinant insulin decrease the chances of insulin reactions. In the present study no

adverse drug reaction to oral hypoglycemic drugs and insulin was seen, while other studies also reported minimal adverse drug reactions^{5,13}. In the present study, when a comparison of pattern of cutaneous manifestations Vs HbA1c was done, it was found that the cutaneous infections, dermatoses associated with microangiopathy and miscellaneous cutaneous findings were more common in patients with HbA1c ≥ 7 . Diabetic patients may have one or more than one cutaneous manifestations of above said groups. In the present study 26%, 25%, 21%, 12%, 9%, 7% patients had 3, 4, 2, 1, 5, 6 cutaneous manifestations respectively, While similar observations were reported by Goyal et al²⁵. Number of cutaneous manifestations in present studies were more because most of the patients had uncontrolled diabetes, poor hygiene, lower socioeconomic status, illiterate and rural background.

CONCLUSION- Skin is not spared by complications of diabetes, being it's a multisystemic disease. Manifestations like infections appear early in the disease since diabetes remain undetected till its diagnosis and usually patient is not tuned to regular treatment and proper diet control in early diabetes, thus leading to persistent hyperglycaemia which in turn predisposes patient to infections. Other complications like microangiopathy, neuropathy etc appear late due to advanced end glycosylation. Some/ extensive cutaneous manifestations can heighten the suspicion of a dermatologist regarding the diagnosis of diabetes. Hence it is very important to educate/ counsel patient for proper self examination, proper diet control and regular treatment at regular intervals to detect early infections. Since skin is a largest organ and any abnormalities/ lesions on skin can be easily picked up by the patient or dermatologist. So, a proper diagnosis and timely treatment of the same can improve quality of life.

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TABLE – Pattern of Cutaneous Manifestations

S. NO.	CUTANEOUS MANIFESTATIONS		(N = 100)			PERCENTAGE (%)
			PRESENT	ABSENT	TOTAL	
1.	INFECTIONS (total pts)		71	29	100	71
		Fungal	48			
		T.CORPORIS	17			
		T. CRURIS	14			
		ONYCHOMYCOSIS	14			
		T.PEDIS	4			
		T. UNGIUM	3			
		CANDIDAL BALANOPOSTHITIS	6			
		PARONYCHIA	6			
		VAGINAL CANDIDAL	5			
		CUTANEOUS CANDIDIASIS	3			
		Bacterial	17			
		FOLLICULITIS	7			
		FRUNCULOSIS	7			
		CARBUNCLE	2			
		CELLULITIS	2			
		Viral	6			
	HERPES SIMPLEX	3				
	HERPES ZOSTER	3				
2.	Cutaneous condition associated with dm (total pts)		67	33	100	67
		SKIN TAG	33			
		CHERY ANGIOMA	21			
		XEROSIS	19			
		ACANTHOSIS NIGRICANS	18			
		GEN. PRURITUS	12			
		XANTHELASMA PALPEBRARUM	8			
		DIABETIC DERMOPATHY	7			
		YELLOW DISCOLOURATION OF HAND	5			
		DIABETIC THICK SKIN	2			
		RUBEOISIS FACIEI	2			

	GRANULOMA ANNULARE	1			
3.	CUTANEOUS CONDITION ASSOCIATED WITH TREATMENT OF DM	NIL	100	100	NIL
4.	MISSCELLANEOUS COMPLICATIONS (total pts)	45	55	100	45
	DISCOLOURATION OF NAIL	11			
	↓ HAIR LOWER LIMB	10			
	ECZEMAS	10			
	PSORIASIS	5			
	PIGMENTED PURPURIC DERMATOSES	5			
	LICHEN PLANUS	4			
	SEBORRHEIC KERATOSIS	4			
	ALOPECIA	3			
	NEVUS	3			
	MACULAR AMYLODOSIS	2			
	VITILIGO	2			
	PRURIGO NODULARIS	2			
	PERFORATING DERMATOSIS	1			
	SYRINGOMA	1			
	URTICARIA	1			
	ACNE KELOID NUCHAE	1			