"A CROSS SECTIONAL STUDY OF CUTANEOUS MANIFESTATIONS IN 100 PATIENTS OF DIABETES MELLITUS."

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Place : Belgaum

LIST OF ABBREVIATIONS USED

DM	=	Diabetes Mellitus
DNA	=	Deoxyribonucleic acid
ADA	=	American Diabetes Association
WHO	=	World Health Organisation
IDDM	=	Insulin Dependent Diabetes Mellitus
HLA	=	Human Leukocyte Antigen
MHC	=	Major Histocompatibility Complex
PP	=	Pancreatic Polypeptide
ICA	=	Islet Cell Autoantibodies
IIA	=	Insulin Autoantibodies
GAD	=	Glutamic Acid Decarboxylase
IGT	=	Impaired Glucose Tolerance
BMI	=	Body Mass Index
NIDDM	=	Non Insulin Dependent Diabetes Mellitus
HbA1c	=	Glycosylated/ Glycated Hemoglobin
PAI-1	=	Plasminogen Activator Inhibitor-1
OGTT	=	Oral Glucose tolerance test
FPG	=	Fasting plasma glucose
BG	=	Blood glucose
DKA	=	Diabetic ketoacidosis
MDI	=	Multiple daily injection
NPH	=	Neutral Protamine Hagedorn
CVD	=	Cardiovascular disease
KATP	=	ATP sensitive posstasium channels

PPAR	=	Peroxisome Proliferator-Activated Receptor
WBC	=	White blood cells
HMP	=	Hexose monophosphate shunt
NADPH	=	Nicotinamide adenine dinucleotide phosphate-oxidase
BP	=	Blood pressure
GLUT	=	Glucose transporter
AGE	=	Advanced glycosylation end-products
VCAM-1	=	Vascular cell adhesion molecule 1
VEGF	=	Vascular endothelial growth factor
PKC	=	Protein kinase C
NO	=	Nitric oxide
UDP	=	Uridinediphosphate
GFAT	=	Glutamine: fructose-6-phosphate amidotransferase
TGF	=	Transforming growth factor
Ps	=	Pseudomonas
Pr	=	Proteus
RCM	=	Rhinocerebral mucormycoses
sp.	=	species
NLD	=	Necrobiosis lipoidica diabeticorum
GA	=	Granuloma annulare
PUVA	=	Psoralen + Ultraviolet A treatment
DD	=	Diabetic dermopathy
UV	=	Ultraviolet
PVD	=	Peripheral vascular disease
PCT	=	Porphyria cutanea tarda

LPL	=	Lipoprotein lipase
TCA	=	Trichloroacetic acid
NME	=	Necrolytic migratory erythema
SD	=	Scleredema diabeticorum
GAG	=	Glycosaminoglycans
LJM	=	Limited Joint Mobility
PIP	=	Proximal interphalyngeal
MCP	=	Metacarpophalyngeal
NEG	=	Non enzymatic glycosylation
LP	=	Lichen planus
Ca	=	Carcinoma
PPD	=	Pigmented purpuric dermatoses
SLE	=	Systemic lupus erythematosus
DH	=	Dermatitis herpetiformis
PAS	=	Periodic acid-Schiff

ABSTRACT

Background and objectives:

Diabetes Mellitus (DM) is a worldwide problem and the most common endocrine disorder. The skin is affected by both the acute metabolic derangements and the chronic degenerative complications of diabetes The objectives of the study was to analyze the clinical pattern of cutaneous manifestations in patients of Diabetes Mellitus, to study the relation of these cutaneous manifestations with demographic data like age, sex and duration of Diabetes and to compare the cutaneous manifestations in controlled and uncontrolled Diabetes.

Materials and Methods:

The present study was a one-year cross sectional study from January 2010 to December 2010. All confirmed cases of Diabetes Mellitus with cutaneous manifestations irrespective of age, sex, duration of illness and associated diseases, willing to participate in the study were included in the study. Routine haematological and urine investigations, FBS, RBS and HbA1c levels were carried out in all patients.

Results:

A total of 100 patients of diabetes mellitus with cutaneous manifestations were studied. Majority belonged to the 5^{th} decade (33%) and 4^{th} decade (27%) respectively.

Males constituted 69% of the cases and male to female ratio was 2.2:1.Type 2 DM was most commonly observed (96%) as compared to Type 1 DM (4%). Among the 100 diabetic patients, 22 patients (22%) had moderate control of DM with HbA1c levels in the range of 7.1%-8%, while 63 patients (63%) had a poor control of DM with HbA1c levels >8%. Hypertension was the most commonly associated systemic illness (46%). Cutaneous infections (62%) were the most commonly observed manifestation of which fungal infections (37%) were most frequently observed. Some

of the other dermatoses observed were generalized pruritus (23%), acrochrodons (8%), diabetic dermopathy (7%), peripheral vascular disease (4%), diabetic foot (4%), vitiligo (4%) xanthelasma palpebrerum(2%) diabetic bullae (1%) and macular amyloidosis(1%). Cutaneous infections, dermatoses associated with microangiopathy, metabolic diseases and cutaneous reactions to diabetic therapy were more common in the uncontrolled diabetic patients which was meaningfully significant.

Conclusion:

Infections were the most common cutaneous manifestations in diabetics, followed by dermatoses most commonly associated with diabetes. Proper skin care and long-term control of blood glucose levels may reduce the risk of some of the skin lesions in diabetic subjects.

Key words: Cutaneous manifestations, Diabetes Mellitus, glycosylated hemoglobin

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INTRODUCTION

It is a well-known fact that the skin is referred to as window or mirror to the body. It is very much true as many internal ailments are detected by interrogating the various cutaneous signs and symptoms. This has got tremendous significance in most of the situations as early diagnosis is very valuable in the management of systemic disease

The skin is the largest and the most visible organ of the body. In some instances, the initial and the most prominent complaints of the patient are related to alterations in the skin and therefore the dermatologist will at times be the first physician consulted.

Diabetes Mellitus (DM) is a worldwide problem and the most common endocrine disorder. Its prevalence is increasing in the present scenario of a sedentary lifestyle in the general population. Abnormalities of insulin and elevated blood glucose levels lead to metabolic, vascular, neurological and immunological abnormalities. Affected organs include the cardiovascular, renal and nervous systems, eyes and the skin.

The skin is affected by both the acute metabolic derangements and the chronic degenerative complications of diabetes. Although the mechanism of many diabetes associated skin conditions remains unknown, the pathogenesis of others is linked to abnormal carbohydrate metabolism, other altered metabolic pathways, atherosclerosis, microangiopathy, neuron degeneration and impaired host mechanisms.

Skin manifestations can be the first presenting sign of diabetes but more often appear in known diabetic patients during the course of the disease as observed in 43-

66% of diabetic patients. The cutaneous manifestations are well known and considered common.

This work is an attempt to analyze the pattern of cutaneous manifestations of diabetes in view of the increasing prevalence of diabetes in the present scenario of sedentary lifestyle in the general population.

OBJECTIVES

Primary Objective:

To study the clinical pattern of cutaneous manifestations in patients of Diabetes Mellitus.

Secondary objectives:

1. To study the relation of these cutaneous manifestations with demographic data like age, sex and duration of Diabetes.
2. To compare the cutaneous manifestations in controlled and uncontrolled Diabetes.

REVIEW OF LITERATURE

HISTORICAL ASPECTS

Diseases with the clinical features of diabetes have been recognized since antiquity. The **Ebers papyrus** dating from **1550 BC**, describes a polyuric state that resembles diabetes.

Figure 1: The Ebers Papyrus

The word "diabetes" was 1st used by **Aretaeus of Cappadocia** in the **2nd century AD**. It comes from the Greek, meaning syphon. Aretaeus gave a clinical description of the disease, noting the increased urine flow, thirst and weight loss, features that are instantly recognizable today.[1]

The sweet, honey - like taste of urine in polyuric states, which attracted ants and other insects, was reported by Hindu physicians such as **Sushrut (Susruta)** during the **5th and 6th centuries AD.**[2] These descriptions even mention two forms of diabetes, the more common occurring in older, overweight and indolent people, and

the other in lean people who did not survive for long. This empirical subdivision predicted the modern classification into type 1 and type 2 diabetes.

In 17th century English physician, **Thomas Willis (1621 – 75)**, rediscovered the sweetness of diabetic urine. Nearly a century later, the Liverpool physician **Matthew Dobson (1735 – 84)** showed that the sweetness of urine and serum was caused by sugar. **John Rollo (1809)** was the first to apply the adjective 'mellitus' to the disease.

In the 19th century, the French physiologist **Claude Bernard (1813 – 78)** made many discoveries relating to diabetes. Among these was the finding that the sugar that appears in the urine was stored in the liver as glycogen. Bernard also demonstrated links between the central nervous system and diabetes when he observed temporary hyperglycaemia (piqûre diabetes) when the medulla of conscious rabbits was transfixed with a needle.

In 1889, **Oskar Minkowski (1858 – 1931)** and **Joseph von Mering (1849 – 1908)** from Strasbourg removed the pancreas from a dog to see if the organ was essential for life. The animal displayed typical signs of diabetes, with thirst, polyuria and wasting, which were associated with glycosuria and hyperglycaemia. This experiment showed that a pancreatic disorder causes diabetes, but they did not follow up on the observation.

Paul Langerhans (1847 – 88) from Berlin, in his doctoral thesis of 1869, was the first to describe small clusters of cells in teased preparations of the pancreas. He did not speculate on the function of the cells, and it was **Edouard Laguesse** in France who later **(1893)** named the cells 'islets of Langerhans' and suggested that they were endocrine tissue of the pancreas that produced a glucose - lowering hormone.

In the early 20th century, several workers isolated impure hypoglycaemic extracts from the pancreas, including the Berlin physician **Georg Zuelzer (1840 – 1949)**, the Romanian **Nicolas Paulesco (1869 – 1931)**, and the Americans **Ernest Scott (1877 – 1966)** and Israel **Kleiner (1885 – 1966)**.

Insulin was discovered in **1921** at the University of Toronto, Canada, through a collaboration between the surgeon **Frederick G Banting (1891 – 1941),** his student assistant **Charles H Best (1899 – 1978),** the biochemist **James B Collip (1892 – 1965)** and the physiologist **JJR Macleod (1876 – 1935).**

Banting and Best made chilled extracts of dog pancreas, injected them into pancreatectomised diabetic dogs, and showed a fall in blood glucose concentrations.

Banting and Best's notes of the dog experiments refer to the administration of 'isletin', later called insulin by them at the suggestion of Macleod. They were unaware that the Belgian Jean de Meyer had already coined the term 'insuline' in 1909. (All these names ultimately derive from the Latin for 'island').

Collip improved the methods for the extraction and purification of insulin from the pancreas, and the first diabetic patient, a 14 - year - old boy called Leonard Thompson, was treated on 11th January 1922. A commercially viable extraction procedure was then developed in collaboration with chemists from Eli Lilly and Co. in the USA, and insulin became widely available in North America and Europe from 1923. The **1923 Nobel Prize for Physiology or Medicine** was awarded to Banting and Macleod, who decided to share their prizes with Best and Collip.

The American physician **Elliot P Joslin (1869 – 1962)** was one of the first doctors to gain experience with insulin.

The elucidation in **1955** of its primary structure (amino acid sequence) was done by the Cambridge UK scientist **Frederick Sanger (1918)**, who received the Nobel Prize for this work in 1958.

Oxford - based **Dorothy Hodgkin (1910 – 1994),** another Nobel Prize winner, and her colleagues described the **three - dimensional structure of insulin** using X - ray crystallography **(1969).**[1]

Other milestones in insulin pharmacology have included invention of delayed-action preparations in 1930s and 1940s; synthetic human insulin in 1979; and in the 1990s novel insulin analogs by recombinant DNA technology

The first sulfonylurea carbutamide was introduced in 1955, followed by tolbutamide in 1957 and chlorpropamide in 1960. The biguanide phenformin became available in 1959 and metformin in 1960.[3]

DEFINITION AND CLASSIFICATION OF DM

Diabetes mellitus is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat, and protein metabolism resulting from defects in insulin secretion, insulin action, or both.[4]Insulin is essentially the only hormone that can lower blood glucose.

There are two main categories of diabetes:

- **Type 1** is caused by an autoimmune destruction of the insulin - producing β cell of the islets of Langerhans in the pancreas (absolute deficiency)
- **Type 2** is a result of both impaired insulin secretion and resistance to its action – often secondary to obesity (relative deficiency).

Diabetes is common and is becoming more common. Age - adjusted prevalence is set to rise from 5.9% to 7.1% (246 – 380 million) worldwide in the 20 – 79 year age group, a 55% increase .The relative proportions of type 1 to type 2 vary from 15:85 for Western populations to 5:95 in developing countries.[5]

The effects of diabetes mellitus include long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, heart, and blood vessels. Diabetes may present with characteristic symptoms such as thirst, polyuria, blurring of vision, weight loss, and polyphagia, and in its most severe forms, with ketoacidosis or nonketotic hyperosmolarity, which, in the absence of effective treatment, leads to stupor, coma, and death.[4]

The current clinical classification, proposed by the American Diabetes Association (ADA) in 1997 and adopted by the World Health Organization (WHO) in 1999 is as follows:[4]

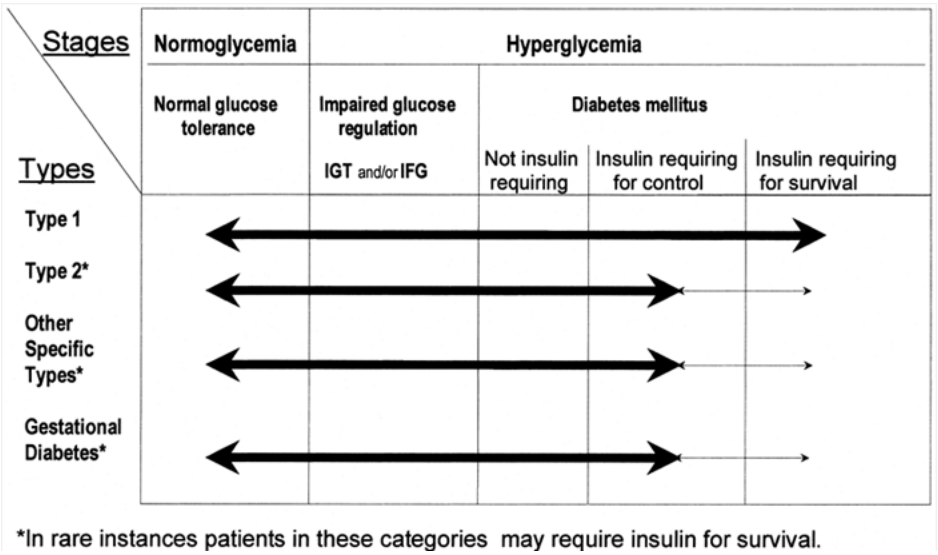

Figure 2: Clinical classification of Diabetes Mellitus proposed by ADA and adopted by WHO

WHO classification of DM and allied categories of glucose intolerance adopted in 1980 and modified in 1985 is as follows: [6]

I. Clinical classes

A. Diabetes mellitus

1. Insulin-dependent diabetes mellitus

2. Non-insulin-dependent diabetes mellitus

(a) Non-obese

(b) Obese

3. Malnutrition-related diabetes mellitus

4. Other types of diabetes associated with certain conditions and syndromes:

(a) Pancreatic disease

(b) Disease of hormonal aetiology

(c) Drug-induced or chemical-induced conditions

(d) Abnormalities of insulin or its receptors

(e) Certain genetic syndromes

(f) Miscellaneous

B. Impaired glucose tolerance

(a) Non-obese

(b) Obese

(c) Associated with certain conditions and syndromes

C. Gestational diabetes mellitus

II. Statistical risk classes (subjects with normal glucose tolerance but substantially increased risk of developing diabetes)

1. Previous abnormality of glucose tolerance

2. Potential abnormality of glucose tolerance

The etiologic classification of diabetes mellitus currently recommended by WHO and the ADA is as follows:[4]

I. **Type 1**(β-cell destruction, usually leading to absolute insulin deficiency)

II. **Type 2** (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly secretory defect with or without insulin resistance)

III. Other specific types

a. Genetic defects of β-cell function

b. Genetic defects in insulin action

c. Diseases of the exocrine pancreas

d. Endocrinopathies

e. Drug- or chemical-induced

f. Infections

g. Uncommon forms of immune-mediated diabetes

h. Other genetic syndromes sometimes associated with diabetes

IV. **Gestational diabetes**

Table 1: Difference between Type 1 and Type 2 Diabetes[7]

Type 1 Diabetes	Type 2 Diabetes
Sudden onset with severe symptoms of thirst and ketoacidosis (vomiting, hyperventilation, dehydration)	Usually insidious onset of tiredness, thirst, polyuria, nocturia
Recent, marked weight loss	Often no recent weight loss
Usually lean	Usually overweight or obese
Spontaneous ketosis	Frequent infections, e.g. urine, skin, chest
Life-threatening; needs urgent insulin replacement	Symptoms may be minimal and/or ignored by patient
Absent C peptide	C peptide detectable
Markers of autoimmunity present (e.g-islet cell antibodies)	No markers of autoimmunity. Often other features of metabolic syndrome, e.g hypertension

EPIDEMIOLOGY

According to recent estimates, approximately 285 million people worldwide (6.6%) in the 20-79 year age group will have diabetes in 2010 and by 2030, 438 million people (7.8%) of the adult population, is expected to have diabetes. The largest increases will take place in the regions dominated by developing economies.[8]

Table 2: The "Top 10" countries in the world, in terms of the number of people with diabetes, for 2010 and 2030 [9]

Rank	Country/Territory	2010 (Millions)	Country/Territory	2030 (Millions)
1	India	50.8	India	87.0
2	China	43.2	China	62.6
3	U.S	26.8	U.S	36.0
4	Russian Federation	9.6	Pakistan	13.8
5	Brazil	7.6	Brazil	12.7
6	Germany	7.5	Indonesia	12.0
7	Pakistan	7.1	Mexico	11.9
8	Japan	7.1	Bangladesh	10.4
9	Indonesia	7.0	Russian Federation	10.3
10	Mexico	6.8	Egypt	8.6

The global increase in the prevalence of diabetes is due to population growth, aging, urbanization and an increase of obesity and physical inactivity. The primary determinants of the epidemic are the rapid epidemiological transition associated with changes in dietary patterns and decreased physical activity. Unlike in the West, where older populations are most affected, the burden of diabetes in Asian countries is

disproportionately high in young to middle-aged adults. This could have long-lasting adverse effects on a nation's health and economy, especially for developing countries.[8]

TYPE I DM (IDDM)[10]

The most common cause of type 1 diabetes (over 90% of cases) is T-cell mediated autoimmune destruction of the islet ß cells. The exact aetiology is complex and still not perfectly understood. However, it is probable that environmental factors trigger the onset of diabetes in individuals with an inherited predisposition. Unless insulin replacement is given, severe insulin deficiency results in hyperglycemia and ketoacidosis, the biochemical hallmarks of type 1 diabetes.

Familial clustering of type 1 diabetes provides evidence for complex genetic factors in its aetiology. In siblings of children with type 1 diabetes, 5-6% have developed type 1 diabetes by the age of 15 years, while 20% develop diabetes if they are human leukocyte antigen (HLA) identical with their diabetic sibling (for comparison, the general population is about 0.4%). However, only 10-15% of type 1 diabetes occurs in families with the disease ('multiplex') and most cases are said to be 'sporadic'.

The frequency of type 1 diabetes is increasing in many countries. In Europe, the overall increase is 3.4% per year, but the increase is particularly notable in those diagnosed under the age of 5 years, where it is 6.3% per year. Based on these figures, the incidence of type 1 diabetes may be 40% higher in 2010 than in 1998. This sharp rise in frequency over a short period of time suggests the changing environmental factors that operate in early life, rather than any influence of the genetic pattern of the population.

Genetic susceptibility to type 1 diabetes is most closely associated with HLA genes that lie within the major histocompatibility complex (MHC) region on the short arm of chromosome 6 (this locus is now called $IDDM_1$). Over 95% of Caucasian type 1 diabetic subjects carry HLA-DR3 and/or DR4 (class II antigens) , as compared with only 50% in non-diabetic individuals.

Class II HLAs (HLA-D) play a key role in presenting foreign and self-antigens to T-helper lymphocytes and therefore in initiating the autoimmune process. Polymorphisms in the DQB_1 gene that result in amino-acid substitutions in the class II antigens may affect the ability to accept and present autoantigens derived from ß cell. This is a critical step in 'arming' T lymphocytes, which initiate the immune attack against the ß cells.

Evidence for **autoimmunity** in the pathogenesis of type 1 diabetes includes the presence of chronic inflammatory mononuclear cell infiltrate (**'insulitis'**) associated with the residual ß cells in the islets of recently diagnosed type 1 diabetic patients.The infiltrate consists mainly of T lymphocytes and macrophages. Later in the disease, there is complete loss of ß cells, while the other islet cell types (α, δ and PP cells) all survive.

A major marker of **insulitis** is the presence in newly diagnosed type 1 diabetic patients of circulating islet-related autoantibodies, such as islet cell autoantibodies (ICAs), insulin autoantibodies (IAAs), IA-2 antibodies and glutamic acid decarboxylase (GAD) autoantibodies. Type 1 diabetes manifests clinically after a prodromal period of months or years, during which immunological abnormalities, such as circulating islet autoantibodies, can be detected, even though normoglycemia

is maintained. The greatest risk of developing type 1 diabetes is associated with the presence of more than one circulating autoantibody.

An autoimmune basis for type 1 diabetes is also suggested by its association with other autoimmune diseases:

- Addison's disease
- Graves' disease
- Hypothyroidism
- Hypogonadism
- Pernicious anaemia
- Vitiligo
- Autoimmune polyglandular syndromes, type 1 and 2

Environmental and maternal factors: The factors most often implicated are viruses, and diet and toxins, but a number of other influences, such as early feeding with cow' s milk and psychological stress, are being investigated.

Many people with recent - onset type 1 diabetes have serological or clinical evidence of **coxsackie B virus infection**, particularly the B4 serotype. Marked islet cell damage has been detected in children who died from coxsackie B virus infection. Viruses may target the β cells and destroy them directly through a cytolytic effect or by triggering an autoimmune attack.

Wheat gluten is a potent diabetogen in animal models of type 1 diabetes and 5-10% of type 1 diabetics have gluten-sensitive enteropathy (coeliac disease). Wheat may induce subclinical gut inflammation and enhance gut permeability to lumen

antigens in some type 1 diabetic patients, which may lead to a breakdown in tolerance for dietary proteins. Other possible diabetogenic factors in diet include N-nitroso compounds, speculatively implicated in Icelandic smoked meat.

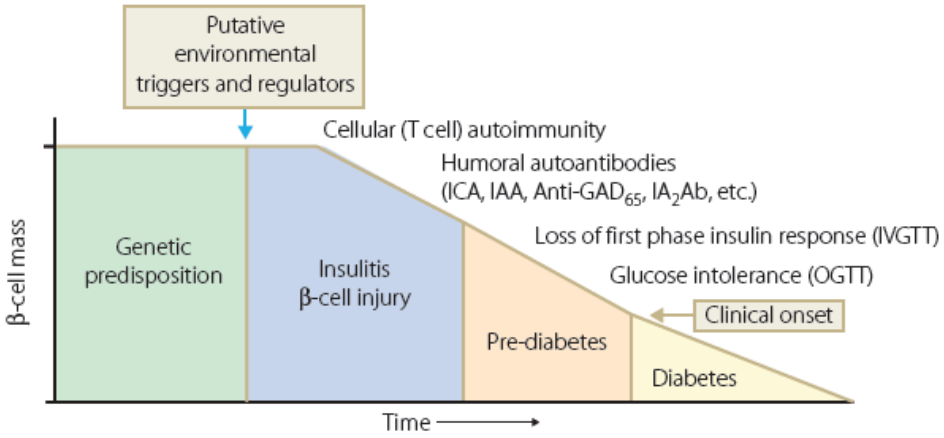

Figure 3: Depiction of evolution of type 1 diabetes.

TYPE 2 DIABETES[11]

It is the most common type of diabetes, and accounts for about 85% of cases in Caucasian populations. Various clinical risk factors are associated with the disease, such as

- Race/geographical location
- Age
- Obesity
- Physical inactivity
- Family history of diabetes
- Previous gestational diabetes

The prevalence of Type 2 diabetes is set to increase to around 380 million persons worldwide by 2025, with the highest rates in the Eastern Mediterranean and Middle East, North and South America.

There is a large variation in its prevalence in different countries. The highest rates are found in some Native American tribes, notably the Pima Indians in Arizona, USA (50%) and in the South Pacific Island of Nauru (30.7%) Low rates are found in poorly developed rural communities, such as parts of Africa (Tonga, 12.9%), the Philippines 7.6% and China 4.1%.

The highest number of people with diabetes is currently in the 40 – 59 - year - old age group, but there will be almost parity with 60 – 79 year olds by 2025, at 166 and 164 million worldwide respectively.

The prevalence of type 2 diabetes and IGT increases with age. Each affect about 10-20% of subjects over the age of 65 years in many western countries.The peak age of onset in developed countries is about 60-70 years.

In developing countries, the peak age of onset is now 40-45 years, 10-20 years earlier as compared to the western world. Type 2 diabetes is now starting to present in children and adolescents, usually developing in a background of obesity and a positive family history of diabetes. First reported in susceptible ethnic groups, such as Native Americans, childhood cases are now being reported throughout the world.

Urban vs Rural

There is a global trend for rates of diabetes to increase in populations as they move from a rural to an urban existence. Social deprivation, unemployment and

poverty in city dwellers may co-segregate with diabetogenic lifestyle factors, such as decreased physical activity, westernized diet and obesity.

Obesity plays an important role in development of type 2 diabetes. About 80% of type 2 diabetic subjects are obese, and the risk of developing diabetes increases progressively as the body mass index [BMI, weight/height (m^2)] increases. BMI > 35 kg/m^2 increases the risk of type 2 diabetes developing over a 10 - year period by 80 - fold, as compared to those with a BMI < 22 kg/m^2 . The pattern of obesity is also important in that central fat deposition has a much higher risk for development of diabetes compared to gluteofemoral deposition.[11]

Low levels of **physical exercise** also predict the development of type 2 diabetes, possibly because exercise increases insulin sensitivity and help prevent obesity. Subjects who exercise the most have a 25 – 60% lower risk of developing type 2 diabetes regardless of other risk factors such as obesity and family history.[12]

Evidence for a **genetic basis** for type 2 diabetes comes from a clear familial aggregation, but it does not segregate in a classic Mendelian fashion. About 10% of patients with type 2 diabetes have a similarly affected sibling.

The main defects in ß cell function in type 2 diabetes include:[13]

- Markedly reduced first and second - phase insulin response to intravenous glucose, and a delayed or blunted response to mixed meals
- Alterations in pulsatile and daytime oscillations of insulin release
- Increase in proportions of plasma proinsulin
- Split of proinsulin peptides relative to insulin.

Insulin resistance is often associated with a clustering of clinical and biochemical features, known as '**metabolic syndrome X**' or the '**insulin resistance syndrome**' which manifests as glucose intolerance, hypertension, hyperinsulinemia, central obesity, accelerated atherosclerosis, dyslipidemias (elevated triglycerides and low HDL), increased fibrinogen, and increased PAI-1.

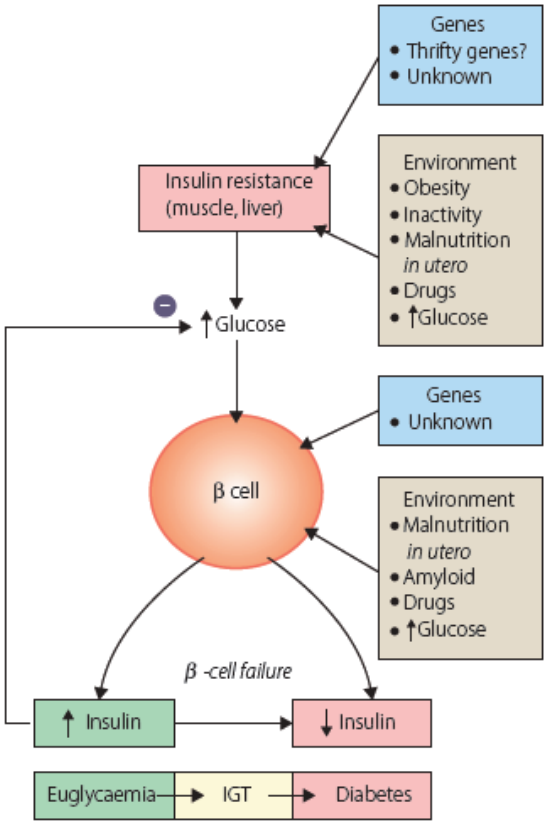

Figure 4 : Pathogenesis of Type 2 Diabetes. Both genetic and environmental factors contribute to both insulin resistance and beta cell failure[17]

Insulin resistance can occur in various tissues, liver, muscle etc. After glucose ingestion, insulin is released into the portal vein and is carried to the liver where it binds to specific receptors on the hepatocytes and suppresses the hepatic glucose output.

Failure of the liver to perceive this signal results in the increased hepatic glucose output and is manifested as raised blood glucose levels in NIDDM.[11]

DIAGNOSIS:[7]

Diabetes can be diagnosed in several ways.

• HbA 1c ≥ 6.5% (48 mmol/mol).

• A casual (random) plasma glucose level ≥ 11.1 mmol/L (200 mg/dL) in someone with typical symptoms of diabetes.

• A fasting plasma glucose level ≥ 7.0 mmol/L (126 mg/dL).

• A plasma glucose level ≥ 11.1 mmol/L (200 mg/dL) 2 hours after a 75 g load of glucose given by mouth (the oral glucose tolerance test – OGTT).

Intermediate categories of hyperglycemia: prediabetes

During the natural history of all forms of diabetes, the disease passes through a stage of impaired glucose tolerance (IGT), defined as a plasma glucose of 7.8-11.0 mmol/L (140-200mg/dl) 2 hours after an OGTT.

Impaired fasting glycemia is an analogous category based on fasting glucose levels, and is defined as FPG of 6.1-6.9 mmol/L (110-126 mg/dL).

Impaired glucose tolerance and IFG are intermediate metabolic stages between normal glucose homeostasis and diabetes. They are both risk factors for future diabetes and cardiovascular disease, but the 2 - hour plasma glucose concentration is a particularly strong predictor of cardiovascular risk and mortality.

For an OGTT, the subject is tested in the morning after an overnight fast, in the seated position. After taking a fasting blood sample, 75 g of glucose is given by

mouth, often in the form of a glucose drink. For children, the glucose dose is calculated as 1.75 g/kg. A further blood sample is taken at 2 hours, and the fasting and 2 - hour glucose values are interpreted as below:

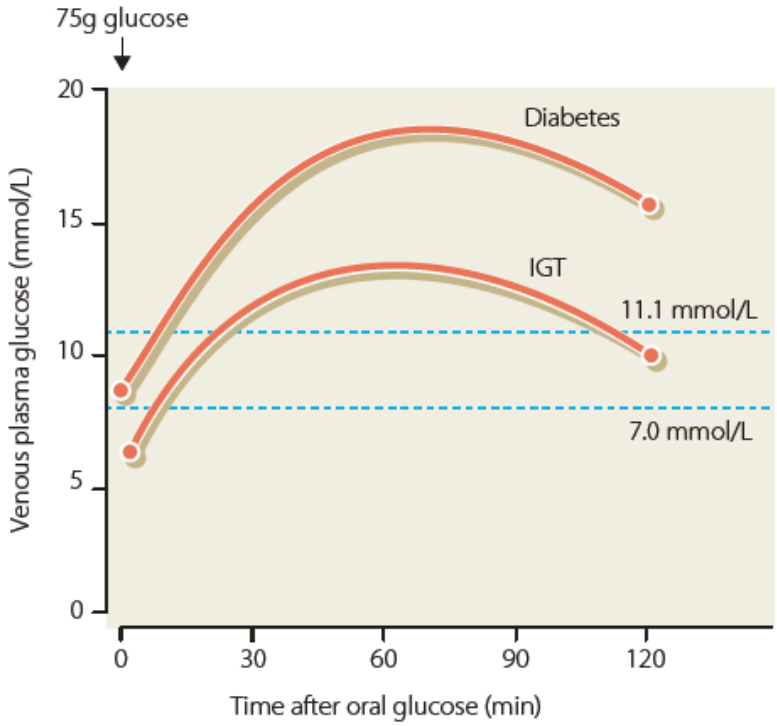

Figure 5:Diagnosis of diabetes and IGT by the oral glucose tolerance test.

Longer term indices of hyperglycaemia include the glycated haemoglobin percentage (HbA1c), a measure of integrated blood glucose control over the preceding few weeks. HbA1c is used primarily to assess glycaemic control among people with diabetes on treatment (aiming for HbA1c 6 – 7%).

Table 3: INDICATORS OF GLYCEMIC CONTROL[14]

Indicator	Main clinical use
Urine glucose	Poor index of BG, useful for surveillance in stable non-insulin treated type 2 diabetes
Blood glucose Fasting Diurnal circadian profiles	 Correlated with mean daily BG and HbA1c in type 2 diabetes Self-monitoring of BG, hospital assessment
Glycated haemoglobin	Glycemic control (mean) over preceding 1-3 months
Glycated serum protein, e.g-fructosamine	Glycemic control (mean) over preceding 2 weeks
Urine and blood ketones	Insulin deficiency, warning of DKA, monitoring during intercurrent illness
Other blood metabolites/hormones Cholesterol (total and HDL) and triglyceride	 Cardiovascular risk factors

In clinical practice, HbA1c provides an objective measure of long-term glycemic control in a single measurement. As a result of the links established between control and tissue complications by major trials in type 1 and type 2 diabetes, the HbA1c level can also be regarded as a risk factor for the development of microangiopathy.[14]

The American Diabetes Association recommends that the goal of diabetes therapy should be to achieve an HbA1c <7%, and that the treatment action should be taken when values are consistently >8% .[15]

TREATMENT

Type 1 Diabetes:[16]

Modern management of type 1 diabetes comprises a package of measures including:

1. Multiple daily injections for a more physiological insulin replacement
2. Assessment of glycaemic control using blood glucose self - monitoring as well as clinical tests such as glycated haemoglobin (HbA1c)
3. Insulin dosage adjustment according to diet and exercise
4. A healthy diet and carbohydrate counting
5. Intensive diabetes education.

Insulin replacement:[17]

The objective of insulin replacement is to mimic the insulin secretion pattern in the person without diabetes with multiple subcutaneous injections. Insulin is usually injected subcutaneously and regimens comprise short - acting (soluble, regular or analogue) insulin to simulate the normal meal time surge, together with longer acting insulin which is used to provide the background or basal concentration. This combination is called the 'basal - bolus ' regimen or multiple daily injection (MDI) therapy.

Other routes of insulin administration such as intravenous infusion or intramuscular injection have not proven practical in the long term and despite intensive research, oral insulin preparations are not yet available.

Table 4: Approximate Pharmacokinetic Characteristics of Human Insulin and Insulin Analogues Following Subcutaneous Injection:

Insulin	Onset of action	Peak of action	Duration of action	Blood glucose targets
Mealtime insulins				
Lispro	10-15 min	1-1.5 h	4-5 h	Postprandial
Aspart	10-15 min	1-2 h	4-6 h	Postprandial
Regular	15-60 min	2-4 h	5-8 h	Postprandial
				Prior to next meal
Basal insulins				
NPH	2.5-3 h	5-7 h	13-16 h	Midafternoon (for morning NPH)
				Fasting glucose next morning (for bedtime NPH)
Lente	2.5-3 h	7-12 h	Up to 18 h	Similar to NPH
Glargine	2-3 h	No peak	Up to 30 h	Similar to NPH
Ultralente	3-4 h	8-10 h	Up to 20 h	Similar to NPH
Detemir	2-3 h	No peak	Up to 24 h	Similar to NPH

Type 2 diabetes[18]

Life style modification

- Restrict fat and energy intake
- Encourage exercise
- Stop smoking

The major aims are to reduce the weight of obese patients and improve glycaemic control, but also to reduce risk factors for cardiovascular disease (CVD), such as hyperlipidemia and hypertension, which accounts for 70 – 80% of deaths in type 2 diabetes.

Weight loss is achieved by decreasing total energy intake and/or increasing physical activity and thus energy expenditure. Gradual weight loss is preferred – not more than 0.5 – 1 kg/week. Reduced calorie diets result in clinically significant weight loss regardless of which macronutrients they emphasize.

Dietary recommendations: Saturated fat should be reduced and replaced with monounsaturated fat such as olive oil or polyunsaturated fats. Polyunsaturated fat, found in vegetable oils, is also beneficial for cholesterol lowering and improving glycaemic control. Dietary cholesterol may be more detrimental in diabetics than in the general population, so the consumption of foods such as eggs should be limited. Fish oils are rich in omega - 3 fatty acids and have lower triglyceride levels, and there is evidence that higher fish intake is associated with less CVD in diabetes

'Diabetic' foods that contain sorbitol or fructose as sweeteners are not recommended. Sucrose need not be banned from the diabetic diet, and a moderate amount for sweetening is acceptable. The focus of dietary plans should be on balancing energy intake to energy expenditure and the quality of fat and carbohydrate, rather than the quantity alone.

Structured education: Clinical studies have shown that structured education programmes focused on behavior change can successfully engage those with newly diagnosed type 2 diabetes in starting effective lifestyle changes that are sustainable.

Table 5: Oral anti diabetic drugs

Drugs	Action	Mechanism
Biguanides		
Metformin	Reduce insulin Resistance Reduce hepatic glucose output	Not known
Sulphonylureas		
Gliclazide Glimipiride Glipizide Glibenclamide	Increase insulin secretion	Bind to SU receptor on ß cells, leading to closure of KATP channels
Meglitinide analogues		
Repaglinide Nateglinide	Increase insulin secretion	Bind to SU receptor on ß cells, leading to closure of KATP channels
Thiazolidinediones		
Pioglitazone Rosiglitazone	Reduce insulin resistance	PPAR gamma agonist
α-Glucosidase inhibitors		
Acarbose	Decreases carbohydrate absorption in gut	Inhibits α-glucosidase in intestinal brush border
GLP-1 agonists		
Exenatide Liraglutide	GLP-1-like effects on insulin secretion, satiety and gastric emptying	Bind to GLP-1 receptors on ß cells and α cells
DPP-4 inhibitors		
Sitagliptin Vildagliptin Saxagliptin Alogliptin	Inhibits breakdown of endogenous GLP-1	Cleaves amino acids and inactivated DPP-4
Weight loss therapies		
Orlistat	Reduces fat absorption in gut	Inhibits pancreatic lipase
Sibutramine	Centrally acting appetite suppressant	Serotonin and noradrenaline reuptake inhibitor

Cutaneous manifestations in Diabetes mellitus (DM)

DM has taken on the mantle of 'syphilis' of pre-antibiotic days of being a clinical imitator with an impressive array of signs and symptoms affecting every organ of the body.

The manifestation of diabetes of the integument are numerous and varied. There is considerable uncertainity about the pathogenesis of many of the cutaneous conditions affecting diabetics.

Many cutaneous signs are readily recognizable as **Diabetic Markers** like diabetic dermopathy, diabetic bullae, waxy skin syndrome which are virtually diagnostic of DM.[19]

Some cutaneous conditions appear to be caused by the primary abnormalities of diabetes or by its major complications, vasculopathy and neuropathy, others are linked to altered immunologic conditions, to changes in collagen, and some are a consequence of treatment.

Dermatologic disorders associated with DM generally appear after the primary disease or they may signal or appear coincidentally with its onset, or even precede DM by many years. The cutaneous clinical signs are numerous and varied as 1/3rd of patients with diabetes are estimated to have cutaneous changes.[19]

No disease of skin is absolutely peculiar to diabetes, yet there are diseases, the incidence of which is more in diabetics than in non-diabetics.[20]

Prevalence

Skin involvement of diabetes mellitus is very common and some form of cutaneous involvement has been found in 43-66% of Indian diabetics.[21,22] Although,

the overall prevalence is the same in IDDM and NIDDM patients, the former more frequently develop autoimmune-type lesions, while the latter have more frequent cutaneous infections.[23,24]

Age Incidence:

The incidence of bacterial infections in DM shows a striking variation with age. Staphylococcal infections are higher in those who are over 40 years of age.[25]

Monilial balanitis and monilial intertrigo are common in the age between 31-40 years. Dermatophytosis are more common in the 21-30 years age group.[26]

Sex incidence

It is generally accepted that candidial infections are more prevalent in diabetic females.

The incidence of staphylococcal infections is higher in males than in females particularly in hospital diabetics.[25]

The incidence of monilial balantits in uncircumcised males is 6%.They also report that monilial vulvovaginitis in diabetic girls is 8%.[27]

Classification of cutaneous manifestations of DM

According to **Frank Parker**, classification of cutaneous manifestations of diabetes is as follows: [28]

1) Infections :

a) Bacterial:

i. Pyodermas (especially from staphylococcal aureus)

ii. Malignant otitis externa (Pseudomonas aeruginosa)

iii. Necrotizing fasciitis (gram positive and gram negative and anaerobic mixed infections)

iv. Erythrasma

b) Mycotic:

i. Superficial-dermatophytosis or candidiasis

ii. Deep- mucormycosis

2) Skin changes thought to be related to microangiopathy:

a. Punched out skin ulcers on lower legs

b. Necrobiosis lipoidica diabeticorum

c. Diabetic dermopathy

d. Bullous eruptions of diabetes

e. Rubeosis

3) Skin changes thought to be related to neuropathy:

a. Neuropathic ulcers (mal perforans)

b. Charcot joints

4) Skin changes thought to be related to microvascular insufficiency:

a. Ischemic skin ulcers and digital gangrene

b. Erysipelas – like erythema

5) Skin changes related to lipodystrophy:

a. Insulin injection sites lipodystrophy

b. Syndromes of lipodystrophy and diabetes (Seip-Bernardinelli syndrome and acquired lipodystrophy-Lawrence-Seip syndrome)

6) Other skin diseases that may be associated with diabetes:

a. Granuloma annulare

b. Scleredema diabeticorum (adultorum)

c. Eruptive xanthomas

d. Perforating cutaneous disease of diabetes

e. Pruritus

f. Vitiligo

g. Acanthosis nigricans

7) Drug reactions:

a. Insulin reactions (local wheal and urticarial)

b. Oral hypoglycemic reaction.

According to Bonnie T.Mackool et al, cutaneous manifestations of DM are classified as :[29]

1) Cutaneous infections in diabetics

a. Candidiasis

i. Oral mucosal candidiasis

ii. Candidial paronychia

iii. Monilial balanitis

b. Dermatophyte infections

c. Phacomycetes infection

d. Bacterial infection

e. Malignant otitis externa

f. Erythrasma

2) Neuropathic and ischemic diabetic skin disease

a. Diabetic polyneuropathy

b. Peripheral vascular disease

c. Diabetic ulcers

3) Disorders of collagen

a. Necrobiosis lipoidica

b. Granuloma annulare

c. Scleredema diabeticorum

d. Waxy skin

4) Metabolic diseases

a. Porphyria cutanea tarda

b. Yellow skin

c. Xanthomatosis

d. Eryptive xanthoma

e. Xanthelesma palpebrerum

f. Haemochromatosis

g. Lipodystrophy

h. Glucagonoma syndrome

5) Other skin disease strongly associated with diabetes

a. Diabetic dermopathy

b. Diabetic bullae

c. Rubeosis

d. Vitiligo

e. Acanthosis nigricans

f. Perforating disorders

g. Generalized pruritus

6) Cutaneous reactions to therapy for diabetes

a. Insulin induced disorders

b. Hypoglycemic agents

The review conducted by **Martiza I Perez and Steven R Kohn (1994)** classified cutaneous findings of DM into four categories:[30]

1) Skin disease with strong to weak association with DM
2) Cutaneous infections
3) Cutaneous manifestations of diabetic complications
4) Skin reaction to diabetic treatment.

Pathogenesis of cutaneous complications of DM

The ratio of skin glucose to blood is slightly higher in diabetics (70%) than in normal people (55%).[31]It is higher in diabetics taking insulin than those controlled by oral hypoglycemic or diet alone.[32]

The changes in normal skin of diabetic are:

a. Increased mast cells in the dermis
b. Increased capillary fragility
c. Thickening of capillaries and other vessels
d. Anhidrosis

Factors favoring infection in DM

The infections due to Candida albicans and corynebacterium minutissimum are exceptions to the belief that diabetics are more susceptible to bacterial and fungal infections, which is incorrect. By contrast, patients with poorly controlled diabetes and ketotic patients will have compromised resistance to infection. They are more susceptible to infections and infections are more severe and resistant to treatment.[19]

The various predisposing factors that influence the occurrence of infection in diabetics are:

Level of glucose control	Ketoacidosis
Abnormal phagocytic function	Peripheral vascular disease
Neuropathy	Dry skin
Trauma	Malnutrition

The strict control of blood glucose level is important in preventing infections. Hyperglycemia by itself has probably little influence on the growth of cutaneous microorganisms because of a high carbohydrate environment. Sugar and honey have successfully been used topically in healing ulcers of the skin. It probably affects the phagocytic function of WBCs.[33]

Infection is the most important triggering factor for ketoacidosis and conversely, ketoacidosis predisposes the patient to infection.

Peripheral vascular disease leads to vascular insufficiency which can influence the host defence by:

1. Decreasing blood flow to peripheral tissues
2. Decreasing oxygen concentration in tissues thereby enhancing the growth of microaerophilic and anaerobic organisms.
3. Thickened capillary basement membrane may slow down leukocyte chemotaxis.

Sensory impairment, a part of diabetic neuropathy, particularly of the legs and feet, makes the patient unaware of minor trauma that invites the secondary infection.

Dry skin either due to dehydration or normal xerotic process of elderly predisposes diabetic patients to infection.[34]

Impairment of phagocytic function

Neutrophils are the first line of defence against bacterial infection. Functional abnormalities of neutrophils such as chemotaxis, adherence, phagocytosis, intracellular bacterial adherence activity and serum opsonic activity have been reported in diabetes.[35]

a) **Chemotaxis** – Abnormalities of neutrophil movement have been described in patients with diabetes[36] and their first degree relatives.[37]This defect was independent of blood glucose level. Interestingly, the poor movement could be improved by the invitro administration of insulin, but the mechanism was unclear; a flux of potassium ion into the cell following insulin administration may be the possible explanation. Potassium ion is essential for the normal cell movement.[25]

b) **Phagocytosis** – It was demonstrated in a study that neutrophils from 26 IDDM patients had a lower initial rate of phagocytosis compared with 28 controls. This finding suggests that the initial phase of attachment of the target to the neutrophil may be at fault. Also, low neutrophil membrane sialic acid level from diabetic patients was observed.

They suggested that this was due to an increase in the breakdown of sialidase which was present in increased amount in poorly controlled diabetic patients. Tuftin of bacterial cell wall reacts with sialic acid in the initiation of phagocytosis. Thus low membrane sialic acid would reduce binding of tuftin and therefore inhibit phagocytosis.[24]

c) **Killing-** Following phagocytosis, killing proceeds by both oxidative and non-oxidative means. Oxidative killing occurs at an earlier stage than non-oxidative. Oxidative killing is initiated by membrane oxidase which utilizes the electron donor NADPH, and produces superoxide radicals. The neutrophil membrane is permeable to glucose and high intracellular level of glucose greatly reduces the availability of NADPH.[38]

Under normal circumstances, glucose enters the hexose monophosphate shunt (HMP) and generates NADPH. But in hyperglycemia, high glucose level swamps the HMP and is metabolized by aldose reductase through the polyol pathway. Aldose reductase is an NADPH requiring enzyme and competes for this, thereby reducing the cell's ability to mount an attack and thereby inhibit killing.[25]

Pathogenesis of cutaneous manifestations of DM due to chronic degenerative complications

Long standing hyperglycemia is the basis for many of the degenerative changes. Recent multicenter studies show delayed progression of diabetic complications by strict control of hyperglycemia.

Much of the impact of chronic diabetes results from the development of tissue complications, mainly microvascular disease (angiopathy, retinopathy, nephropathy and neuropathy) and macrovascular disease (atherosclerosis).

Microangiopathy is characterized by progressive occlusion of the vascular lumen with impaired perfusion, increased vascular permeability and increased elaboration of extracellular material by perivascular cells, which results in basement membrane thickening. There is strong evidence that microvascular disease is related to the duration and severity of hyperglycemia in both type 1 and type 2 diabetes. A

classic observational study demonstrated this link in 4400 type 1 and 2 patients followed up for up to 25 years.[39]

The structural hallmark of diabetic microangiopathy is thickening of the capillary basement membrane. Veil cells are seen more frequently surrounding cutaneous vessels, it has been postulated that these cells produce excessive amount of basement membrane like material accounting for vascular thickening. Biochemically, thickened basement membrane shows increased type IV collagen and its glycosylated products, decreased heparin sulfate, proteoglycan and increased binding of plasma protein.[40]

It seems that individual susceptibility to glucose-induced tissue damage is influenced by other factors. One of the most important if these is blood pressure. This was clearly demonstrated in a trial, in which 1148 hypertensive patients with type 2 diabetes were allocated to either tight or less tight control of blood pressure (mean BP over 9 years 144/82 vs 154/87 mmHg). Microvascular endpoints were reduced by 37% in the group with the lower blood pressure.[41]

Diabetes particularly affects tissues that cannot downregulate glucose uptake when extracellular glucose increases, leading to raised intracellular glucose concentrations. One mechanism by which hyperglycemia may cause complications is by an increased flux of glucose through the polyol pathway.[42]

Many mechanisms linking hyperglycemia to the degenerative complications have been explored.

Two such important mechanisms are:

a) **Non Enzymatic Glycosylation:** This refers to the process by which glucose chemically attaches to the amino group of protein without the aid of enzymes. Glucose forms chemically reversible glycosylation products with protein (called Schiff bases) that may rearrange to form more stable Amadori- type early glycosylation product. The early glycosylation product on collagen and other protiens in interstitial tissue and blood vessel wall undergo a slow series of chemical rearrangement to form irreversible advanced glycosylation products. These accumulate over the vessel wall and they have a number of chemical and biological properties which are potentially pathogenic.[43]

b) **Polyol pathway-** In this pathway, the rate limiting enzyme aldose reductase reduces glucose to its sugar alcohol, sorbitol. Sorbitol is then oxidized by sorbitol dehydrogenase into fructose. Aldose reductase is found in tissues such as nerves, retina, glomerulus and the blood vessel wall, where glucose uptake is independent of GLUT-4 and insulin. This pathway in normally inactive because of the high K_m of aldose reductase, but hyperglycemia increases flux through the pathway and leads to accumulation of intracellular glucose and glucose-derived substances, such as methylglyoxal and acetol (which rapidly glycate proteins). Sorbitol does not diffuse easily across cell membranes and damage may occur because of sorbitol-induced osmotic stress (currently throught to be less likely).

Alternative mechanisms may involve **decreased NADPH**, thereby decreasing reduced gluthathione, an important scavenger of reactive oxygen species; or an increased $NADH/NAD^+$ ratio, which inhibits glyceraldehyde 3-phosphate

dehydrogenase, increasing intracellular triose phosphate and the formation of methylglyoxal and activation of protein kinase C.[42, 44]

Another mechanism for glucose damage is thought to be increased intracellular formation of **advanced glycation end-products (AGEs).** AGEs are formed by the reaction of glucose and other glycating compounds, such as methylglyoxal with proteins and other long-lived molecules, such as nucleic acids. Early glycation products are reversible, but eventually they undergo irreversible changes through cross-linking, which impairs protein structure and function.

AGEs can damage cells by altering cellular protein function and by cross-linking extracellular matrix molecules, such as collagen and laminin, which in blood vessels increases wall thickness and permeability, and decreases elasticity. AGE-modified circulating proteins bind to specific receptors (RAGEs) on several types of cells, including monocyte/macrophages, glomerular mesangial cells and endothelial cells. This binding leads to the generation of reactive oxygen species, activation of the transcription factor NFκB and stimulation of cytokine and growth factor production, inflammatory cell adhesion (via increased VCAM-1) , procoagulant protein expression and increased vascular permeability (e.g via vascular endothelial growth factor, VGEF).[42]

Protien kinase C (PKC) is an enzyme that phosphorylates several target proteins. Excessive activation of PKC is a further mechanism by which glucose might induce tissue damage. Over activity of PKC has been implicated in increased vascular permeability, blood flow changes and increased basement membrane synthesis. Some of the effects maybe mediated by PKC's inhibition of nitric oxide (NO) production.

Hyperpglycemia might also cause diabetic complications by shunting glucose into the hexosamine pathway. Fructose-6-phosphate is diverted from glycolysis to form UDP-N-acetylglucosamine, used in the synthesis of glycoproteins. The rate-limiting step in the conversion of glucose to glucosamine is regulated by glutamine: fructose-6-phosphate amidotransferase (GFAT). Possibly, glycation of transcription factors by N-acetylglucosamine increases the transcription of key genes such as TGF-ß, acetyl CoA carboxylase (the rate-limiting enzyme for fatty acid synthesis), plasminogen activator inhibitor-1 (PAI-1) and probably many other genes.

All the mechanisms mentioned above have a common effect of increasing reactive oxygen species and thus increasing oxidative stress. [42]

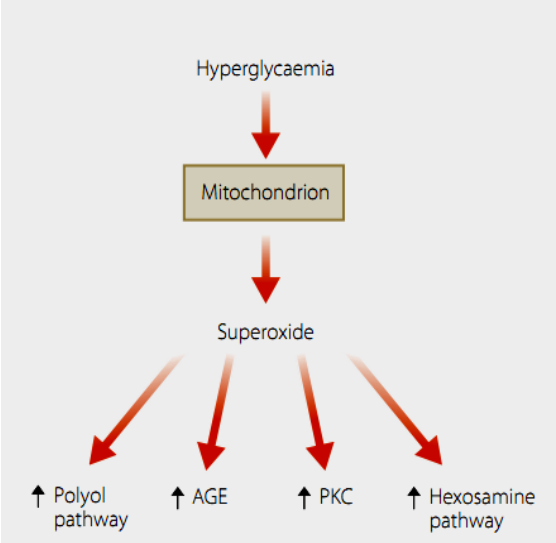

Figure 6: Superoxide links glucose and diabetic complications

CLINICAL FEATURES OF SKIN MANIFESTATIONS IN DM

I. CUTANEOUS INFECTIONS IN DM :

In diabetic patients, there is no strong evidence for an increased susceptibility to infections in general, but several skin infections do occur more commonly, with greater severity, or with a greater risk for complication in patients of DM. [45] The

incidence of furuncles, carbuncles and candidiasis are higher in diabetics (30%). Another study of 50 cases, suggests the incidence of chronic pyodermas to be 14%, dermatophytosis 30% and candidiasis 14%.[19]

Increased colonization of the nose by staphylococcus has been reported in diabetics, expecially in those with poor metabolic control or among insulin users compared to those on hypoglycemic agents.[46]

a. Bacterial infections : The common conditions encountered are infections caused by staphylococcus aureus and beta hemolytic streptococci which include impetigo, folliculitis, furuncle, carbuncle, ecthyma, cellulitis, erysipelas and necrotizing fasciitis of the lower leg. [47]

i. **Impetigo** (bullous and non-bullous form) occurs over the face, scalp and extremities. The initial lesion of non-bullous impetigo is thin walled vesicle on an erythematous base, which rupture to form thick 'honey coloured' crust giving the 'stuck on appearance'. In bullous impetigo, the bullae are usually flaccid and rupture less rapidly. After rupture, the lesion dries to forma thin, hard, brown crust.[48]

ii. **Folliculitis** originates within the hair follicle. There are superficial and deep types. This condition is characterized by multiple pustules emerging from hair follicles. It commonly occurs over lower limbs, forearms and beard area.

iii. **Furuncle** is an acute, usually necrotic infection of the hair follicle. It first presents as a small follicular, inflammatory nodule, soon becoming pustular and then necrotic and healing after discharge of necrotic core to leave a violaceous macule or permanent scar. Tenderness is invariable and the lesions tend to appear in crops. The sites commonly involved are face, neck, arms,

fingers, buttocks and anogenital region. The legs and nasal areas are other common sites.

iv. **Carbuncles** are aggregation of furuncles with multiple pointings. Lesions start as a tender dome shaped nodule, which increases in size to reach a diameter of 3-10 cm. Suppuration begins after 5-7 days and pus is discharged from multiple follicular orifices. Constitutional symptoms may be associated. They are commonly present on the back of the neck, shoulders, hips and thighs. Carbuncles and furuncles constitute 30% of skin infections in diabetes. Bacterial infections are treated with appropriate systemic antibiotics and local compresses. Surgical incision and drainage is often required to treat furuncles and carbuncles.[48]

v. **Ecthyma** is a pyogenic infection of the skin characterized by the formation of adherent crusts, beneath which ulceration occurs. The base is indurated and red oedematous areola is often present. The buttocks, thighs and legs are commonly affected.

vi. **Cellulitis** is an acute, subacute or chronic inflammation of loose connective tissue, particularly subcutaneous tissue. It is associated with constitutional symptoms like fever, malaise etc.

vii. **Erysipelas** is a bacterial infection of the dermis and upper subcutaneous tissue characterized by well demarcated, raised edge. It is the superficial form of cellulitis.

Face and legs are commonly affected in erysipelas and cellulitis.[48]

viii. **Necrotizing fasciitis** is a fulminating infection of the superficial and deep fascia resulting in thrombosis of the subcutaneous vessel and gangrene of the underlying tissues. The head, neck and legs are commonly affected. Signs of acute inflammation are present early in the course and a pathognomonic sign develops between the 2^{nd} - 4^{th} day. The affected skin assumes a blue, dusky tinge. The mortality rate remains high despite vigorous therapy.[30]

ix. **Erythrasma** is a superficial infection caused by corynebacterium minutissimum usually affecting intertrigenous areas. It manifests as reddish brown, fine, scaly, usually asymptomatic patches in axilla and groin. Fifty percent of patients with extensive erythrasma of the groin, axilla and trunk in a study, were diabetics.Treatment includes topical and systemic erythromycin and clindamycin. Compresses, drying powders and meticulous oral hygiene reduce the risk of recurrence.[49]

x. **Malignant otitis externa** is a severe necrotizing infection caused by Pseudomonas aeruginosa occurring almost exclusively in diabetics. It starts in the external auditory canal, then invades local soft tissues and ultimately leads to osteomyelitis of the temporal bone and fatal meningitis.[25]

xi. **Nail infections** of bacterial origin are common in patients with DM and are caused by Ps. Aeruginosa, S.aureus, E.coli and Pr.mirabilis.[30]

xii. **Fournier's gangrene** is characterized by a subcutaneous infection and subsequent gangrene of the skin of scrotum, base of penis and sometimes the abdominal wall. It is especially common in diabetics and the onset is often explosive. It is caused by mixed aerobic and anaerobic organisms. Treatment is aggressive surgical debridement and appropriate antibiotics.[25]

b. Fungal infections

I. Candidial infection (moniliasis) can be an early sign of undiagnosed diabetes. Perleche is a classic sign of diabetes in children, and localized candidial infection of the female genitalia has strong association with diabetes. This infection appears as erythema with scaling and typical satellite papules and pustules. It is important to remember that in men, candidial balanitits, balanophosthitis and intertrigo can be presenting signs of diabetes.[50]

Candidial infections improve with adequate metabolic control and treatment with topical imidazoles or nystatin.[50]

i. **Candidial vulvovaginitis** is characterized by pruritus, vulvar erythema and occasionally fissuring and pustules.[51] Glycosuria promotes the growth of Candida albicans. In a study, 77% of diabetic girls had positive culture for Candida albicans.[52]

ii. **Candidial balanophosthitis** commonly occurs in middle ages or elderly uncircumscised diabetic males. Patients complain of intense pruritus or burning pain and there may be a white or slightly purulent discharge. The prepuce is fissured and difficult to retract and on retraction, inner surface of prepuce and glans may show erythema with dispersed white patches and sometimes vesicles and erosions. Recurrent attacks of balanitis can lead to phimosis. In one study, 35% of 100 males who required circumcision for phimosis were diabetic.[53]

iii. **Oral candidiasis** can present as oral thrush (curd-like white colonies over the tongue and buccal mucosa),atrophic candidiasis resembling median rhomboid glossitis and angular chelitis (perleche). Angular chelitis is commonly seen in

juvenile diabetics. The high glucose level in the saliva seems to account for oral lesions.[54]

iv. **Candidial intertrigo** commonly occurs in webspaces and crural region. There is erythema and moist exudation with tiny erosions associated with soreness and itching. This is more common in obese individuals and in those who frequently immerse their hands and feet in water.[48]

v. **Candidial paronychia** usually begins in the lateral nail fold and then involves the posterior nail fold. It is characterized by erythema, swelling and pain in the nail fold. Intermittent exacerbations with remissions are common, giving the nail plate a rippled appearance.[55]In one study of 250 diabetics, candidial paronychia was found in 9.6% compared with 3.4% of non-diabetic control group.[56]

II. Dermatophytosis :

Diabetics are more prone to dermatophyte infections. The incidence of dermatophytosis is about 40% in diabetics The real significance of dermatophyte infections in diabetes is that the low grade infection may result in fissuring of the skin, creating an entry point for bacterial invasion.

Dermatophytosis can involve the intertrigenous area, crural region and glabrous skin.

These infections are treated with topical imidazoles and griseofulvin orally for extensive lesions. Ketoconazole and other drugs including haloprogin, tolnaftate are useful. Nail infections are best treated new systemic antifungals like fluconazole, terbinafine and itraconazole.[57]

III. **Pityriasis versicolor:** This is usually asymptomatic infection of stratum corneum caused by pityrosporum orbiculare, a constituent of normal resident flora of skin. P.orbiculare changes from the round budding blastophore to pathogenic hyphal from under the influence of high skin glucose level.[58]

IV. **Phycomycetes infections:** Hyperglycemia may permit organisms that are usually non-pathogenic to establish an infection in traumatized skin, that may lead to gangrene and loss of limb. Patients with DM who have leg ulcers or non-healing surgical wounds may have a complicating phycomycete infection.

Patients with uncontrolled DM and ketosis may be predisposed to deep fungal infections or rhinocerebral mucormycoses (RCM) of the turbinates, septum, palate and maxillary and ethmoid sinuses.[59]RCM, caused by Zygomycetes (*Mucor and Rhizopus sp*.) often presents with headache, fever, lethargy, nasal congestion, facial, ocular pain and swelling. Subsequent findings include unilateral proptosis, ophthalmoplegia and palate or nasocutaneous necrosis. Seventy five percent to eight percent of all cases occur in patients with diabetes, and diabetic ketoacidosis is the most important risk factor.

Ketoacidosis reportedly blunts the normal inhibitory activity of serum against Rhizopus. Amphotercin B and surgical debridement are the treatments of choice. Voriconazole, capsofungin and other azoles are ineffective against Zygomycetes. The investigational triazole, posaconazole may be efficacious in these infections.

Mortality rates for RCM are reportedly as high as 50%. Mucor species have also been observed, complicating skin ulcers on the legs and hands of diabetics.[45]

c. VIRAL INFECTIONS

Herpes zoster:

Diabetics are more susceptible to developing herpes zoster. Herpes zoster occurs at a younger age group among the diabetic population. Depressed immune response in poorly controlled diabetics could be the reason for high prevalence of zoster. They also observed that incidence of post herpetic neuralgia was twice as common in diabetics as in general population.

Regeneration of damaged nerves is slow in diabetes, which accounts for the prolonged pain. A good diabetic control may reduce the chance of development of zoster by improving immunological function and also of post herpetic neuralgia by diminishing the underlying metabolic neuronal damage.[60]

II. DERMATOSES DUE TO MICROANGIOPATHY

According to Jelinek, the various dermatoses due to microangiopathy are:

1) NECROBIOSIS LIPOIDICA DIABETICORUM (NLD)

Necrobiosis lipoidica diabeticorum is a relatively rare dermatosis, even in diabetics in whom it is estimated to occur in 3 out of 1000 patients (0.3%).NLD is rare but best known cutaneous marker of DM.

Its incidence varies from 0.3% - 3% . NLD is 4 times more common in women, with an average age of onset at 34 years. The onset is considerably earlier in IDDM than NIDDM patients. [61, 62]

A retrospective study revealed that frank diabetes, abnormal glucose tolerance test or family history of diabetes in at least one parent was present in 90% at the time

of diagnosis of NLD. A significant minority of patients with NLD do not develop diabetes.[61]

NLD precedes the onset of diabetes in about 15% of patients by about 2 years. In 25%, NLD and diabetes appear concomitantly. In the rest, NLD appears after diabetes has been diagnosed.[34]

Typical lesions of NLD start in the pretibial area as erythematous non scaly papules that gradually enlarge and coalesce into a larger plaque. The older lesion consists of a large, irregular plaque with yellow atrophic center and erythematous or violaceous border. Surface telagnectasia and scattered hyperkeratotic plugs are sometimes seen. The lesions are usually multiple and bilateral with ulceration occurring in approximately 35% cases.[30]

Lesions may have decreased or no sensation to pin prick and fine touch. Koebner's phenomenon along the line of injury can be seen in NLD.[63]

In about 90% cases, NLD is localized to one or both shins. In the remaining cases it may be seen on trunk, arms, scalp or glans penis.[64]

The exact cause of NLD is not known.[65] Significant hyperglycemia is not necessary for the development of NLD. The proposed causative factors of NLD are : a) microangiopathy , b) alteration of microcirculation, c) obliterative endarteritis, d) immune-mediated vasculitis, e) delayed hypersensitivity, f) non-enzymatic glycosylation, g) other defects in collagen, h) trauma, i) platelet aggregation, j) defective mobilization of neutrophils, and k) vascular insufficiency.[66]

Histopathological study reveals normal or atrophic epidermis, degenerative collagen in dermis, particularly in lower 2/3rd , with histiocytes arranged in a

palisading pattern around the necrobiotic collagen. Occasionally, epitheloid cells, lymphocytes and giant cell infiltration are seen around the necrobiotic area. Blood vessels show obliterative granulomatous vasculitis.[66]

Ultrastructural studies show defective collagen fibres and the amount of collagen is reduced, probably due to decreased synthesis of collagen by affected fibroblasts.[67]

There is no treatment that reverses the atrophic changes associated with this lesion. [68]Inflammatory infiltrate of NLD extends from the lesion into the apparently normal skin surrounding clinically active lesions. Thus intradermal steroid injections administered to perilesional areas might help halting the disease progression. This can be used both for ulcerated and non-ulcerated lesions.

NLD can be treated by avoiding trauma and control of glucose. Topical corticosteroids can be used in both asymptomatic and symptomatic lesions. This can be used under polythene occlusive dressing.

Dipyridamole is one of the inhibitors of platelet aggregation, usually given with aspirin. A dose of 40-225mg of aspirin every 2^{nd} or 3^{rd} day and dipyridamole 150-225 mg/day is recommended. Fibrinolytic agents are used to reduce angiopathy of NLD. Stanazolol and pentoxyfylline have also been tried.

In severe or extensive cases and in some resistant cases, systemic steroids, chloroquine and cyclosporine have been used with some success.[69,70,71]

2) GRANULOMA ANNULARE (GA):

GA, a condition occurring predominantly in children and young adults, is characterized by a ring of small, firm papules that are either skin-coloured or erythematous. Dorsa of hands are commonly affected. Several clinical variations include serpiginous, disseminated, actinic, perforating and deep dermal forms. Generalized form consists of numerous flesh coloured papules, which are distributed symmetrically, often on sun exposed areas. Perforating GA consists of small nodular lesions with central umbilication, commonly occurring on the hands and margins of fingers.

A strong association was reported between diabetes and granuloma annulare, particularly the disseminated and perforating forms. In a study DM was found in 21% patients with generalized GA and in 10% of localized GA. However, other studies have been unable to show any significant association.[72]

Histologically there is focal degeneration of collagen in the upper and mid dermis, histiocytic palisaded arrangement around collagen bundles and abundant mucin.

Treatment for generalized form in presence of DM has been reported successfully with isotretinoin and PUVA.[19]

3) DIABETIC DERMOPATHY (DD):

Diabetic dermopathy is the most common cutaneous manifestation of diabetes mellitus.[73]DD refers to atrophic, hyperpigmented macules characteristically located on shins of patients with diabetes. It has an unfavorable association with the three most common microangiopathic complications of DM : neuropathy, nephropathy and

retinopathy. A relationship between DD and coronary artery disease has also been demonstrated.

In the early 1960s, Swedish physician Hans Melin studied and characterized a 'cricumscribed, brownish skin lesion' on the lower extremities of patients with diabetes. In 1965, Binkley coined the term 'diabetic dermopathy', reflecting his concept that DD is a cutaneous manifestation of diabetic microangiopathy. It has been referred to as 'atrophic lesions, 'shin spots', 'pigmented pretibial patches' and 'spotted leg syndrome' by various authors. 'Diabetic dermopathy' is currently the most widely used term. It represents the association of DD with complications of long standing diabetes mellitus.[74]

The incidence of DD ranges from 9% to 55%. The lowest incidence was noted among Indian patients, whose complexion may render DD more difficult to be detected. DD is considered as the most common cutaneous sign of diabetes with an overall incidence of 50% as reported in Western literature and 17.8% in an Indian study.[75]Diabetic dermopathy was found in 50% of male and 29% of female diabetics who were more than 50 years of age.[76]

DD is seen more frequently in older patients, especially those older than 50 years, and those who have had DM for a long period of time. It may affect male patients twice as often as female ones, but this is not consistently seen.

The incidence of DD increases as the number of microangiopathic complications of DM rises. It is unlikely that DD represents local ischemia. However, it is still possible that impaired skin perfusion is involved in its development.[75,76]

The lesions of DD are smooth and hyperpigmented. The intensity of brown pigmentation has been correlated with the degree of atrophy.

DD is asymptomatic and does not itch or cause pain. It is typically located bilaterally on the pretibial region and is asymmetrically distributed. Although it is rare, DD can occur on the upper extremities, thighs, trunk and lower aspect of the abdomen.[74]

The progression of DD is variable and does not appear to be affected by glycemic control. Individual lesions persist for 18 to 24 months on an average, but may remain indefinitely. They may fade slowly, leaving behind pigmentation without atrophy or may resolve completely. As older lesions fade, new lesions appear. Thus the overall clinical picture does not change.

The association of DD with neuropathy, nephropathy, retinopathy and coronary artery disease indicates that it may be a marker of severity of diabetic complications.

Although patients without diabetes may rarely have one or two similar lesions, it has been suggested that the presence of 4 or more with typical features of DD is characteristic of DM.[74]

Histopathologically, the epidermis shows atrophy of rete ridges, moderate hyperkeratosis and variable pigmentation of basal cells. The papillary dermis exhibits telangectasias, fibroblastic proliferation and edema. Hyaline microangiopathy, extravasated erythrocytes and hemosiderin deposits are universally seen. Periodic acid-Schiff staining is essential to accentuate the mucopolysaccharide infiltrate in the vessel wall. A mild perivascular infiltrate composed of lymphoid and histiocytes is present.

Treatment is neither recommended nor effective. [74]

4) BULLOUS DIABETICORUM:

Diabetic bullae are distinct diabetic markers characterized by sudden appearance of bullae on the extremities. This condition also is described as *phlyctenar lesions in the feet of diabetics, idiopathic bullae in diabetes* and *bullosis diabeticorum.*[34]

The sudden appearance of tense bullae generally on acral parts is a clinically distinct diabetic marker. Both sexes are affected and age of onset ranges from 17-79 years.[77]

Patients usually present with sudden, spontaneous eruption of one or more tense blisters, most commonly on the dorsa and sides of the lower legs and feet, sometimes associated with similar lesions on the hands and forearms. Generally, few or no subjective symptoms are present, but burning and pain have been reported. The lesions remain dry for six weeks and usually heal without scarring, even when located subepidermally. In rare cases, they may ulcerate or leave brown, atrophic areas that are indistinguishable from lesions of diabetic dermopathy. These two diabetic conditions may co-exist. The bullae may recur.[34]

Lesions are asymptomatic and there is no surrounding erythema. The bullae range from 0.5 cm to several centimeters, often bilateral and usually contain clear, sterile fluid. This occurs commonly in adult males and their diabetes is often severe and long standing. They heal in few weeks leaving behind no scars.[78]

Electron-microscope studies have revealed subepidermal blisters with split occurring at level of lamina lucida.[79]

The cause of diabetic bullae is not known. Several theories exist regarding the causal and contributory factors related to this condition.[80]It is usually associated with diabetic microangiopathy, retinopathy and dermopathy.

Occurrence of similar lesions after UV light exposure has been observed. Diabetic bullae resemble those seen in patients in coma from barbiturate or carbon monoxide poisoning, but the clinical picture is easily differentiated.[19, 60]

5) DIABETIC RUBEOSIS

Von Noorden and Issac were the first , in 1927, to note the peculiar rosy facial color, which they claimed also occasionally affected the hands and feet and subsided when metabolic control improved.[60]

Many diabetic individuals have peculiar rosy reddening of the face, neck and even extremities and it is called Rubeosis.[81] These are more pronounced in fair skinned individuals. The cause is said to be due to dilatation of dermal venous plexus and erythema may result from the decreased ability of the thickened dermal vessels to vasoconstrict[82] or diabetic microangiopathy.[60]

6) ERYSIPELAS LIKE ERYTHEMA

Well demarcated, red areas occur on the legs or feet of elderly diabetics. Some of the patients have an underlying destructive bone disease caused by small vessel insufficiency. It is seen mostly in elderly patients with an average duration of diabetes mellitus of five years. Cardiac decompensation may be involved. [48]

III.NEUROPATHIC AND ISCHEMIC DIABETIC SKIN DISEASE

The number of foot problems can be expected to increase because the diabetic population is growing by 6% per year and doubling every 15 years. Ninety percent of diabetic population is over 50 years of age and most foot problems occur after this age. Twenty percent of all diabetics who are hospitalized are admitted for foot problems. Thirty percent of these patients have symptomatic peripheral vascular disease (PVD) and 7% percent require lower extremity vascular surgery.

i. **Diabetic neuropathy:** Various clinical syndromes of diabetic neuropathy are recognized. Nerve damage can be classified into an acute and reversible 'hyperglycemic neuropathy' and other persistent neuropathies, such as distal symmetrical and focal and multifocal neuropathies.

Hyperglycemic neuropathy occurs in patients whose diabetes has been controlled poorly for weeks or months, when uncomfortable sensory symptoms appear in the lower legs, and clear when control improves. Nerve conduction velocity is slowed. The mechanism is unknown. Distal and symmetrical polyneuropathy with mixed motor and mixed motor and sensory nerve involvement is the most common form of diabetic neuropathy.[48] The motor neuropathy is characterized by paralysis of intrinsic muscles of the feet, which causes the feet to adopt unusual position resulting in claw toes, hammer toes or charcot joint.

Involvement of sensory nerves leads to loss of touch, pain and temperature sensations. Lack of sensation may lead to burns, callouses and subsequent ulcerations.[30]Peroneal nerve is usually more involved than the median and radial nerves, and the leg is more severely affected than the arm.[51]

One of the earliest signs of diabetic neuropathy is loss of the ankle jerk reflex. In autonomic neuropathy there is disturbance of sweating, often decreased or absent sweating of lower extremities. With severe involvement the patient can develop the sympathectomy syndrome, manifested by both total body absence of sweating and skin that is warm and red due to hyperemia.

The central autonomic nervous system may be involved, resulting in considerable morbidity including diabetic diarrhea and defective orthostatic regulation of blood pressure. The characteristic signs of advanced autonomic vasomotor neuropathy are edema, erythema and atrophy.

Management of diabetic neuropathy begins with explanation and empathy, the exclusion of other causes of neuropathy (e.g, alcoholism, vitamin B_{12} deficiency and uremia), and then the institution of tight glycemic control.[83]

ii. **Peripheral vascular disease –** Peripheral vascular disease in diabetic patients can be diffuse and early in onset. The predilection for atherosclerosis and microangiopathy plays a role in the vessel occlusion. The skin of the lower extremities in diabetic patients with peripheral vascular disease is thin, smooth, cold and often mottled in the dependent position. Hair is either sparse or absent, other signs include pallor or cyanosis with elevation, dependent rubor, and delayed capillary refill. Late gangrene may set in which maybe further complicated by secondary infection.[84]

iii. **Diabetic foot ulcers-** Neuropathic ulcers, the classic plantar or mal perforans ulcer of diabetes is typically located in the weight bearing areas of the foot, i.e, over the metatarsal heads. The ulcers are small initially, but if the trauma or

infection continues, the ulcer may become enlarged. Penetration into the bone by means of sinus tracts results in osteomyelitis.[84]

Classically, the ulcer is painless and a hypertrophic callus occurs usually surrounding the ulcer. The skin temperature may be normal. Warmth and redness may be present with infection. This ulcer is generally circular and punched out. Infection is common and frequently leads to an area of localized gangrene.

Diabetic gangrene is common in males after middle age. When larger vessels are involved, diabetic patients may complain of intermittent claudication and nocturnal burning, discomfort of feet secondary to significant tissue ischemia. Other findings include cyanosis and rubor, pallor with elevation of the extremities and decreased or absent arterial pulsation on palpation.[85]

The affected foot appears cold and skin becomes atrophic, shiny and hairless associated with dystrophy of the nails. Gangrene develops usually after minor trauma or local infection.

The common site is toes. Gangrene develops suddenly and spreads rapidly so that extensive destruction may result. It is usually of wet variety which often leads to putrefaction. Wet gangrene is due to occlusion of larger vessels.[48]

Neuropathic ulcers are treated with number of topical substances which include proteolytic enzymes, antibiotics, antimicrobial agents and even topical insulin. The most important measures in healing these ulcers, however involve keeping the patient off his feet, daily mechanical debridement and parenteral antibiotics.[84]

IV.METABOLIC DISORDERS

i) **Yellow skin (Carotenoderma, xanthochromia)**– As many as 10% patients with diabetes may have yellow discoloration of the skin. This is due to associated hypercarotenemia, with concentration of carotene in areas of prominent sebaceous activity (face, forehead and axilla) and areas of thick stratum corneum (palms and soles). Hypercarotenemia in diabetes may be due to consumption of food with high carotene content or impaired conversion of carotene to vitamin A in liver.[81] Yellow skin may also be due to glycosylation of dermal collagen and protein, particularly in individual with poor glycemic control.[30]

About 50% of diabetics may have yellow nails, best seen in the distal hallux. This may be related to nonenzymatic glycosylation. Patients with carotenoderma are advised to reduce dietary intake of food which is high in carotene such as oranges, yellow fruits and egg yolk.[19]

ii) **Porphyrias**- They are a group of inherited disorders of haem synthesis in which large amounts of porphyrins, or their percursors are produced. Although diabetes has been reported in several forms of hepatic porphyrias, most of the studies report the association between porphyria cutanea tarda (PCT) and diabetes.

The classical picture of PCT includes appearance of vesicles, bullae and erosions over the sun exposed areas, the primary lesions heal slowly leaving behind scars and milia.

PCT is due to deficiency of uroporphyrinogen decarboxylase, which occurs in both a familial (autosomal dominant) form and a sporadic form.[38]

iii) **Hemochromatosis-** This is s storage disorder in which there is an inappropriate increase in intestinal iron absorption resulting in deposition of iron with eventual

tissue damage and functional impairment of the organs involved, especially liver, pancreas, heart and pituitary. It is characterized by the triad of cutaneous hyperpigmentation, cirrhosis of liver and diabetes mellitus (Bronze diabetes).

In a case report of a 26 year old female with IDDM and idiopathic hemochromatosis (confirmed by serum iron and liver biopsy), phlebotomy was done to remove 20 grams of iron after which the patient's symptoms improved.[86]

iv) **Xanthomatosis:**

a) Eruptive xanthoma: Diabetes mellitus is the most common cause of eruptive xanthomatosis. Eruptive xanthomatosis associated with diabetes is accompanied by hyperlipidemia, glycosuria and hyperglycemia.[30]

They characteristically arise during the hypertriglyceridemic phase (when serum triglyceride is > 1000 mg/dl) of uncontrolled diabetes. It occurs in 1 per 1000 patients with diabetes. The eruption consists of multiple, non-tender, firm, yellow waxy papules with an erythematous areola, appearing in crops on the extensor surfaces. They may show Koebner's phenomenon.

Histologically, the dermis shows presence of macrophages containing lipid particles (foam cells) and inflammatory infiltration of the superficial dermis.[34]

Treatment of hypertriglyceridemia involves strict dietary fat restriction and control of the underlying diabetes. LPL activity returns to normal after treatment with long term insulin or glucose-lowering agents. The eruptive xanthomas respond rapidly and usually resolve completely in 6 to 8 weeks.[87]

b) **Xanthelasma palpebrerum :** These are small yellow-orange macules which thicken to form oval foamy plaques, occurring in the eyelids, commonly in middle aged females. Though they are the commonest type of cutaneous

xanthomas, they are least specific because about 50% of persons with xanthelasma have normal lipid levels. The reported incidence is 1.5% in diabetics and 0.8% in non-diabetics. Chemicals like phenol, salicylic acid and T.C.A are used to cauterize the lesions of xanthelasma palpebrebrum.[20]

v) **Lipodystrophy:** There is idiopathic loss of subcutaneous tissues in a localized or generalized pattern. The exact etiology is not known, but best available evidence suggests hypothalamic dysfunction.[34]

In partial lipodystrophy, loss of subcutaneous fat first occurs in the face and then slowly extends downwards to involve the neck, chest, back and upper limb (progressive lipodystrophy). About 1/3rd of patients with partial lipodystrophy develop DM.[28]

Lawrence-Seip syndrome is characterized by congenital or acquired total lipodystrophy with loss of subcutaneous and visceral fat, hepatomegaly with abdominal prominence, acanthosis nigricans, increased bone growth, hypertrichosis, abundant curly scalp hair and insulin resistant non-ketotic DM. glucose intolerance can be detected earlier.[48]

For insulin lipodystrophy, use of intralesional injections of corticosteroids combined with insulin are advised and the patient is also advised to change the old insulin to purified insulin. No treatment is available for generalized and partial lipodystrophy.

vi) **Glucagonoma syndrome:** This syndrome is caused by tumours of the alpha- cell glucagon secreting portions of the pancreas. It has four manifestations - a) hyperglucagonemia , b) DM , c) weight loss and d) necrolytic migratory erythema (NME).

NME is a chronic fluctuating dermatosis characterized by an annular and figurative erythema that forms bullae and erosions. The periphery of the lesions often extends with vesiculopustules. This condition is mainly seen in intertrigenous and periorificial areas. The patients are most often middle aged women who have characteristic indolent skin lesions on the face with mild diabetes.[88] Marked elevations of plasma glucagon level confirm the diagnosis.

The characteristic histopathological change in acute lesions is well demarcated necrosis of the upper layers of stratum spinosum ('sudden death'). Neutrophilic chemotaxis to the necrotic area is seen. Older regions show various degrees of dyskeratosis, acanthosis and lymphocytic infiltrate in the dermis.[38]

V.COLLAGEN DISORDERS

Diabetic thick skin: Diabetes Mellitus is generally associated with a thickening of the skin, measurable by ultrasonography [89], and this thickening may increase with age in all diabetic patients, unlike normal aging skin.

Diabetic thick skin occurs in three forms- First is a general asymptomatic, but measurable thickening. Second is a clinically apparent thickening of the skin involving fingers and hands. Third is diabetic scleredema, an infrequent syndrome in which the dermis of the upper back becomes markedly thickened.[90]

Thickening of the skin on the dorsum of the hands occurs in 20% to 30% of all diabetic patients, regardless of the type of diabetes. Manifestations range from pebbled knuckles to diabetic hand syndrome.

Pebbled knuckles or Huntley's papules are multiple minute papules grouped on the extensor side of the fingers, knuckles or on the periungual surface.[91]The

prevalence of diabetic hand syndrome varied from 8% to 50%. It begins with stiffness of the metacarpophalangeal joints and progresses to limited joint mobility. Dupuytren contracture (or palmar fascial thickening) may further complicate diabetic hand syndrome.[92]

Scleredema diabeticorum (SD) was recognized as a syndrome in 1970. It presents with insidious onset of painless, symmetric induration and thickening of the skin on the upper back and neck. Spread to the face, shoulders and anterior torso may occur. The skin retains a non-pitting, woody, 'peau d' orange' quality.[45]

The classic type is known as Scleredema adultorum of Buschke which is usually preceded by an acute infection, especially streptococcal pharyngitis. It has a sudden onset and remission occurs over 18 months.[19]

The indurated areas are typically erythematous and finely papular. Patients may notice decreased sensation in the affected areas. It is reported in 2.5% to 14% of patients with diabetes.[93] SD is a disease of long standing diabetes and is associated with obesity and type 2 DM.[45]

The pathogenesis is postulated to be unregulated production of extracellular matrix molecules by fibroblasts leading to thickened collagen and increased deposition of glycosaminoglycans (GAGs-hyaluronic acid). Studies using in vitro fibroblast analysis from lesional skin have demonstrated increased synthesis of GAGs and type 1 collagen.[94]

Scleredema commonly occurs in middle aged males. Both type 1 and type 2 diabetics are affected and in most instances diabetes is long standing. The affected patients have high frequency of other microvascular complications. Unlike classical type (Scleredema of Buschke), Scleredema diabeticorum has little tendency to

resolution and improved glycemic control does not affect the course of scleredema. Treatment for SD is usually not successful. Case reports describe treatment with radiotherapy, low-dose methotrexate and prostaglandin E1.[45]

Limited Joint Mobility (LJM) and Waxy Skin Syndrome:

LJM or cheiroarthropathy, originally described in IDDM patients, consists of two major components – limitation of mobility of small joints of the hands and thickening and stiffness of skin, most marked on the dorsa of fingers. It appears to be the earliest clinically detectable complication of diabetes in childhood and adults.[19]

The stiffness usually begins in the metacarpophalangeal and proximal interphalangeal joints and it is bilaterally symmetrical and painless. It can be demonstrated by the inability to flatten the affected hand on a table top and by failure to approximate the two palms with fingers fanned (Prayer sign)[19]

However, the most accurate sign is limitation of extension with examiner passively testing the PIP and MCP joints.[95] Thickening of the skin is assessed by palpation and can also be demonstrated by ultrasound-A scanning.[96]

Thirty to fifty percent of adult patients with type 1 DM have LJM. It is also commonly seen in type 2 diabetics. LJM is associated with increased duration of diabetes and poor glucose control.

One longitudinal prospective study showed a 2.5 fold increase in the risk of LJM for every unit increase in the glycosylated hemoglobin. Most importantly, LJM is directly correlated with microvascular disease.[97]The incidence of LJM ranged from 8% to 50%. One third of the patients with joint limitation had thick, light waxy skin,that was more evident over the dorsum of hands.

Biopsy of the wrist skin shows markedly thickened dermis with sparse glands and hair follicles.

LJM is due to stiffening of the collagen of the periarticular tissues. The abnormal collagen in both components may be a reflection of NEG of protein. The major importance of this condition is the association with retinopathy, peripheral neuropathy and nephropathy.

Treatment of LJM is difficult and should focus on tight control of blood sugar as well as physical therapy to preserve active range of motion.[98]

VI. DERMATOSES STRONGLY ASSOCIATED WITH DM

(i) **Vitiligo –** It is an acquired condition of the skin characterized by symmetrical, circumscribed macular depigmentation in a localized or generalized pattern.It is most often seen periorificially and on the extensor aspect of extremities. Overlying hair can be white or normally pigmented.

It occurs in approximately 1% of general population and affects both sexes equally. Thirty five percent patients give a positive family history.[99]

About 48% of NIDDM patients have vitiligo. A high incidence of diabetes in families of patients with vitiligo has been demonstrated. In patients with vitiligo and diabetes, only 24% developed vitiligo before 40 years of age. Thus late onset vitiligo would have a closer association with DM.

Vitiligo also occurs more frequently in IDDM patients. The treatment of vitiligo is unsatisfactory. Systemic psoralens combined with exposure to sunlight or longwave UV light is effective in a proportion of cases.

Alezzzandrini's syndrome includes unilateral retinal detachment with ispilateralvitiligo and poliosis and this has been associated with IDDM.[100]

(ii) **Psoriasis:** Some authors have described an increased incidence of diabetes in psoriasis. A study 27.7% of their psoriatic patients having abnormal GTT or cortisone primed GTT.[101] Another study found diabetes in 8.88% of psoriatic patients.[26]

The incidence of psoriasis was more in persons above 40 years of age. Most of the psoriatic patients with abnormal GTT have extensive lesions.[101]

Psoriasis is treated with simple emollients, corticosteroids, salicylic acid and topical tars. Systemic therapy includes methotrexate, aromatic retinoids and PUVA therapy.[101]

(iii) **Pustulosis palmaris et plantaris :** Chronic, symmetric, erythematous plaques studded with small pustules on the palms and soles have been thought to be manifestations of psoriasis, a bacterid secondary to focal infection, or unknown cause. Forty one such patients had glucose intolerance: 68% had abnormal results, 8 were diabetic and 20 were were borderline.[102] These researchers postulated that an impairment of function was possibly the pathogenic mechanism, but this hypothesis,as well as the association with diabetes awaits confirmation.[60]

(iv) **Lichen planus (LP) :** Impaired GTT has been observed in LP patients. Verma et al, Jain et al and Powell et al found 56%, 60% and 62% of their LP patients had abnormal GTT or steroid primed GTT respectively. They also found that LP of recent onset had higher percentage of glucose intolerance.

An increased incidence of HLA-A28 among non-diabetic LP compared to LP with diabetes was noted. This finding raised the possibility that there may be two forms of LP- one of an immunologic origin and other of a metabolic defect. [103]

Grinspan syndrome is a constellation of diabetes, hypertension and oral erosive lichen planus.[104]

(v) **Perforating disorders:** Perforating folliculitis, Kyrle's disease, reactive perforating collagenosis and elastosis perforans serpenginosa are four primary perforating disorders with a common characteristic feature of transepidermal elimination of amorphous material.

All the four disorders can occur in patients of DM and chronic renal failure,most often due to diabetic nephropathy, many of whom are undergoing haemodialysis. In the same patient, different lesions showed different pathologic changes, when they occur in the setting of diabetes or renal failure. This has led several authors to suggest that they are variants of the same disease process and could be more accurately grouped under the term "acquired perforating dermatoses".[105]

Clinically patients have multiple, pruritic, hyperkeratotic umbilicated papules. They are both follicular and perifollicularly oriented and favour the extensor surface of trunk extremities. Lesions are most commonly dispersed, but occasionally they are grouped to form small verrucous plaques, or arranged in a linear fashion showing Koebner's phenomenon.[106]Cutaneous perforating diseases are treated, primarily for pruritus. UVB light therapy used for pruritus and topical retinoids have been used to treat perforating lesions.[105]

(vi) **Acanthosis nigricans:** It presents as hyperpigmented, velvety plaques in the skin folds. The dark colour is due to thickening of keratin containing superficial epithelium. [107] It is a sign of paraneoplasm (particularly in Ca stomach), as an adverse effect of certain drugs like nicotinic acid, corticosteroids (traditionally classified as benign in insulin resistant states). It also occurs in various endocrinopathies (e.g acromegaly, cushing syndrome, leprechaunism). Even in the insulin resistant diabetic patient, an underlying pathologic condition should be excluded.[50]

The pathogenesis is most likely related to high levels of circulating insulin which binds to insulin like growth factor receptors to stimulate the growth of keratinocytes and dermal fibroblasts.

Although the lesions are asymptomatic, they can be painful, malodorous, or macerated.[69]The most effective treatment is lifestyle alteration. Weight reduction and exercise can reduce insulin resistance. It is reversible with weight reduction if it is seen as a complication of obesity. If the lesions are asymptomatic, they need no treatment. Ointments containing salicylic acid or retinoid acid can be used to reduce thicker lesions in areas of maceration in order to decrease odour and promote comfort. Systemic isotretinoin improves acanthosis nigricans, but it recurs when the drug is discontinued.[92, 108]

(vii) **Skin tags (Acrochordon, soft wart):** These are benign connective tissue tumors of the dermis. They are small, soft pedunculated, often pigmented lesions, usually occurring on the eyelids, neck and axillae mostly in obese patients.

The estimated male to female incidence is 1:2. Their size is about 2mm in diameter and number increases with age. They are not only associated with diabetes, but also with pregnancy, menopause and colonic polyposis.They may also be regarded as a sign of increased cardiovascular risk.[109, 112]

It was reported that 72.3% male patients with skin tags had elevated fasting glucose.[110]In a study of 216 patients with skin tags ,overt diabetes was noted in 26.3% and impaired GTT in another 7.9%. [111] Histologically, epidermis is thin and the basal layer is flat and often hyperpigmented. The bulk of the lesion consists of loosely arranged well vascularized collagen.

An association of obesity, multiple skin tags, abnormal glucose tolerance, pseudo acanthosis nigricans and seborrheic keratosis, was proposed in the form of a syndrome. Also if skin tags occur in multiple sites and >3 in number, they could be taken as a marker for diabetes mellitus.[109] Skin tags can be removed with grade one scissors, cryotherapy or electrodessication.[112]

(viii) **Pruritus:**Generalized pruritus was noted in 16 of 500 diabetics in a study. Pruritus of anogenital region, legs and the body as a whole was considered a classical symptom of diabetes.

Localized anogenital pruritus is due to associated candidiasis which is more common in diabetics. Itching on the legs in elderly diabetics is not related to degree of hyperglycemia, but is a manifestation of diabetes. [48]

(ix) **Pigmented purpuric dermatoses:** Pigmented purpuric dermatoses (PPD) is an uncommon condition characterized by patched of orange or brown pigmentation and ‘cyanne pepper’ spots usually found on the extremities of

men. This condition results from red blood cell extravasation from the superficial vascular plexus.[30]Its etiology is unknown. [113]

Petechiae occurred on the legs and on the dorsa of feet which transformed into coexisting non-atrophic pigmented spots. For most patients, cardiac decompensation with edema on legs could be established as a precipitating factor for purpura. [115]Clinically the lower extremity purpura found in diabetic patients may resemble the purpura of Schamberg's disease. This condition may be a marker for microangiopathy in patients with DM.[114]

(x) **Cherry angiomas:** They are also known as Campbell de Morgan spots or senile hemangiomas. They are multiple, small red papules, scattered on the trunk of adults. They increase in number with age. Cherry angiomas have been reported to be more numerous and prominent in majority of untreated diabetics. This finding has not been confirmed and remains unproven.[48]

(xi) **Diagonal ear-lobe crease:**A significant association has been reported between a diagonal ear-lobe crease and diabetic retinal angiopathy (51.4%) and only a 7.6% rate of co-incidence in diabetics with normal blood vessels. The earlobe crease therefore may be an indication of generalized angiopathy and an additional skin sign of diabetes.

A study conducted on 150 patients with adult onset diabetes and 50 juvenile diabetics showed that 12 patients of adult onset diabetes were found to have well developed linear crease on their ear lobes and none of the juvenile diabetics had this ear lobe crease. In 75% of affected patients, the crease was situated in in the upper half of anterior surface of the earlobe.[115]

(xii) **Systemic lupus erythematosus (SLE):** The autoimmune mechanisms may play a role in certain types of diabetes, as has been suggested by reports of diabetic patients with SLE and antibodies to pancreatic islet cells.[116]

The association of SLE and DM in twins further supports this hypothesis, although the incidence of the inter-relationship has not been clearly established.[117]

(xiii) **Beau's lines:** They are transverse furrows in the nail plates caused by transient nail matrix growth arrest, sometimes attributable to trauma and infections or other causes such as fever and systemic diseases.

Two reports have linked the phenomenon to diabetes. In the first study, it was thought to indicate poor metabolic control of the diabetes[118]and the second study reported an association of diabetes, gout and hypertension.[119]

(xiv) **Crusted scabies:** Crusted scabies or Norwegian scabies was first described by Danielssen and Boeck in 1687 in Norway. It has been reported in association with wide variety of conditions including DM. The lesions consist of crusted papules, most commonly seen on the hands and feet. Palms and soles may be irregularly thickened and fissured. Erythema and scaling occur on the face, neck, scalp and trunk or it may be generalized. Itching is often absent, mild or may occasionally be severe. Generalized lymphadenopathy may be present in some cases.[120]

VII.DERMATOSES LESS COMMONLY ASSOCIATED WITH DM

a) **Alopecia areata:** Many of the organ-specific autoimmune diseases occur in association with each other and they also occur with increased frequency in patients with alopecia areata and their relatives. In a study of 108 patients with alopecia areata, 1 patient had IDDM (9%) and 11 patients (10%) had relatives with diabetes.[60]

b) **Bullous Pemphigoid:** In a case control study, it was found that the occurrence rate of primary DM prior to the administration of systemic corticosteroids was significantly higher in patients with bullous pemphigoid than in the controls. Hence, this study suggested a higher than chance association of bullous pemphigoid and primary DM.[121]

c) **Dermatitis herpetiformis (DH):** Co-existent DH and DM have been reported in several studies. The HLA association of DH and IDDM (HLA D3, HLA DRW2) may be a possible explanation. Severe renal complications of diabetes were noted in patients with such association.[122]

d) **Kaposi sarcoma:** Multiple idiopathic hemorrhagic sarcomas were described by Kaposi in 1872.[123]This uncommon, multifocal neoplasm generally begins on the lower aspects of the legs, often in elderly Jewish and Italian men. The lesions are purple macules, nodules or plaques. Later, other areas of the skin, mucous membranes and internal organs may be involved. Edema is frequent in the lower extremities, sometimes occurring even in patients with few lesions or as a prodromal symptom. The disease is generally indolent, but at times the course is rapid and aggressive. Histologic examination in the early patch or plaque stage shows bizzare, think-walled, endothelial lined spaces and in the later, tumour-

form stage, fascicles of the spindle cells. The spaces between the fascicles contain erythrocytes.[60]

Diabetes mellitus has been reported to occur with greater than expected frequency in patients with Kaposi's sarcoma by a number of authors. In an epidemiologic study, there were 12 diabetics in 37 patients with Kaposi sarcoma, the diabetes in these patients was predominantly mild and of adult onset. These figures suggest an association of the two diseases, but confirmation is needed from an age-matched control group.[124,125]

e) **Lipoid proteinosis (hyalinosis cutis et mucosae):** It is an autosomal recessive disease marked by popular and nodular vegetations on the dorsa of the hands, elbows, knees, margins of eyelids, nose and mouth. Morphea like plaques are found frequently on the body and involvement of the mucous membranes is common. Laryngeal involvement results in characteristic hoarseness.

A PAS positive, sudan positive, amorphous, eosinophilic, subepithelial material is seen under the microscope.[60]

Diabetes has been mentioned as an accompaniment in some cases and in other cases to occur more frequently in relatives than in the patients themselves. [126,127]

f) **Localized cutaneous amyloidosis:** An increased incidence of localized macular amyloidosis was reported on the shoulders and extensor aspects of the forearms of diabetics. Brown pigmentation was present corresponding with dermal papillary foci of amyloid. Pruritus, a symptom normally prominent in this dermatosis, was curiously slight or absent.[128]

g) **Pentazocine complications:** Severe, characteristic cutaneous complications consisting of sclerosis, ulceration and pigmentary changes can occur at sites of injected pentazocine in persons who abuse this analgesic. Of 17 such patients, 18% had diabetes mellitus and 65% had a personal or family history history (or both) of diabetes. Characteristic histologic findings include fibrosis of the dermis and panniculus, with vascular alterations, fat necrosis, granulomatous inflammation, vascular thrombosis and occasional endarteritis.[129]

h) **Yellow nails:** They are common in elderly diabetics, many of whom have cardiac decompensation. This sign was present in 50% of 36 diabetic patients and none of the 9 control patients. This finding, if confirmed, maybe related to peripheral vascular disease or to local causes such as onychomycosis. This sign is more evident in the toe nails and is often associated with purpura, pigmentation, erythema and impending gangrene.[65]

The yellowing of nails probably represents glycosylation end products. This finding has not been confirmed yet, but one study of fingernails has demonstrated that diabetics have high levels of fructose-lysine, another marker for NEG.[130]

i) **Intracutaneous herniation of fat:** Three cushion like lesions were described on the distal parts of the extremities that were more distinct on the dorsa of the hands.[131]The swellings, which were flesh coloured, doughy and non-pitted, proved to be intracutaneous fat herniation. Vascular changes consistent with diabetic microangiopathy were present. This condition should be differentiated from myxedema and edema secondary to cardiac and renal diseases to save the patients from both an intensive workup and unsuccessful attempts with therapy, including diuretics.[60]

j) **Onychodermal bands:** In 1955, Terry described a pink to red or reddish-brown narrow band transversely situated across the distal portion of the nail bed, immediately proximal to the free edge of the nail.[132] Pinching the skin proximal to the nail made the onychodermal band more prominent. This feature, together with a ground glass opacity extending from the base of the nail to the band was seen in a variety of conditions, most significantly hepatic cirrhosis, but also in young diabetics.[133]

A brown arc was found in the distal part of the fingernails just proximal to the point of separation from their beds in 12 of 34 patients with chronic renal disease.[134] This sign was associated with several diseases, including cirrhosis, congestive heart disease and adult onset diabetes mellitus. The risk of associated systemic abnormalities was more in younger patients, Tissue biopsy showed distal telangiectasia. This sign may be a marker of liver and kidney disease as well as diabetes.[60]

k) **Clear cell syringoma:** Clear cell syringoma is an unusual variant of the normal form of syringoma and is clinically similar to it in morphology, age and sex distribution.

The clear cell has two noteworthy features, namely, the histologic preponderance of clear cells and frequent co-existence of diabetes mellitus. Of 21 cases reported, mostly in Japanese, 15 were diabetic. This link may exist because in diabetic patients there may be a phosphorylase deficiency secondary to elevated glucose levels that in turn results in the formation of the clear cells.[135]

l) **Periungual telangectasias:** These lesions appear as red, dilated, capillary veins and are easily visible to the naked eye. They are a result of loss of capillary loops and dilation of the remaining capillaries. A prevalence upto 49% has been reported in diabetic patients. Connective tissue diseases may also involve periungual telangectasias, although these lesions are morphologically different.[136]

In diabetes, periungual telangiectasia is often associated with nail fold erythema, accompanied by fingertip tenderness and 'ragged' cuticles.[50]

ORAL MANIFESTATIONS OF DIABETES:

A wide spectrum of oral manifestations of DM has been reported. They include xerostomia, taste impairment, pain on percussing the teeth, sialosis, dental caries, periodontal disease, oral candidiasis, rhicocerebral mucormycosis, aspergillosis, oral lichen planus, geographical and fissured tongue. Dryness of mouth, often accompanied by fruity breath occurs frequently as a part of dehydration in ketoacidotic and comatose diabetic patients. The degree of metabolic control seems to influence the susceptibility of patients of DM to periodontal disease, fungal infections and taste alterations. [60, 137]

CUTANEOUS REACTIONS TO THERAPY FOR DIABETES

1) **Oral hypoglycemic drugs:** Cutaneous reaction to the first generation sulfonylureas usually develops in the first 2 months of therapy and may be either allergic or toxic. The incidence of allergic reactions is between 1-5%. Maculopapular eruption appearing during the first month of therapy is common. These disappear while the patient is receiving maintenance drug regimen. Other forms of rashes include morbilliform eruptions, generalized erythema, urticarial eruptions, photoallergic reaction, lichenoid and rosacea-like eruptions.

Alcohol induced flushing may occur in 10-30% of patients taking chlorpropamide. Other rare skin manifestations include purpura, erythema multiforme and erythema nodosum. Cutaneous reactions are less common with second generation sulfonylureas.[60,138]

2) **Insulin:** Insulin allergy occurs within 1-4 weeks of starting therapy and may be local or systemic reaction.

Local allergic reactions were very common previously, with the use of impure insulin and consist of 3 types of reactions. The most common is late phase reaction mediated by IgE characterized by erythema, pruritus and induration at the site of injection. Two rarer forms are Arthus-type reaction, producing painful pruritic nodule 6-8 hours after injection and the delayed hypersensitivity reaction, a similar reaction developing 12-24 hours after injection. Systemic allergic reactions are rare and consist of generalized urticaria, angioedema, bronchoconstriction, anaphylaxis and cardiovascular collapse.

Insulin lipoatrophy presents as circumscribed, depressed areas of skin at the injection site. This is commonly seen in females. The incidence of insulin lipoatrophy is 24.2%

Insulin lipohypertrophy presents as soft, dermal nodule resembling lipoma. This is commonly seen in males and may be due to lipogenic action of insulin.[138]

Insulin edema presents with edema of the abdomen and legs. It is a rare, self-limiting complication appearing shortly after starting or increasing the dose of insulin. It is commonly seen in females and the exact pathogenesis is unknown.[139]

Idiosyncratic reactions can occur at the injection site and include pigmentation and keloid formation. Bilateral symmetrical plaques resembling acanthosis nigricans have been described at the site of repeated injections.

Genetic engineering techniques using Escherichia coli are capable of producing pure human insulin. Perhaps many of the side effects currently associated with insulin therapy will no longer occur when pure human insulin becomes routine therapy.[138]

Infections associated with chronic continuous subcutaneous insulin infusion:

Two skin complications have been reported with continuous sub-cutaneous insulin infusion-

- Infection and abscess formation at the needle infusion site
- Local allergic reaction.

In a group of 20 IDDM patients, 4 had minor infections, with a small area of induration and erythema without suppuration, and responded well to needle withdrawal, local application of heat and antibiotics.[140]

Hand infections: One study followed 20 diabetic patients with hand infections. Although diabetics constituted <5%, they had a very high morbidity rate with 35% requiring amputation. Cultures obtained grew gram negative organisms. All patients had adult onset diabetes mellitus and in all of them, the infection followed relatively minor trauma. Histopathological examination revealed changes similar to those seen in diabetic gangrene of the lower extremities, with endothelial proliferation of the small arterioles and PAS positive deposits. Peripheral neuropathy was noticed in some of the patients.

Early aggressive treatment, including surgical debridement and intravenous antibiotics, is needed to prevent amputation and to improve residual function in diabetics with hand infection.[141]

Finger sepsis: Self-monitoring of the blood glucose level with finer pricks may be associated with soft tissue infections or even osteomyelitis. Thus it is recommended that blood for sampling be obtained from the side of the finger rather than the tip and that, treatment be instituted at the 1st sign of infection.[142] In a study, three patients had abscess formation secondary to staphylococcus aureus and required surgical intervention along with antibiotics.Initially, needles were changed every 4 to 6 days. When the needle size was changed to 25 gauge and a new needle was used every other day or earlier (at the 1st sign of inflammation), no further skin infections developed.[140]

METHODOLOGY

STUDY POPULATION

The study consisted of 100 cases of Type 1 and Type 2 Diabetes Mellitus with cutaneous manifestations attending Dermatology OPD and Diabetic OPD at K.L.E.S Dr. Prabhakar Kore Hospital and Medical Research Centre attached to Jawaharlal Nehru Medical College, Belgaum, from January 2010 to December 2010 for a period of 12 months.

Inclusion criteria

All confirmed (old and new) cases of Diabetes Mellitus with cutaneous manifestations irrespective of age, sex, duration of illness and associated diseases, willing to participate in the study.

Exclusion criteria

- Patients not willing to participate in the study.

A sample size of 100 was selected and this was calculated by using the formula $4pq/d^2$ where p=prevalence, q=100-p, d=absolute error.

Prevalence of cutaneous manifestations in Diabetes Mellitus is 43-66%.

So considering p=43,

q=100-p=100-43=57

d=10%

$4pq/d^2 = 4x43x57/10^2 = 98 \approx 100$

Ethical clearance was obtained. In the selected patients, a detailed history with particular reference to demographic details, family history of similar complaints and of DM, duration of DM treatment details, duration of various symptoms and evolution of lesions was taken.

The patients were clinically examined in good light, for various cutaneous manifestations of DM such as skin lesions, nail changes, mucous membrane involvement.

Following investigations were done in all the patients:

1) Routine haematological and urine investigations such as Hb%, TC, DC, ESR, RBS, urine routine and microscopy were done in all patients.
2) Fasting blood sugar, random blood sugar
3) Glycosylated (glycated) haemoglobin (HbA1c)
4) Investigations done to diagnose cutaneous manifestations associated with DM
    a. Potassium hydroxide mount
    b. Gram staining
    c. Bacterial and Fungal culture
    d. Skin biopsy

Mycological examination

The specimens from various sites were collected as follows:

Skin: Skin material was scraped with the flat edge of a sterile scalpel blade from the edge of the lesion in case of dermatophytosis.

Nail and Nail bed: Nails were cleansed with 70% isopropyl alcohol and a portion of the infected nail was clipped and excess keratin was scraped from the nail bed. In case of paronychia, the exudates were expressed from below the nail folds and the sample was collected on a moist sterile swab.

Mucous membrane examination:

Vagina: Per speculum examination was done and vaginal discharge was collected using a sterile swab from the posterior fornix or middle 1/3rd of the vagina.

Urethra and glans penis: Discharge was collected, in case of scanty discharge, milking of urethra was done prior to collection and samples collected were subjected for presence of spores and hyphae.

a) Potassium hydroxide (KOH) mount preparation:

Skin and mucous membrane lesions: For direct microscopic examination, a small amount of specimen was spread over the centre of a glass slide and a drop of 10% KOH was added and a cover slip was placed on it. Slide was slightly warmed by passing over a naked flame and after the material softened, gentle pressure was applied over the cover slip to force out any trapped air and to facilitate thinning of the specimen. Examination was conducted first under low power and then under high power objective.

Nails: In case of nail specimens, 40% KOH was first taken in a small test tube, nail clippings were introduced and kept overnight for dissolving the nail keratin. The specimen was then examined under the low and high power objective.

In both cases, attempt was made to identify the oval budding yeasts of pseudohyphae showing regular points of constriction, resembling lengths of

sausages, suggestive of candida or long septate hyphae with branching for dermatophytosis.

b) Gram stain: (i) Candida

(ii) Bacterial infections

One of the swabs containing the specimen was used to prepare smear on a clean glass slide. It was stained by Gram's Method. The smear was prepared on a glass slide and was fixed by gently passing over the flame of a spirit lamp. Then it was stained with gentian violet for one minute and Gram's iodine was added and kept for another one minute. Then it was washed with water and decolorized with alcohol or acetone for 10-30 seconds. After washing again with water, it was counterstained with safranin or carbol fuschin for 20-30 seconds. The stained smears were examined under the microscope using oil immersion lens. The bacterial types, their arrangement and staining characteristics were noted.

c) Culture

Bacterial: The specimen from the other swab was inoculated on to the blood agar and Mac Conkey's agar media. The media were then incubated at 37°C aerobically for 18-24 hours. The organisms were identified on the basis of colonial morphology and biochemical characteristics. Antibiotic sensitivity was done using disk diffusion method on Muller Hinton agar. The zone size was measured and interpreted as per standard methods.

Fungal: The culture medium used was the Sabouraud's Dextrose Agar (SDA), with a pH of 5.6, supplemented with antibiotics like chloramphenicol and gentamycin to prevent bacterial overgrowth. Freshly collected specimens were inoculated onto two tubes of SDA, and were incubated.

In candida species, the growth appears in 3 to 4 days as cream coloured, smooth and pasty colonies.

d) **Skin biopsy:** Skin biopsy was performed for dermatoses such as lichen planus, diabetic dermopathy, diabetic bullae and psoriasis.

Procedure: After an informed consent, thorough cleaning of biopsy site was done using 70% alcohol. The area was then anaesthetized by infiltrating 2% lignocaine subcutaneously. A round body skin biopsy punch was held vertically and twisted as it descends vertically through the dermis and subcutis. The punch was then slowly withdrawn and specimen was elevated and cut at its base. This was transferred to 10% formalin for histopathological examination.

Statistical method used:

The comparison of cutaneous manifestations in controlled and uncontrolled Diabetes mellitus was done using Fisher's Exact test and Chi-square test.

OBSERVATIONS AND RESULTS

Table 6 :Age distribution

Age (years)	No. of cases	Percentage (%)
10-20	2	2
21-30	1	1
31-40	6	6
41-50	27	27
51-60	33	33
61-70	22	22
71-80	6	6
>80	3	3
TOTAL	**100**	**100**

In the present study, peak prevalence was seen in the age group of 51-60 years that is 33%. The youngest patient was 13 years old and eldest was 83 years old.

Graph 1: Age distribution

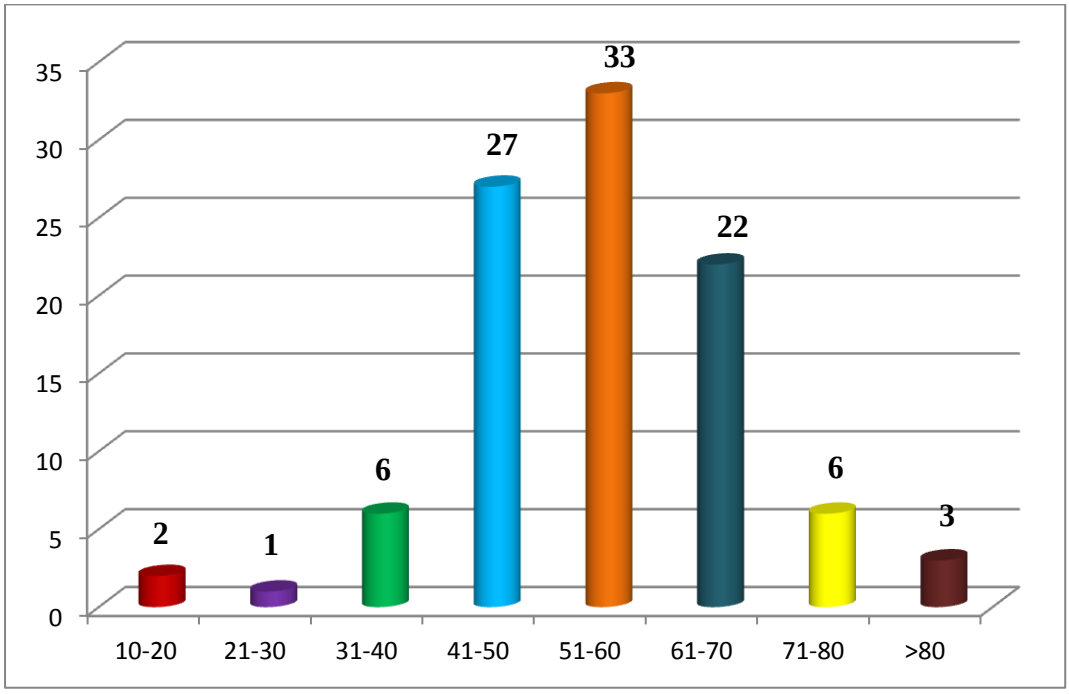

Table 7: Sex distribution

Sex	No. of cases	Percentage (%)
Male	69	69
Female	31	31
Total	**100**	**100**

There was male preponderance in this study. Male to female ratio was 2.2:1

Graph 2: Sex distribution

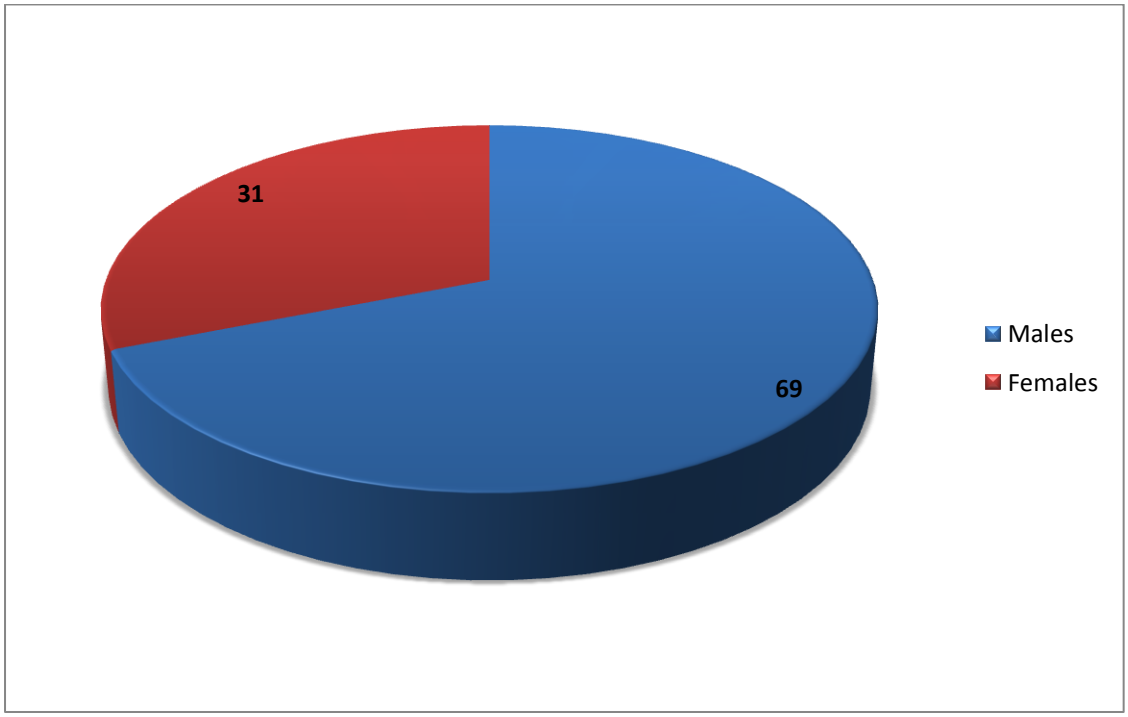

Table 8 : Duration of Diabetes Mellitus

Duration (years)	No. of cases	Percentage (%)
<1	21	21
1-5	40	40
6-10	26	26
>10	13	13
Total	**100**	**100**

In the present study,40% of the patients had diabetes for a duration of 1-5 years and 26% for 6-10 years.

Graph 3: Duration of Diabetes Mellitus

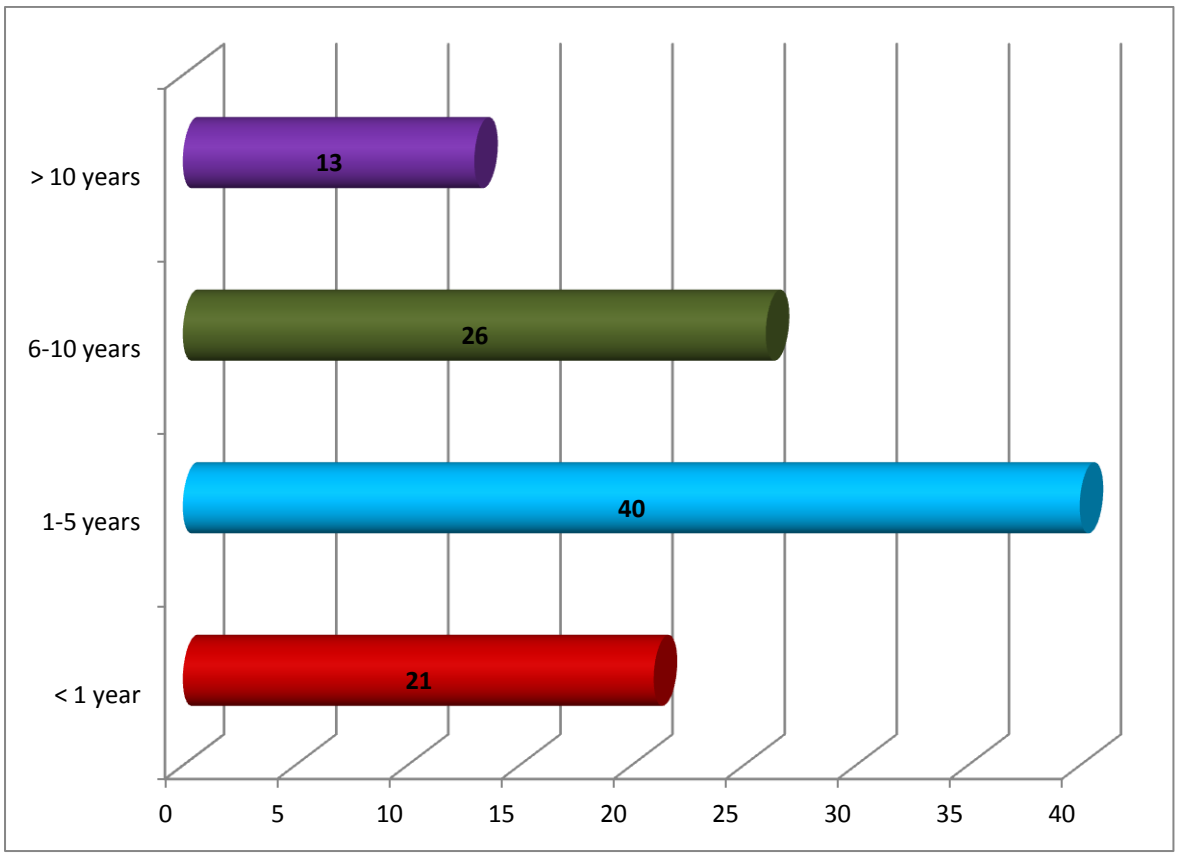

Table 9 :Type of Diabetes Mellitus

Type	No. of cases	Percentage (%)
Type I	4	4
Type II	96	96
Total	**100**	**100**

Majority of the patients in our study had Type II diabetes (96%), while Type I diabetes was seen in 4% of the patients

Graph 4: Type of Diabetes Mellitus

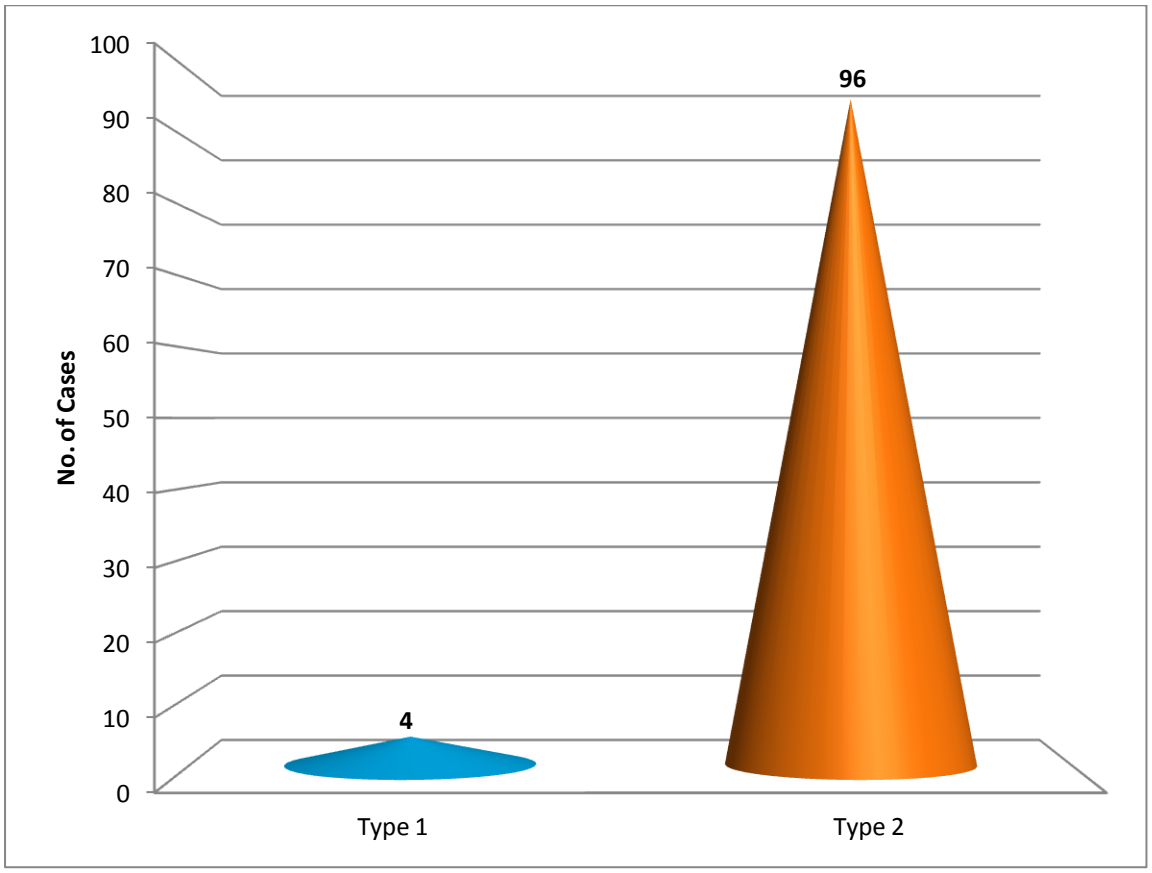

Table 10: Family history

Family history	No. of patients	Percentage (%)
With family history	32	32
Without family history	68	68
Total	**100**	**100**

A positive family history of Diabetes was obtained in 32% patients, while 68% patients gave a negative family history.

Graph 5: Family history

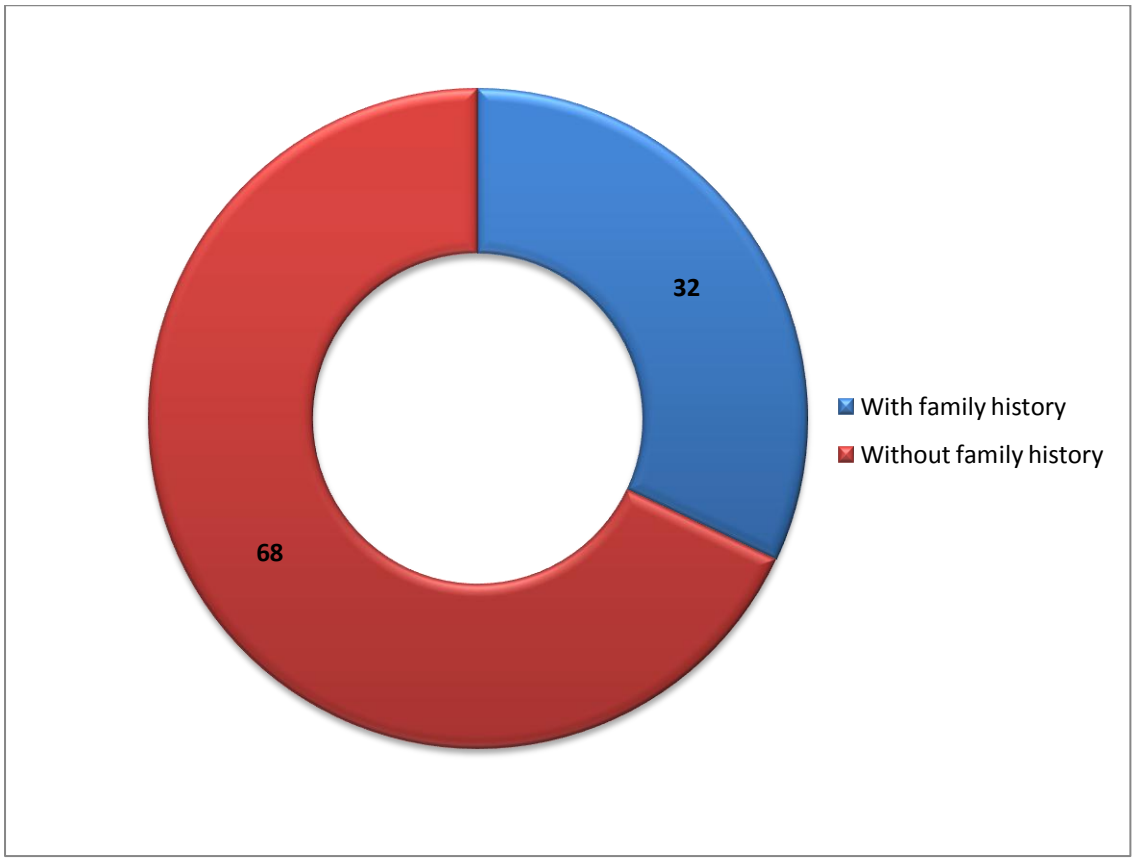

Table 11 :Random blood sugar levels

RBS(mg/dl)	No. of cases	Percentage (%)
70-140	22	22
140-200	49	49
>200	29	29
Total	**100**	**100**

Majority of the patients had random blood sugar levels in the range of 140-200mg/dl (49%), followed by 29% patients with levels >200mg/dl .

Graph 6: Random blood sugar levels

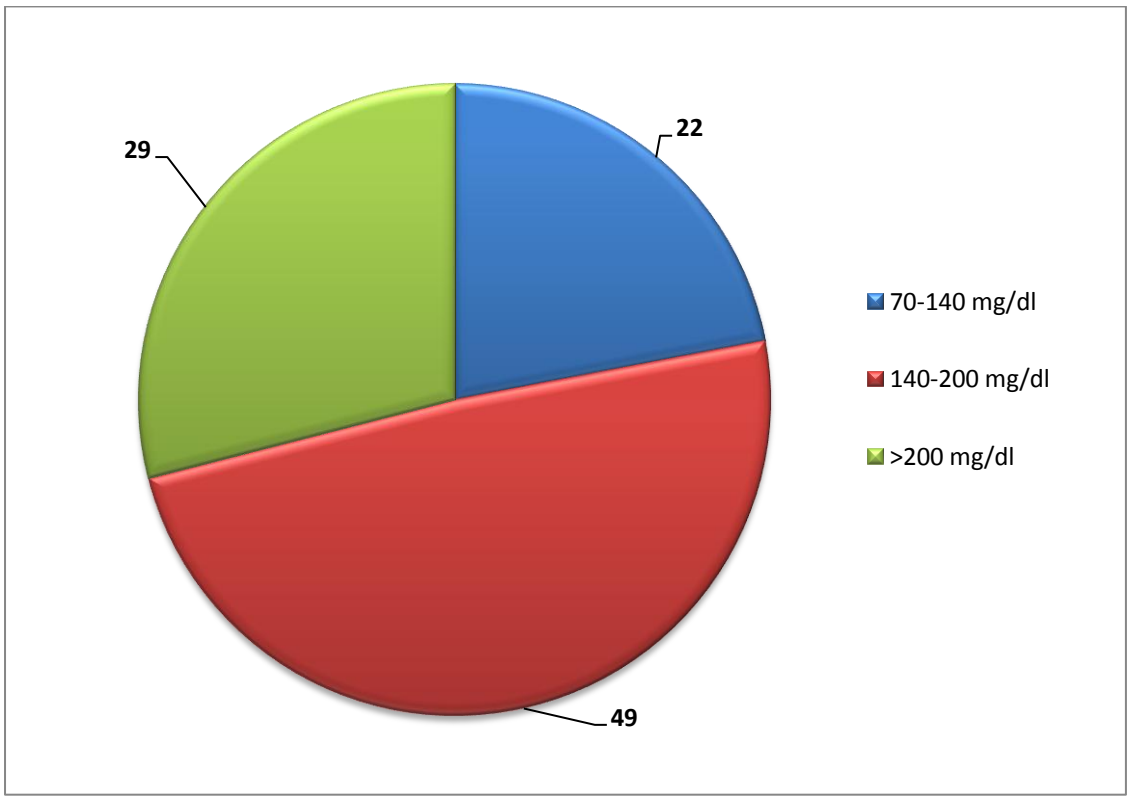

Table 12 :HbA1c levels

HbA1c (%)	No. of cases	Percentage (%)
4.7-6.4	6	6
6.5-7	9	9
7.1-8	22	22
>8	63	63
Total	**100**	**100**

Majority of the patients (63%) had a poor control of diabetes with HbA1c levels >8%, followed by 22% who had a moderate control of diabetes.

Graph 7: HbA1c levels

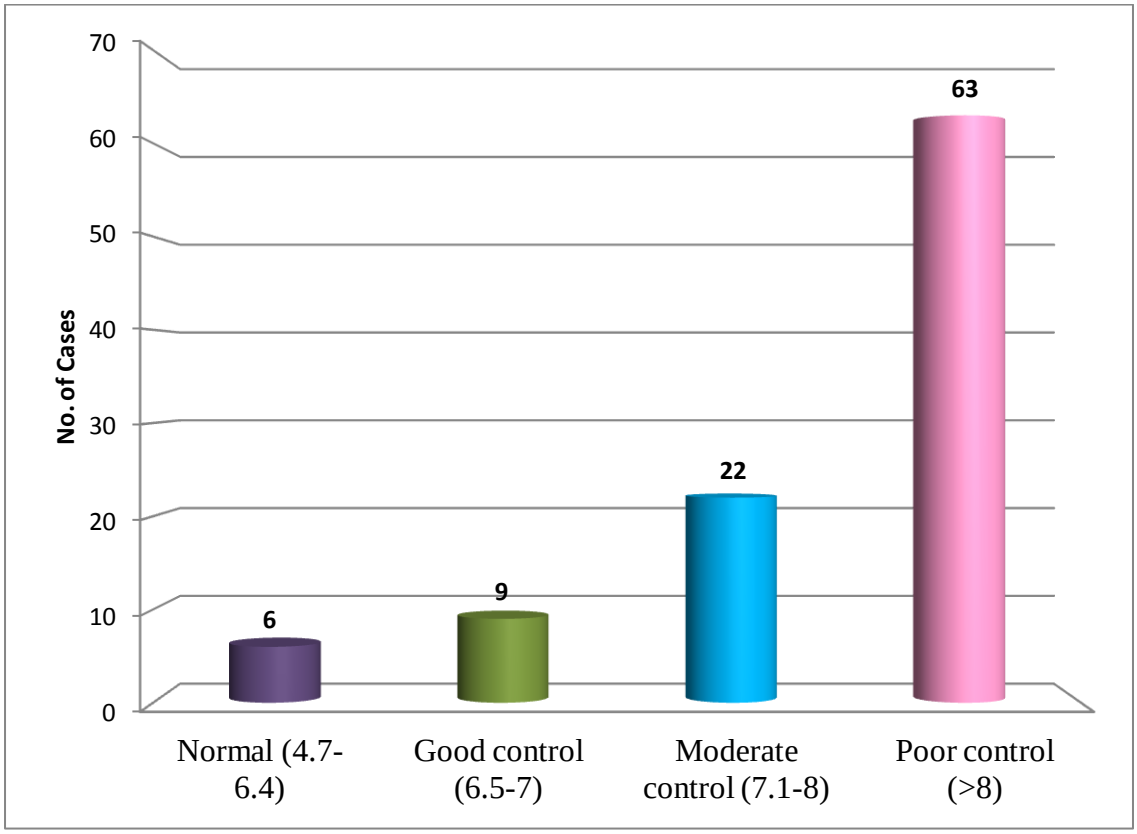

Table 13 : Associated systemic illnesses

Associated systemic illness	No. of cases	Percentage (%)
Present	59	59
Absent	41	41
Total	**100**	**100**

Out of the 100 patients, 59% had associated systemic illnesses, while 41% did not have any other associated systemic illness.

Graph 8: Associated systemic illnesses

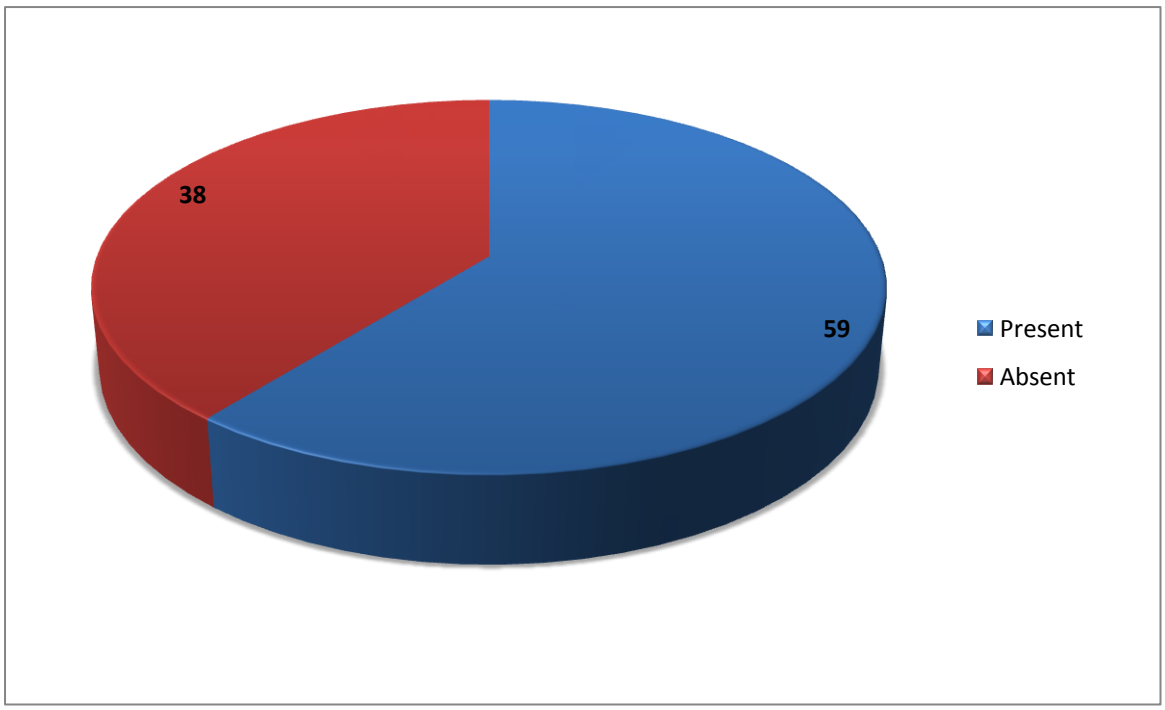

Table 14: Systemic illnesses

Associated illnesses	No. of cases
Hypertension	46
Ischemic heart disease	13
Dyslipidemia	9
Chronic renal failure	5
Hypothyroidism	3
Bronchial asthma	1
Epilepsy	1
Chronic myeloproliferative disorder	1

Hypertension was the most commonly associated systemic illness seen in 46% patients, followed by Ischemic heart disease (13%) and Dyslipidemia (9%). Some of the patients had more than one associated systemic illness.

Graph 9: Systemic illnesses

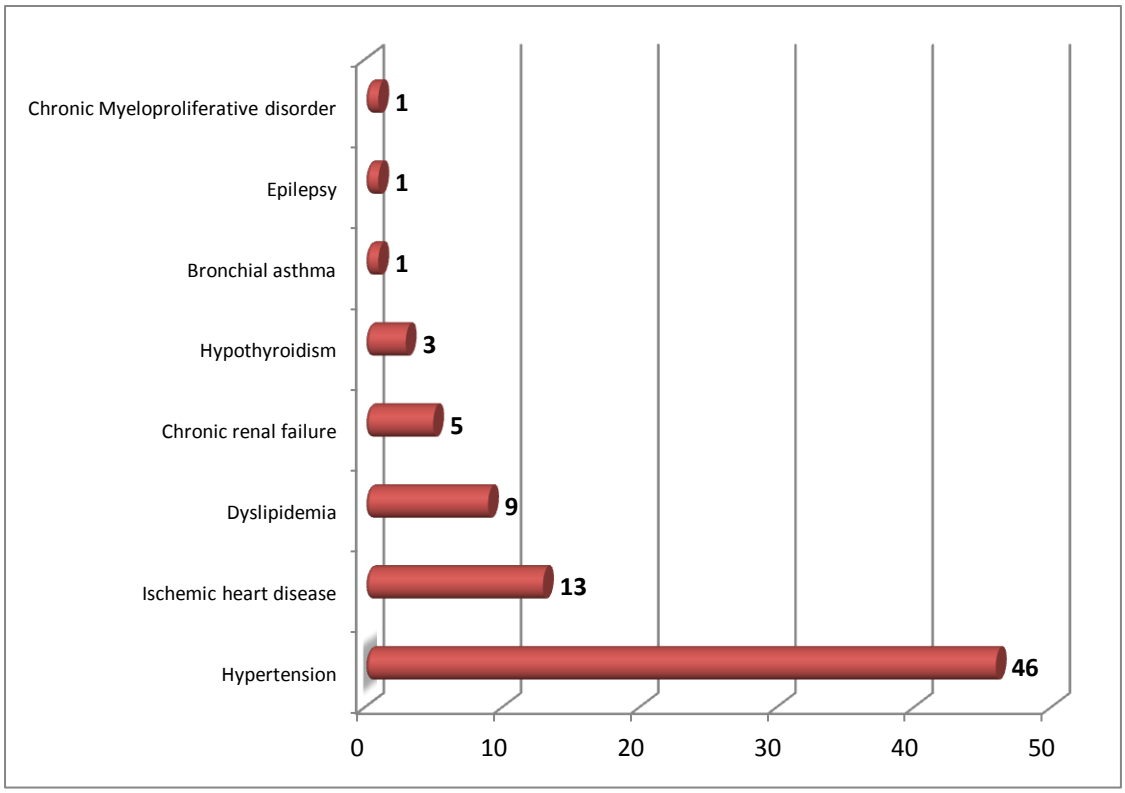

Table 15: Pattern of cutaneous manifestations

Dermatoses	No. of cases	%
Cutaneous infections	62	62
Dermatoses associated with microangiopathy	8	8
Neuropathic and ischemic diabetic skin disease	13	13
Metabolic diseases	2	2
Disorders of collagen	0	0
Dermatoses more commonly associated with diabetes	58	58
Cutaneous reactions to therapy for diabetes	1	1
Non-specific manifestations	41	41

As shown above, cutaneous infections were the most commonly observed dermatoses (62%), followed by dermatoses more commonly associated with diabetes (58%), non-specific manifestations (41%), neuropathic and ischemic diabetic skin disease (13%), due to microangiopathy (8%), metabolic disorders (2%) and cutaneous reactions to diabetic therapy (1%). Some patients had more than one type of cutaneous manifestation.

Graph 10: Pattern of cutaneous manifestations

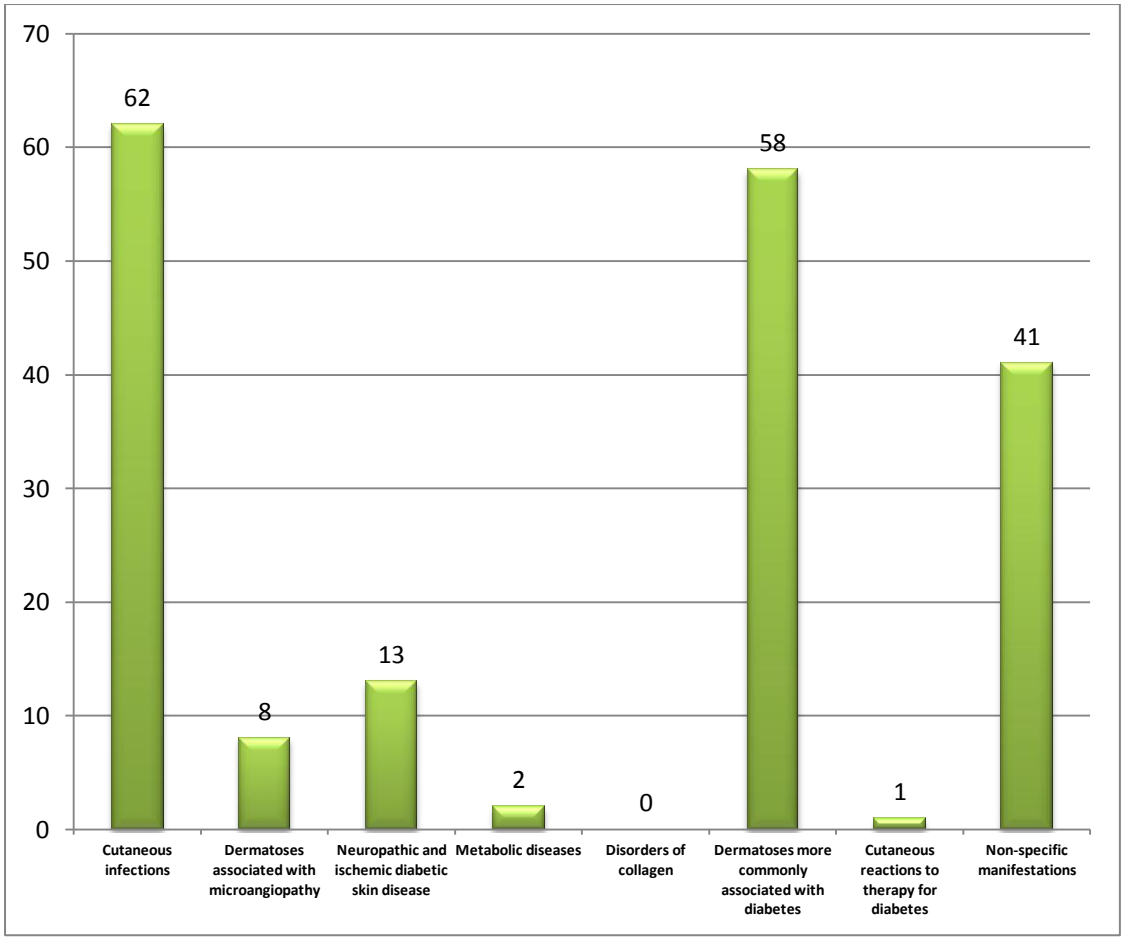

Table 16: Cutaneous infections

Cutaneous infections	No. of cases
Bacterial	21
Fungal	37
Viral	4
TOTAL	**62**

Amongst the 62 patients with cutaneous infections, majority had fungal infections (37%), followed by bacterial infections (21%) and viral infections (4%)

Graph 11: Cutaneous infections

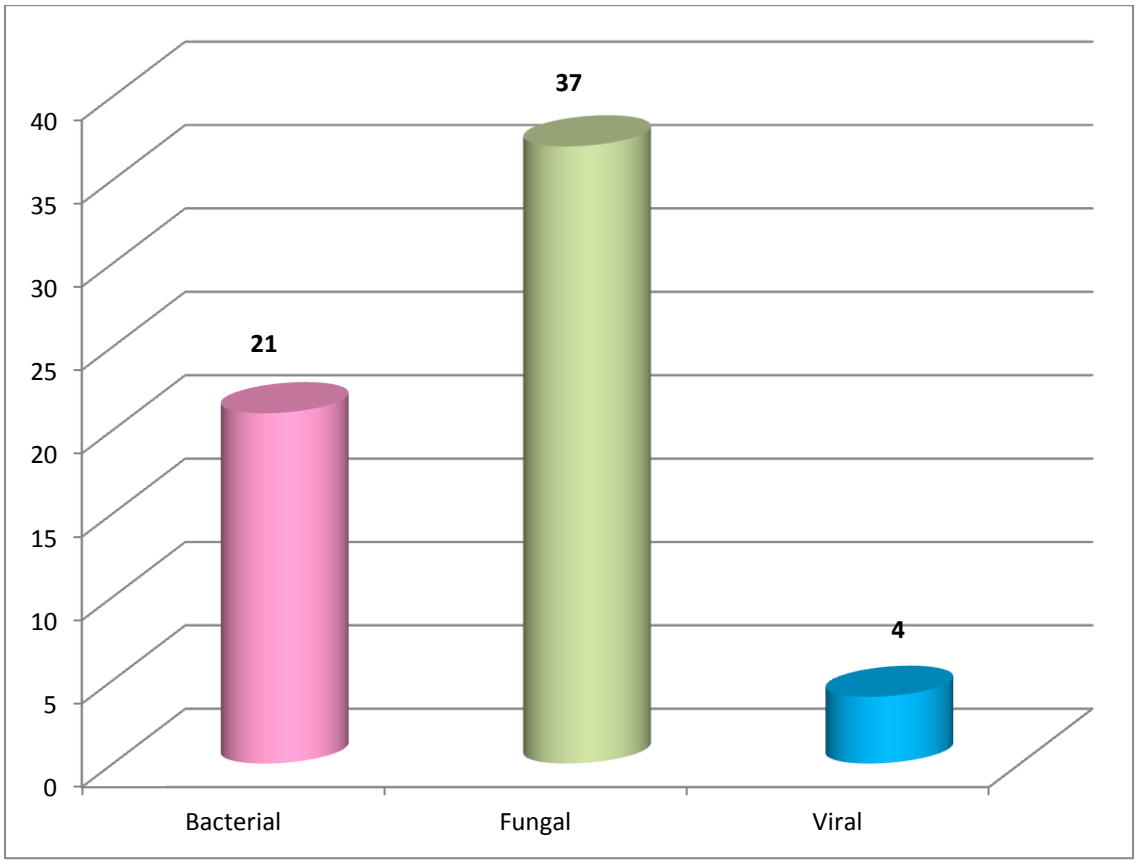

Table 17: Bacterial infections

Bacterial infection	No.of cases
Furunculosis	11
Folliculitis	3
Cellulitis	3
Abscess	2
Carbuncle	1
Ecthyma gangrenosum	1

Among the 100 diabetic patients, 21 had bacterial infections of which the most commonly observed were cases of furunculosis seen in 11 patients (11%), followed by 3 patients each (3%) of folliculitis and cellulitis, 2 patients (2%) with abscess and 1 patient each (1%) of carbuncle and ecthyma gangrenosum.

Graph 12: Bacterial infections

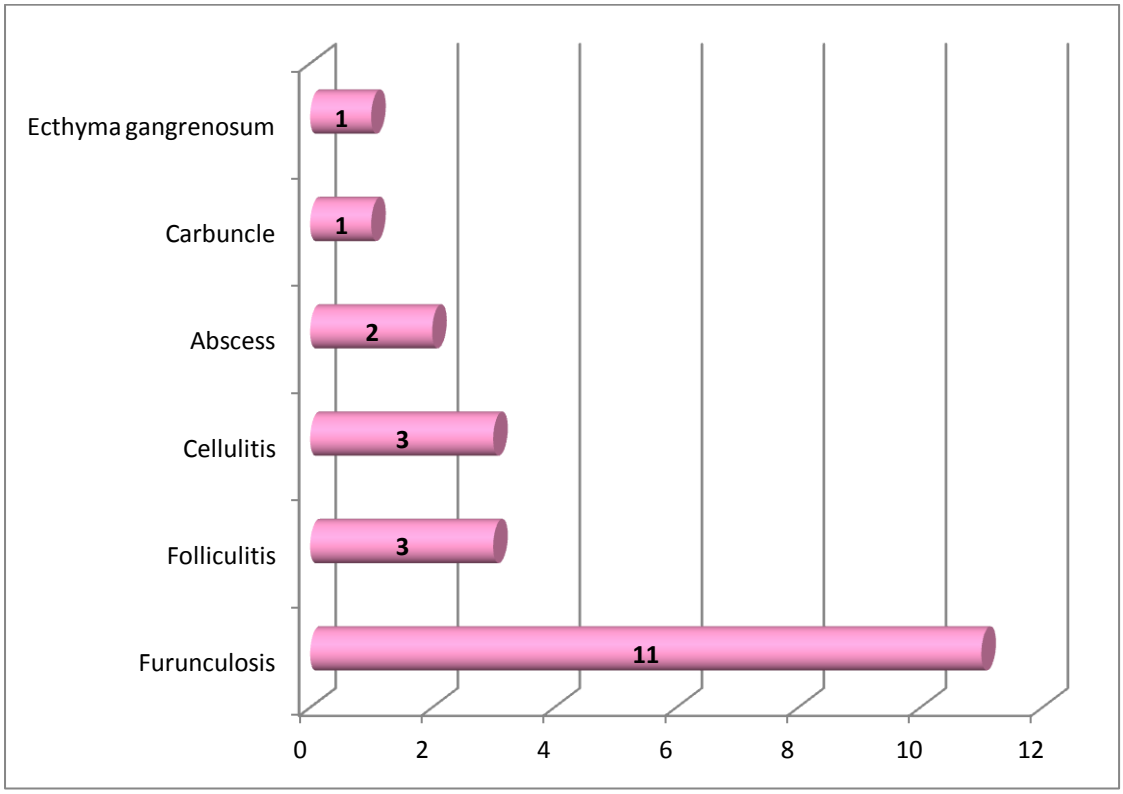

Table 18: Fungal infections

Fungal infection	No. of cases
Tinea cruris	15
Tinea corporis	13
Candidial intertrigo	4
Onychomycosis	3
Pityriasis versicolor	3
Tinea axillaris	2
Candidial balanoposthitis	1
Candidial vulvovaginitis	1
Chronic paronychia	1

Out of the 100 patients studied, 37 had fungal infections of which most commonly observed was tineacruris seen in 15 patients (15%), followed by tinea corporis in 13 patients (13%), 4 cases (4%) of candidial intertrigo, 3 cases each (3%) of onychomycosis and Pityriasis versicolor, 2 cases (2%) of tinea axillaris and one case each (1%) of candidial balanoposthitis, candidial vulvovaginitis and chronic paronychia. Some patients presented with more than one fungal infection.

Graph 13: Fungal infections

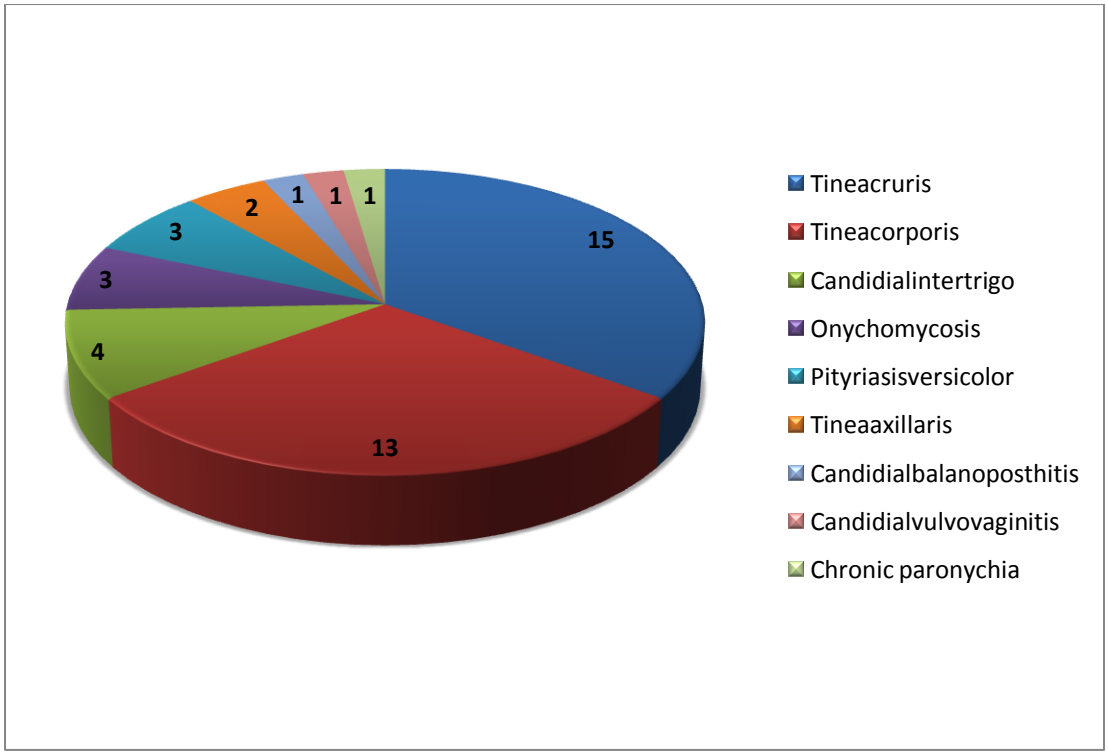

Table 19: Viral infections

Viral infection	No.of cases
Verruca vulgaris	2
Herpes zoster	2

As shown in the above table, out of the 4 patients with viral infections, 2 (2%) patients had verruca vulgaris and 2 patients (2%) were diagnosed to have herpes zoster.

Graph 14: Viral infections

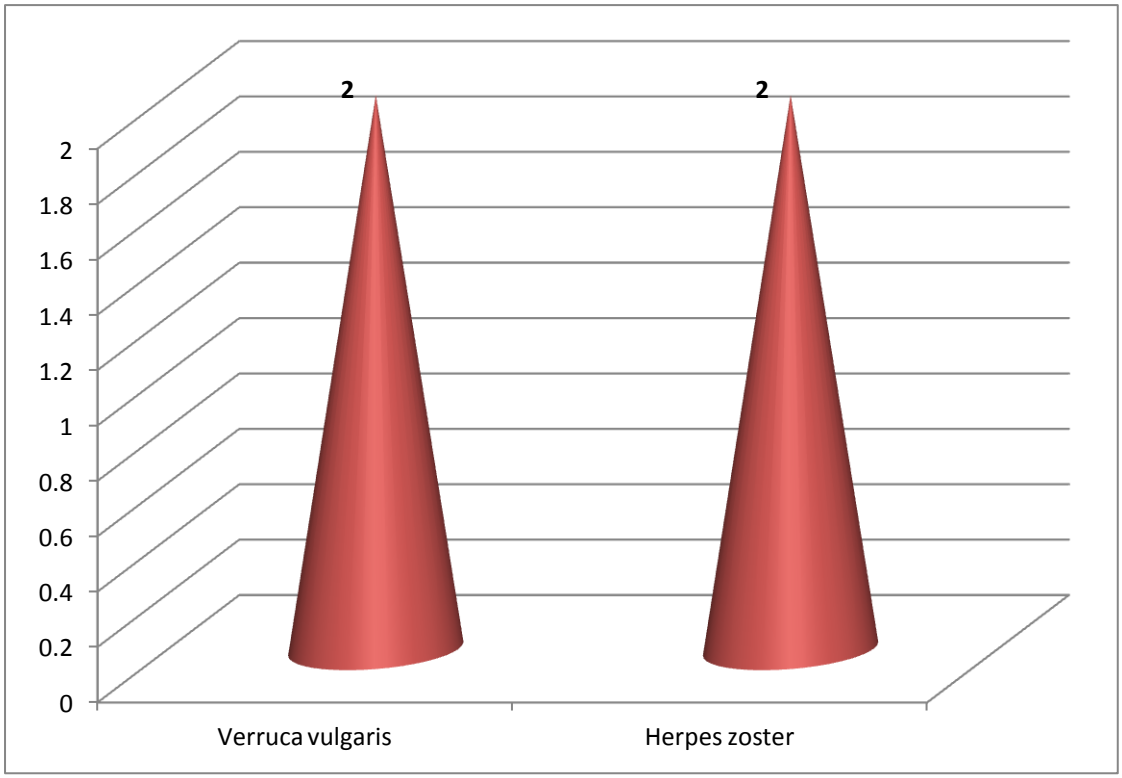

Table 20:Dermatoses associated with microangiopathy

Dermatoses	No.of cases
Diabetic dermopathy	7
Diabetic bullae	1
TOTAL	**8**

Out of the 100 patients studied, 8 patients presented with dermatoses due to microangiopathy, of which 7 patients (7%) had diabetic dermopathy and 1 patient (1%) had diabetic bullae

Graph 15: Dermatoses associated with microangiopathy

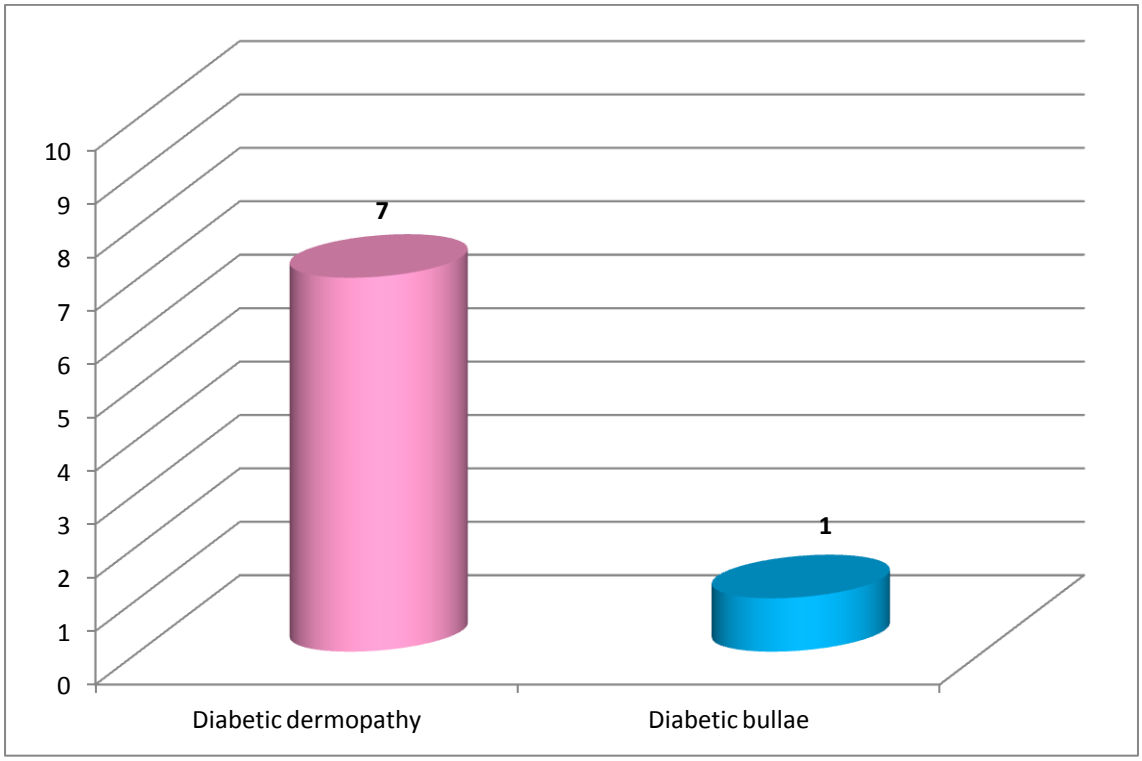

Table 21: Neuropathic and ischemic diabetic skin disease

DERMATOSES	No. of cases
Peripheral vascular disease	5
Diabetic foot ulcers	4
Fissure feet	4
TOTAL	**13**

As shown in Table 16, thirteen patients presented with neuropathic and ischemic diabetic skin disease. 5 patients (5%) had peripheral vascular disease and 4 patients each (4%) had diabetic foot ulcers and fissure feet.

Graph 16: Neuropathic and ischemic diabetic skin disease

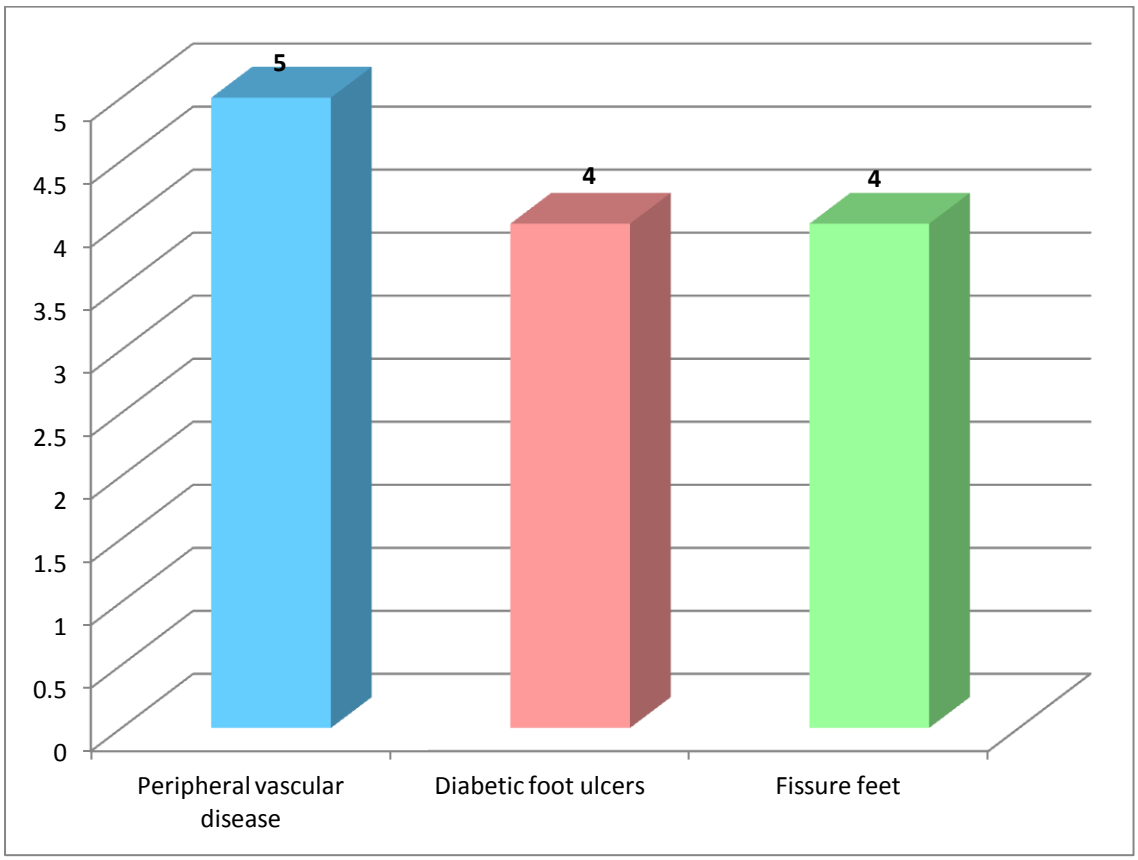

Table 22: Metabolic conditions

DERMATOSES	No. of cases
Xanthelasma palpebrerum	2
TOTAL	**2**

Out of the 100 diabetic patients, 2 patients (2%) presented with xanthelasma palpebrerum.

Graph 17: Metabolic conditions

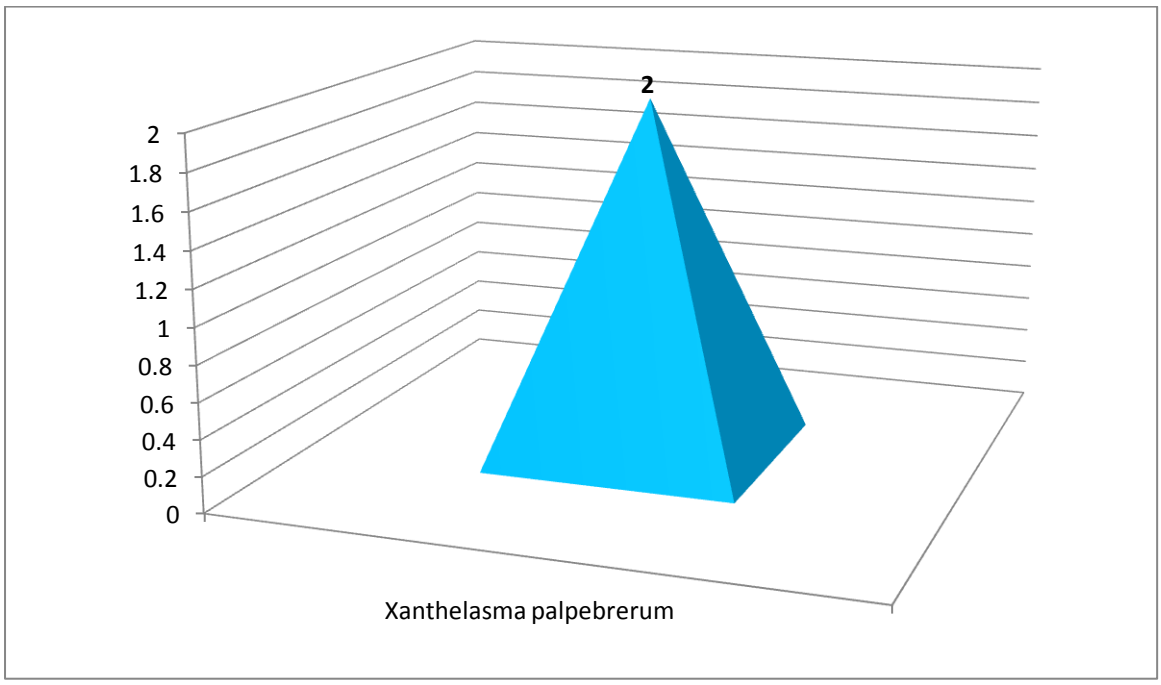

Table 23: Dermatoses commonly associated with DM

Dermatoses	No. of cases
Generalized pruritus	23
Acrochordons	8
Psoriasis	7
Vitiligo	4
Acanthosis nigricans	4
Progressive pigmented purpura	3
Perforating foliculitis	3
Lichen planus	2
Cherry angiomas	2
Macular amyloidosis	1
Alopecia universalis	1

Among the various dermatoses studied in 100 patients of DM, the most commonly associated with diabetes are shown in the table above. Majority presented with generalized pruritus (23 patients, 23%), followed by 8 cases (8%) of acrochordons, 7 patients (7%) of psoriasis, 4 patients each (4%) of vitiligo and acanthosis nigricans, 3 patients each (3%) of progressive pigmented purpura and perforating folliculitis, 2 patients each (2%) of lichen planus and cherry angiomas and one case each (1%) of macular amyloidosis and alopecia universalis. Some of the patients had more than one type of dermatoses which are commonly associated with DM.

Graph 18: Dermatoses commonly associated with DM

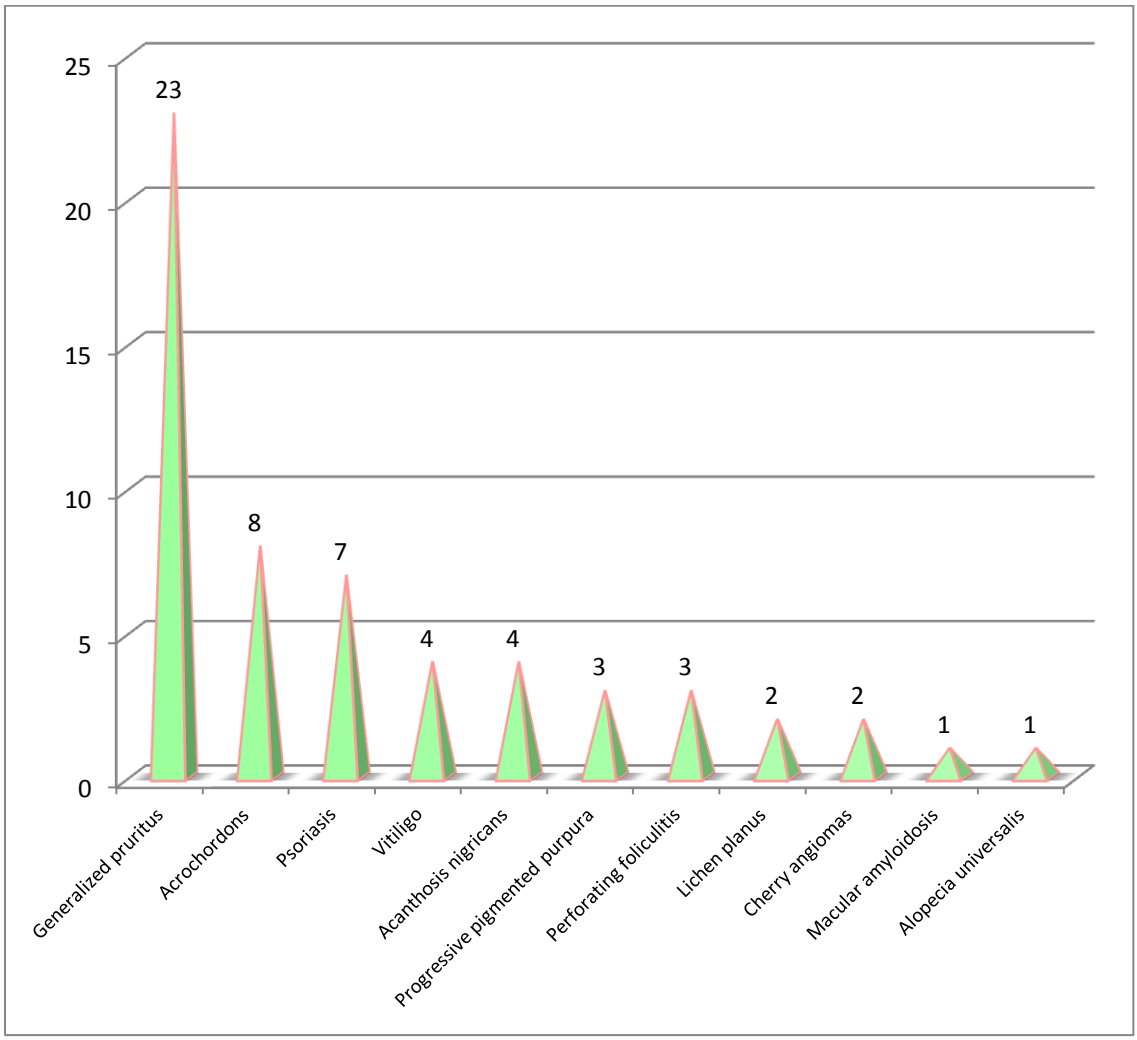

Table 24: Cutaneous reactions to therapy for diabetes

Mode of treatment	No. of cases
Insulin	1
Oral hypoglycemic agents	0
TOTAL	**1**

Of the 82 patients on anti-diabetic treatment, only one patient presented with acute urticaria secondary to insulin therapy.

Graph 19:Cutaneous reactions to therapy for diabetes

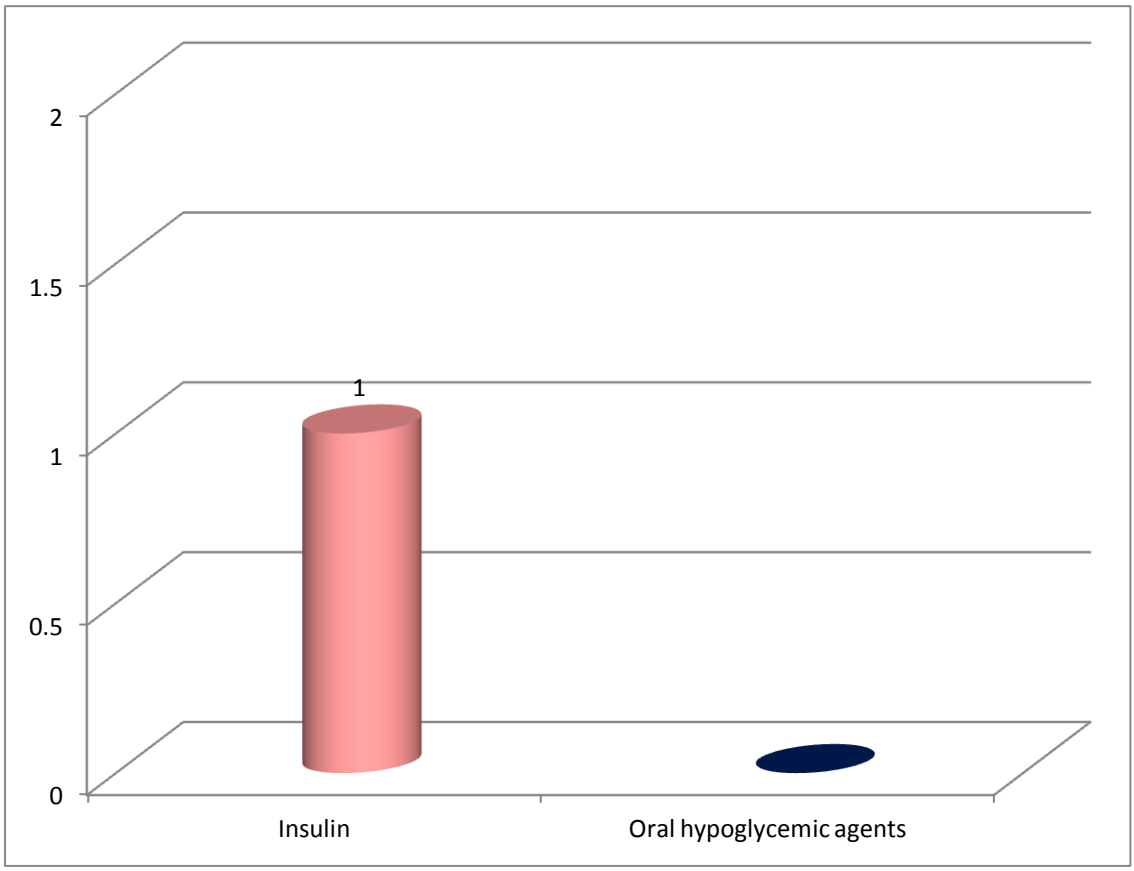

Table 25: Non-specific manifestations

Dermatoses	No. of cases
Eczema	15
Seborrheic keratoses	6
Dermatosis papulosa nigra	4
Pemphigus	2
Contact dermatitis	2
Drug reactions	2
Scabies	2
Sebaceous cyst	1
Polymorphous light eruption	1
Keloid	1
Parapsoriasis	1
Seborrheic dermatitis	1
Melasma	1
Senile comedones	1
Lichen simplex chronicus	1

As mentioned in the above table, eczema was the most common non-specific manifestation observed in 15 patients (15%), followed by seborrheic keratoses in 6 patients (6%), 4 patients (4%) of DPN, 2 patients each (2%) of pemphigus, contact dermatitis, drug reactions and scabies, and one case each (1%) of sebaceous cyst, polymorphous light eruption, keloid, parapsoriasis, seborrheic dermatitis, melasma, senile comedones and lichen simplex chronicus. Some of the patients had more than one non-specific cutaneous manifestation.

Graph 20:Non-specific manifestations

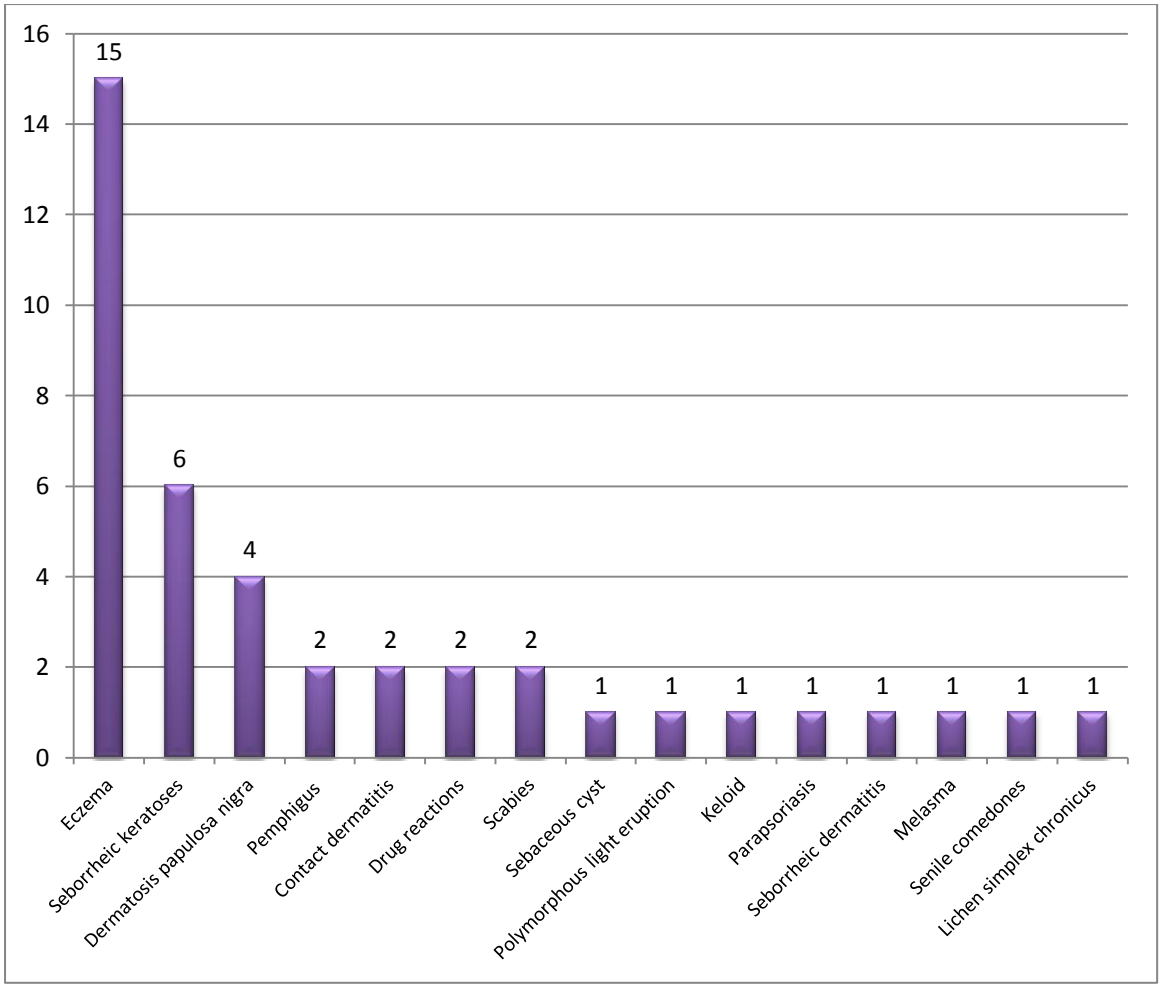

Table 26: Comparison of cutaneous manifestations in Controlled and Uncontrolled diabetes

	n = 37		n = 63		
Dermatoses	**Controlled DM (<7%)**	**%**	**Uncontrolled DM (>7%)**	**%**	***P* value**
Cutaneous infections	20	54.1	42	66.7	0.210
Dermatoses associated with microangiopathy	2	5.4	6	9.5	0.725
Neuropathic and ischemic diabetic skin disease	4	10.8	9	14.3	0.849
Metabolic diseases	0	0	2	3.2	0.529 (Fisher's exact test)
Disorders of collagen	0	0	0	0	0
Dermatoses more commonly associated with diabetes	22	59.5	36	57.1	0.821
Cutaneous reactions to therapy for diabetes	0	0	1	1.58	0.15
Non-specific manifestations	23	62.2	18	28.6	0.001

Among the 100 diabetic patients with cutaneous manifestations, 37 patients had HbA1c <8% (good to moderate control) while 63 patients had a poor control of diabetes (HbA1c >8%).

In the present study, when a comparison of pattern of cutaneous manifestations in the controlled and uncontrolled groups was done, it was found that the cutaneous infections, dermatoses associated with microangiopathy, neuropathic and ischemic diabetic skin disease, metabolic diseases and cutaneous reactions to diabetic therapy were more common in the uncontrolled group, which was meaningfully significant. The increased frequency of non-specific manifestations in the controlled group was statistically significant ($P<0.05$)

DISCUSSION

Age distribution

In the present study of 100 patients of DM with cutaneous manifestations, majority belonged to the 5th and 4th decade with 33% and 27% respectively.

The frequencies of patients with cutaneous manifestations in the first, second, third, sixth and seventh decade is 2%, 1%, 6%, 22%, 6% and 3% respectively.

Similar frequencies were reported by various studies carried out by Mahajan et al[22], Sawhney et al[75] and Nigam et al[21], which are well in accordance with the above frequencies.

The relative increase 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 in these patients.

Sex distribution

In the present study, male diabetics were more prone for cutaneous manifestations than females (69% vs 31%), which was also observed by Sawhney et al[75], Rao et al[143] and Al-Mutairi et al.[144]

Mahajan et al[22], Bhat et al[145] and Nigam et al[21] reported that female diabetic patients had significantly higher incidence of cutaneous manifestations.

Duration of diabetes

In the present study, 40% of the patients had diabetes for a of duration of 1-5 years and 26% patients for 6-10 years.

According to Bhat et al[145], majority of diabetic patients with cutaneous manifestations had 1-5 years of duration of diabetes (37.37%), followed by 6-10 years (24.24%).

Rao et al[143] repoted that majority of skin manifestations occurred within five years of diagnosis of diabetes.

As the duration of diabetes increases, there is non-enzymatic glycosylation of dermal collagen and mucopolysaccharides, leading to various cutaneous manifestations.[145]

Infections were more common during early diabetes, probably due to decrease in the host defense mechanism and decreased phagocytic activity,which is noticed immediately in uncontrolled diabetes.

Manifestations due to diabetic microangiopathies were seen in chronic diabetes because the deposition of PAS - positive material within the lumina of the blood vessels occurs slowly in the disease process.

Type of diabetes mellitus

Non-insulin dependent diabetes mellitus (type 2 DM) was most commonly observed (96%) as compared to Insulin dependent diabetes mellitus (type 1 DM) (4%).

This reflects the general distribution pattern of type 1 and type 2 DM cases in world population. No difference in the prevalence of cutaneous disorders between type 1 and type 2 DM patients has been noted.[144,145]

Similar observations of type 2 diabetes being more common was observed in studies conducted by Mahajan et al[22] (98%), Sawhney et al[75] (80%), Bhat et al[145](97.7%), Nigam et al[21] (82.1%) and Al-Mutairi et al[144] (93%). Thus the present study values are well in accordance with the above mentioned studies.

Family history

A positive family history of diabetes mellitus was obtained in 32 patients (32%), while 68 patients (68%) gave a negative family history.

Random blood sugar levels

Majority of the patients had random blood sugar levels in the range of 140-200mg/dl (49%), while 29 patients (29%) had blood sugar levels of >200mg/dl.

Hba1c levels

Among the 100 diabetic patients with cutaneous manifestations, 22 patients (22%) had moderate control of DM with HbA1c levels in the range of 7.1%-8%, while 63 patients (63%) had a poor control of DM with HbA1c levels >8%.

In a study conducted by Nigam et al[21], uncontrolled diabetes was observed in 52% cases. The incidence of cutaneous diseases in patients with uncontrolled diabetes mellitus was 70.2% while it was only 51% in patients with controlled diabetes.

Studies conducted by Bhat et al[145], Sawhney et al[75], Yosipovitch et al[146] also found majority of diabetic patients with skin lesions having uncontrolled diabetes.

Thus the present study is in accordance with the above mentioned studies.

Uncontrolled diabetes increases the risk of development of microangiopathy, related complications or sequelae[145] and predisposes skin for various infections [21]

A study conducted by Raghunatha et al[147] showed well controlled diabetes in majority of the patients.

Associated systemic illnesses

Of the 100 patients, 59 patients (59%) had associated systemic co-morbidity, such as hypertension in 46 patients (46%), Ischemic heart disease in 13 patients (13%) and dyslipidemia in 9 patients (9%).

According to Mahajan et al[22], 53.1% patients were hypertensive. Similar frequencies were reported by Bhat et al[145] (46.46%), Al-Mutairi et al[144](44%) and Nigam et al[21], wherein hypertension was the most common associated systemic disease.

Hypertension has been hypothesized to accelerate the process of microangiopathy in diabetics.[144]

Pattern of cutaneous manifestations

In the present study, among the various dermatological manifestations, infections were the most common dermatoses (62%), followed by dermatoses having a more common association with diabetes (58%), followed by non-specific cutaneous manifestations (41%), followed by neuropathic and ischemic diabetic skin disease (13%), due to microangiopathy (8%) , metabolic diseases (2%) and cutaneous reactions to therapy for diabetes (1%)

Similar findings were reported by other studies. (Mahajan et al[22], Rao et al[143], Bhat et al[145], Nigam et al[21], Al-Mutairi et al[144])

High incidence of infections was due to the following factors:

1. Hyperosmolality of the hyperglycemic serum which causes diminished chemotaxis.

2. There is impaired release of cytokines as a consequence of lack of insulin.

3. Impaired phagocytosis may be due to diminished leucocyte response caused by thickening of capillary valves.

4. Microangiopathy, atherosclerosis, microaneurysms, increased mast cells in the upper dermis and elevated glucose levels.[148]

Cutaneous infections

Infections were the most common dermatoses (62%), of which fungal infections were most prevalent (37%), followed by bacterial infections (21%) and viral infections (4%).

This is in accordance with other studies where fungal infections were more common, as observed by Mahajan et al[22] (54.68%), Bhat et al[145](34.34%) and Al-Mutairi et al[144] (68%).

Fungal agents formed largest group of cutaneous lesions and it may be because most of our patients belonged to lower socio economic group residing in slum areas where hot and humid conditions, overcrowding and decreased resistance of the body predisposes the individuals for such infections.

Infections are usually common during early diabetes. This may be explained on the basis of decrease in the host defence mechanism, and decreased phagocytic

activity, which is noticed immediately in uncontrolled diabetes and these changes do not require much longer time to develop unlike microangiopathy. [143]

The incidence of cutaneous infections was more in uncontrolled diabetics.

Bacterial infections

As shown in Table 12, Among the 21 patients studied with bacterial infections, 11 (11%) patients had furunculosis, 3 patients (3%) had folliculitis and cellulitis each, 2 patients (2%) had abscess. One case each (1%) of carbuncle and ecthyma gangrenosum was observed.

Similar findings were observed by Nigam et al[21], in which, out of 32 patients with bacterial infections, furunculosis was the commonest (15 cases), followed by folliculitis (8 cases), cellulitis (3 cases) and two cases each of carbuncle, bacterial impetigo and multiple abscesses.

Fungal infections

As shown in Table 13, of the 37 patients with fungal infections, majority had dermatophytoses of which 15 patients had tinea cruris, 13 had tinea corporis and 2 patients had tinea axillaris.

The various candidial infections observed were, candidial intertrigo (4 patients), candidial balanoposthitis (1 patient) and candidial vulvovaginitis in 1 patient. The patient with candidial balanoposthitis was diagnosed to have diabetes later after appropriate investigations.

There were 3 patients of onychomycosis and 1 patient of chronic paronychia. Many patients presented with more than one fungal infection.

Fungal infections were the commonest infections in diabetics as reported by Mahajan et al[22] (21 cases), Rao et al[143](59.42%) and Bhat et al[145](28.18%)

Mahajan et al[22] found a higher prevalence of dermatophytoses in their study, while Bhat et al[145] and found a higher prevalence of candidial infections.

Viral infections

As shown in Table 14, four patients of the 100 patients studied had viral infections, of which 2 (2%) had herpes zoster and 2 patients had (2%) verruca vulgaris.

In a study conducted by Mahajan et al[22], two cases of herpes zoster were reported. Similar frequencies were observed by Bhat et al[145] and Al-Mutairi et al.[144]

Dermatoses associated with microangiopathy

In the present study, 8 patients (8%) had dermatoses associated with microangiopathy, wherein 7 patients (7%) had diabetic dermopathy and 1 patient (1%) had diabetic bullae.

Most of the western studies report a high frequency of diabetic dermopathy (50%), as compared to 17.8% in Indian patients.

The 7% of patients with diabetic dermopathy observed in this study fall in the range of previous reports of 3.5-9.93% [144]

Nigam et al[21] reported 6 cases (3.5%) of diabetic dermopathy and 2 cases (1%) of diabetic bullae.

Similarly, Mahajan et al[22], in their study of 100 diabetics, found diabetic dermopathy in 6 patients and 2 cases of diabetic bullae.

While a comprehensive review on the subject considers diabetic dermopathy to be the most common manifestation, we did not observe it to be so common.

Skin manifestations due to diabetic microangiopathies are usually seen in chronic diabetes because the deposition of PAS - positive material within the lumina of the blood vessels occurs slowly in the disease process.

Neuropathic and ischemic diabetic skin disease

As mentioned in Table 16, of the 13 patients with neuropathic and ischemic diabetic skin disease, 5 patients had peripheral vascular disease, 4 patients had diabetic foot ulcers and 4 patients had fissure feet.

Bhat et al[145], in their study, observed 4 cases of diabetic foot ulcers.

According to Mahajan et al[22], Rao et al[143], Nigam et al[21], Al-Mutairi et al[144], diabetic foot ulcers were reported in frequencies of 8,1,6 and 2 cases respectively.

In the present study, 4 cases of diabetic foot ulcers were observed, which is well in accordance with the study by Bhat et al.[145]

Metabolic conditions affecting diabetic skin

In the present study, 2 patients were observed with metabolic conditions. Both the patients had xanthelasma palpebrerum (2%).

Rao et al[143] reported 2 cases of xanthelasma palpebrerum, whereas Bhat et al[145] observed xanthelasma palpebrerum in 4 cases.

Disorders of collagen

Our study did not report any diabetic patients with disorders of collagen.

Dermatoses more commonly associated with diabetes

As shown in Table 18, among the various dermatoses studied, generalized pruritus was the most common seen in 23 patients(23%), followed by acrochordons in 8 patients (8%), 7 patients had psoriasis (7%), 4 patients (4%) each had vitiligo and acanthosis nigricans.

Three patients (3%) each had progressive pigmented purpura and perforating folliculitis, 2 patients (2%) each had lichen planus and cherry angiomas and 1 patient (1%) each had macular amyloidosis and alopecia universalis.

The above mentioned dermatoses have been reported previously in studies conducted by Paron et al[23] and Al-Mutairi et al.[144]

A review by Jelinek et al questions the relationship between generalized itching and DM. It is believed that generalized itching, at least in some DM cases, cannot be readily explained by any other cause except by the underlying DM. [144]

Autonomic neuropathy or AGE of stratum corneum proteins has been attributed to the pathogenesis of xerosis and pruritus [147]

Acanthosis nigricans and acrochordons are manifestations of insulin resistance, which may be present before the expression of DM. Increased levels of insulin act on insulin like growth factor (IGF) receptors, resulting in development of acanthosis nigricans. Association between multiple acrochordons and DM has been reported. Acrochordon has been regarded as a sign of impaired glucose tolerance, DM and increased cardiovascular (atherogenic lipid profile) risk.

An association between psoriasis and increased cardiovascular risk and metabolic syndrome has been reported. [147]

In a study by Nigam et al[21],dermatoses associated with an increased incidence of DM, like vitiligo (4), lichen planus (2), acquired perforating dermatoses(3) were detected.

Certain dermatoses with underlying pathogenesis like vitiligo are known to occur in DM as a part of polyglandular autoimmune syndrome. Oral lichen planus has been suggested to occur with increased frequency in DM.[147] However, such an association was not noticed in several other studies, including the present one.

Cutaneous reactions to therapy for diabetes

In the present study, out of the 82 patients on treatment, we observed one patient (1%) who presented with acute urticaria secondary to insulin therapy.

The use of highly purified and recombinant insulin reduces the prevalence of insulin reactions. Lower prevalence of insulin reactions in the present study may be due to the use of human insulin.

Non-specific manifestations

As shown in Table 20, of the 41 patients who presented with non-specific manifestations, majority of them had eczema (15%) ,6 patients (6%) had seborrheic keratosis, 4 patients(4%) had DPN and 2 each (2%) had pemphigus, contact dermatitis, drug reactions and scabies.

Other non-specific manifestations observed were sebaceous cyst, polymorphous light eruption, keloid, parapsoriasis, seborrheic dermatitis, melasma, senile comedones and lichen simplex chronicus seen in 1 patient each (1%).

The occurrence of nonspecific cutaneous disorders also has pathogenetic, prognostic, and therapeutic importance in diabetic patients.The loss of cutaneous

barrier in non-specific disorders predisposes already susceptible diabetic patients to chronic and recurrent infections.These disorders could also increase the likelihood of exposure to contact allergens resulting in eczemas.[147]

Accelerated aging of the skin has been reported in patients with both types of DM, especially type I. However, in the present study, skin lesions such as seborrheic keratosis and senile comedones are mainly due to the chronologic and photoaging. [147]

Comparison of cutaneous manifestations in Controlled and Uncontrolled diabetes

Among the 100 diabetic patients with cutaneous manifestations, 37 patients had HbA1c <8% (good to moderate control) while 63 patients had a poor control of diabetes (HbA1c >8%).

In the present study, when a comparison of pattern of cutaneous manifestations in the controlled and uncontrolled groups was done, it was found that the cutaneous infections, dermatoses associated with microangiopathy, metabolic diseases and cutaneous reactions to diabetic therapy were more common in the uncontrolled group, which was meaningfully significant. The increased frequency of non-specific manifestations in the controlled group was statistically significant ($P<0.05$)

CONCLUSION

The present study was undertaken to know the spectrum of cutaneous manifestations in diabetes mellitus. Infections were the most common cutaneous manifestations in diabetics, followed by dermatoses most commonly associated with diabetes. Cutaneous manifestations are more common in patients who have overall poor glycemic control which in turn is reflected by high HbA1c value. Cutaneous manifestations can heighten the suspicion of a physician regarding the diagnosis of diabetes. This further helps to prevent systemic derangements by early institution of appropriate treatment. Proper skin care and long-term control of blood glucose levels may reduce the risk of some of the skin lesions in diabetic subjects.

Thus, dermatologists can play an important role in reducing dermatologic morbidity, improvement of quality of life, and management strategy of diabetic patients.

SUMMARY

The present study was undertaken to know the spectrum of cutaneous manifestations in diabetes mellitus. A total of 100 patients of diabetes mellitus with cutaneous manifestations were studied. The observations and results were tabulated and graphically represented; their significance was discussed after reviewing the available literature.

- Majority belonged to the 5^{th} decade (33%) and 4^{th} decade (27%) respectively.
- Males constituted 69% of the cases and male to female ratio was 2.2:1
- Out of the 100 diabetic patients, 40% of the patients had diabetes for a duration for 1-5 years and 26% patients for 6-10 years.
- Type 2 DM was most commonly observed (96%) as compared to Type 1 DM (4%)
- Out of the 100 patients, 32 patients had a positive family history of diabetes mellitus.
- Majority of the patients had RBS levels in the range of 140-200mg/dl (49%), while 29 patients (29%) had blood sugar levels of >200mg/dl.
- Among the 100 diabetic patients, 22 patients (22%) had moderate control of DM with HbA1c levels in the range of 7.1%-8%, while 63 patients (63%) had a poor control of DM with HbA1c levels >8%.
- Hypertension was the most commonly associated systemic illness (46%) followed by Ischemic heart disease (13%) and dyslipidemia (9%).
- Among the various cutaneous manifestations observed, cutaneous infections (62%) were the most commonly observed.

- Among the cutaneous infections, fungal infections (37%) were most frequently observed, followed by bacterial infections (21%) and viral infections (4%).
- Dermatophytosis was the most commonly observed fungal infections (30 cases) followed by candidial infections (6 cases).
- Furunculosis was the most commonly observed bacterial infections (11%), followed by folliculitis and cellulitis (3%).
- Among the viral infections, 2 cases each (2%) of herpes zoster and verruca vulgaris were observed.
- Dermatoses associated with microangiopathy were observed in 8 patients (8%), of which 7 (7%) had diabetic dermopathy and 1 patient (1%) had diabetic bullae.
- Among the 13 patients of neuropathic and ischemic diabetic skin disease, 5 patients (5%) had peripheral vascular disease, 4 patients each (4%) had diabetic foot ulcers and fissure feet.
- Dermatological manifestations due to metabolic condition were xanthelasma palpebrerum, seen in 2 patients (2%).
- Various dermatoses more commonly associated with diabetes were generalized pruritus (23%), acrochordons (8%), psoriasis(7%), vitiligo (4%), acanthosis nigricans. (4%), progressive pigmented purpura (3%), perforating folliculitis (3%), lichen planus (2%), cherry angiomas (2%), macular amyloidosis(1%) and alopecia universalis(1%).
- Among the 82 patients on antidiabetic therapy, 1 patient (1%) developed acute urticaria secondary to insulin therapy.

- Various non-specific manifestations like eczema (15%), seborrheic keratosis (6%),DPN (4%) and 2 cases each of pemphigus, contact dermatitis, drug reactions and scabies were observed.

- Cutaneous infections, dermatoses associated with microangiopathy, metabolic diseases and cutaneous reactions to diabetic therapy were more common in the uncontrolled diabetic patients. The increased frequency of non-specific manifestations in controlled diabetics was statistically significant.

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ANNEXURE-I: SCREENING FORM

Date of Examination: ☐☐ ☐☐ ☐☐☐☐

IP/OP No.: ☐☐☐☐☐☐☐☐☐☐

No: ☐☐☐☐☐

Name: ☐☐☐☐☐☐☐☐☐☐ ☐☐☐☐☐☐☐☐☐☐ ☐☐☐☐☐☐☐☐☐☐

(First Name) (Middle Name) (Last Name)

Age: ☐☐ Years

Gender: ☐ 1=Male; 2=Female

Address and Phone number:_____

_____

Occupation: ☐☐☐☐☐☐☐☐☐☐

Religion: ☐ 1=Hindu; 2=Muslim; 3=Christian; 4=Sikh; 5=Others (Specify)

Does the patient have Diabetes Mellitus? : ☐ 1=Yes; 2=No

Does the patient have cutaneous manifestations? : ☐ 1=Yes; 2=No

Is the patient eligible for the study? ☐ 1=Yes; 2=No

Has informed consent been taken? ☐ 1=Yes; 2=No

Final Result Information: ☐

1. Eligible ,Participating
2. Eligible ,Refused
3. Ineligible

Name of the Investigator:_____

Signature of the Investigator: _____

ANNEXURE – II: INFORMED CONSENT FORM

I.DO.NO. | | | |

A CROSS SECTIONAL STUDY OF CUTANEOUS MANIFESTATIONS IN 100 PATIENTS OF DIABETES MELLITUS

The study is conducted by Dr. _____ Post graduate student in M.D Dermatology under guidance of Dr. _____, Professor of Dermatology, J N Medical College, Belgaum.

Respected Sir/Madam, we invite you to participate in our study as, you are eligible for the same. During the study you will be asked some questions in detail regarding your present complaints.

Purpose of the study:

The purpose of this study is to know the various skin manifestations of Diabetes Mellitus. You are being asked to participate in this research because you have been diagnosed to have Diabetes Mellitus with skin manifestations. All patients attending the outpatient department, who are diagnosed to have this disease, will be requested to participate in this study during the period of one year.

Procedure and treatment:

Should you choose to participate, you will be asked to give a detailed history of your disease, undergo a physical examination, and consent to a few routine blood and urine investigations. In addition to this, you will agree to undertake HbA1c test and if required other relevant investigations.

Risks and benefits:

You may undergo some amount of discomfort during the process of investigations, which may include slight pain and bleeding. However all necessary steps and precautions will be taken to ensure your safety. The result of you taking part in this research would help health care providers towards a better understanding of this disease, and thus we will be able to provide improved patient care

Alternatives:

If you decide not to participate in this study, you will still be receiving the usual standard care for your disease.

Privacy and confidentiality:

Your privacy will be respected and all information collected about you during the course of this study will be kept confidential. Your identity will remain undisclosed.

Relations with the Institutional policy:

The J N Medical College will provide, within the limitations of the laws of the State of Karnataka, facilities and medical attention to patients who suffer injuries as a result of participating in this project. In the event if you suffer any physical injury as the result of your participation in this study, you may contact Dr. _____, Telephone No. _____ or Dr. _____, Telephone No. _____. In the event of an emergency, you should contact KLE'S Dr. Prabhakar Kore Hospital and MRC on Telephone No. 08312473777.

Financial incentives:

You shall not be receiving any payment or any financial incentives for participating in this study.

Authorization to publish results:

The results of this study may be published for scientific purpose or presented to a scientific group. Your identity, however, will be maintained confidential at all times.

Voluntary participation:

Your participation in this study is voluntary. Your decision whether or not to participate will neither affect the care of your current disease, nor your future relations with the doctor or the hospital. In case you need further information regarding your rights as a study participant, you may please contact Dr. V.D. Patil, principal and chairman of the ethical committee, J N Medical College, Belgaum on telephone No. 08312473777

Statement of Consent:

I.D.NO: | | | |

I Mr/Ms/Mrs

_____

volunteer and consent to participate in this study. I have read the consent document orit has been read to me in my vernacular language. I accept to participate in the study. All the information regarding this study is provided to me and I have understood the same. I have been given the opportunity to ask questions and obtain appropriate answers.

Participant's name:

Signature or left thumb print of participant:

Witness name:

Signature of witness:

Signature of the investigator:

Date:

If the participants are Minors (under 18), the parents sign the form, rather than the participants

ANNEXURE- III: PROFORMA

"A CROSS SECTIONAL STUDY OF CUTANEOUS MANIFESTATIONS IN 100 PATIENTS OF DIABETES MELLITUS."

Presenting complaints and duration:

History of present illness:

Site of lesion:

Face Web spaces

1. Present
2. Absent

☐

1. Present
2. Absent

☐

Oral Cavity

1. Present
2. Absent

☐

Trunk

1. Present
2. Absent

☐

Chest Crural Region

1. Present
2. Absent

☐

1. Present
2. Absent

☐

Back

1. Present
2. Absent

☐

External Genitalia

1. Present
2. Absent

☐

Upper limb

1. Present
2. Absent

☐

Palms

1. Present
2. Absent

☐

Lower limb

1. Present
2. Absent

☐

Soles

1. Present
2. Absent

☐

Onset:

1. Sudden
2. Gradual

Progression:

1. Progressive
2. Stationary

Initial Lesion:

1. Dryness
2. Redness
3. Wheals
4. Fluid filled lesion
5. Pus filled lesion
6. Oozing lesion
7. Change in skin color
8. Swelling
9. Ulcer
10. Scaly lesion

Any associated factors:

1. Itching
2. Pain
3. Burning
4. Discharge
5. Asympomatic

Duration of Diabetes:

1. <1 year
2. 1-5 years
3. 5-10 years
4. >10 years

Type of Diabetes:

1. Juvenile
2. Adult Onset

Mode of Treatment:

1. Oral Hypoglycemics
2. Insulin
3. Diet Control

Past History:

History of similar complaints:

1. Present
2. Absent

History of Hypertension:

1. Present
2. Absent

Family History:

1. Present
2. Absent

Any other Medical Disorders:

_____

_____

Personal History:

Diet: ☐
1. Veg
2. Mixed

Bowel /Bladder: ☐
1. Normal
2. Altered

Appetite: ☐
1. Good
2. Reduced

Smoking: ☐
1. Present
2. Absent

Sleep: ☐
1. Adequate
2. Disturbed

Alcohol intake: ☐
1. Present
2. Absent

General Physical Examination:

Built: ☐
1. Well
2. Moderate
3. Poor

Pallor: ☐
1. Present
2. Absent

Icterus: ☐
1. Present
2. Absent

Vitals:

Pulse: ☐☐☐ /min

BP:(mmHg) Systolic ☐☐☐
Diastolic ☐☐☐

Temperature: ☐☐☐ ^{0}F

Edema:

Weight: ☐☐☐ Kg

Lymph nodes:

Cyanosis: ☐
1. Present
2. Absent

Clubbing: ☐
1. Present
2. Absent

☐
1. Present
2. Absent

☐
1. Palpable
2. Not palpable

Mucocutaneous Examination:

Type of lesion:

Macule ☐
1. Present
2. Absent

Nodule ☐
1. Present
2. Absent

Papule ☐
1. Present
2. Absent

Ulcer ☐
1. Present
2. Absent

Vesicle ☐
1. Present
2. Absent

Patches ☐
1. Present
2. Absent

Pustule ☐
1. Present
2. Absent

Xerosis ☐
1. Present
2. Absent

Bullae ☐
1. Present
2. Absent

Atrophy ☐
1. Present
2. Absent

Plaque ☐
1. Present
2. Absent

Swelling ☐
1. Present
2. Absent

Erythema ☐
1. Present
2. Absent

Maceration ☐
1. Present
2. Absent

Site: Distribution: ☐
1. Face
2. Upper Limbs
3. Trunk
4. Lower Limbs

☐
1. Localised
2. Generalised

Mucosal Examination:

Genital lesion: ☐
1. Present
2. Absent

Oral lesion: ☐
1. Present
2. Absent

Systemic Examination:

Cardiovascular system: ☐
1. Normal
2. Abnormal

Respiratory system: ☐
1. Normal
2. Abnormal

Hair:
1.Normal
2.Abnormal

Nails:
1.Normal
2.Abnormal

Per-abdomen
1. Normal
2. Abnormal

Central Nervous System
1. Normal
2. Abnormal

Investigations:-

Blood:FBS: **RBS:**

Hb: TC: DC: ESR: **HBA1C:**

Urine Routine: Histopathological examination

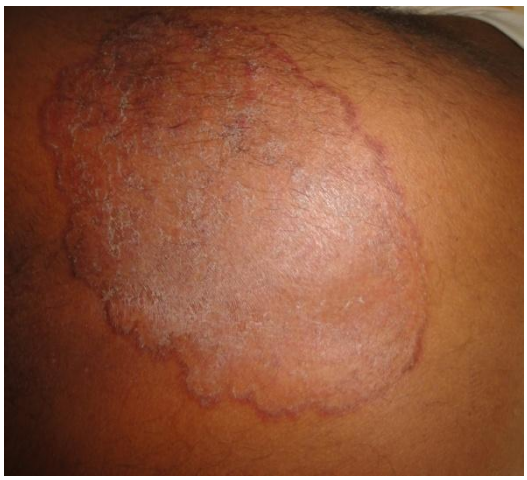
KOH Examination for fungus:
1. Positive
2. Negative

Culture for Bacteria: Others:

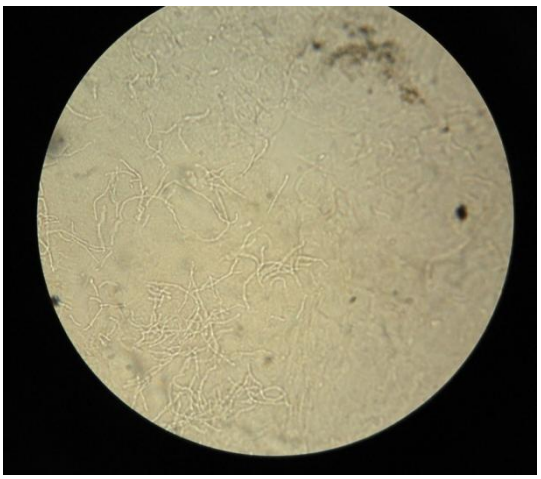
Diagnosis:-

Signature: **Signature of the guide:**

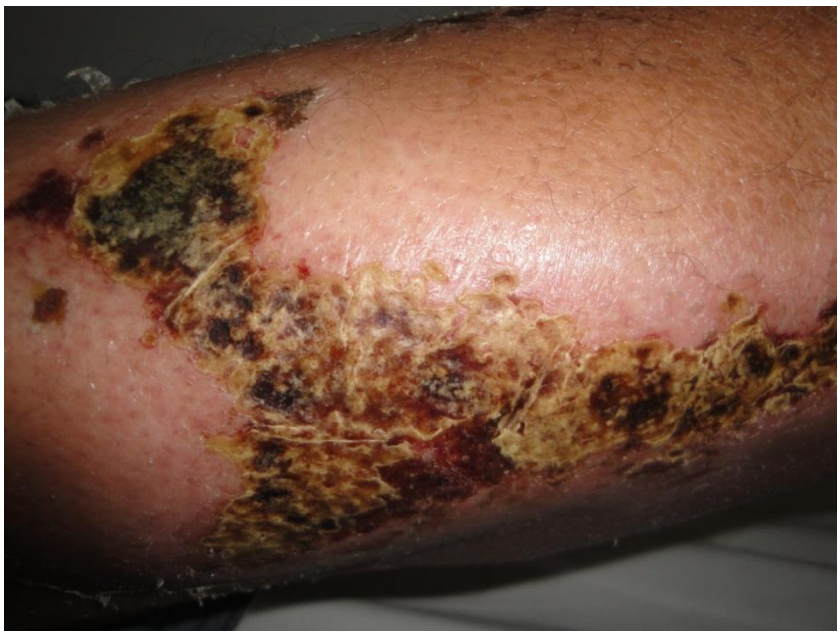
ANNEXURE – IV: PHOTOGRAPHS



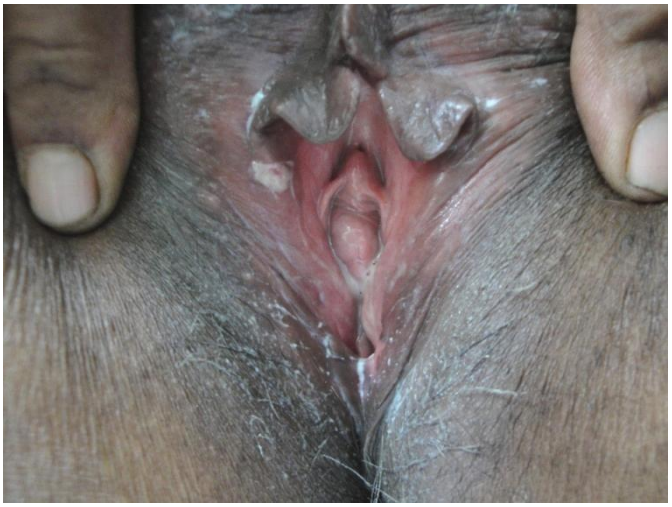
Photograph 1: Tinea corporis



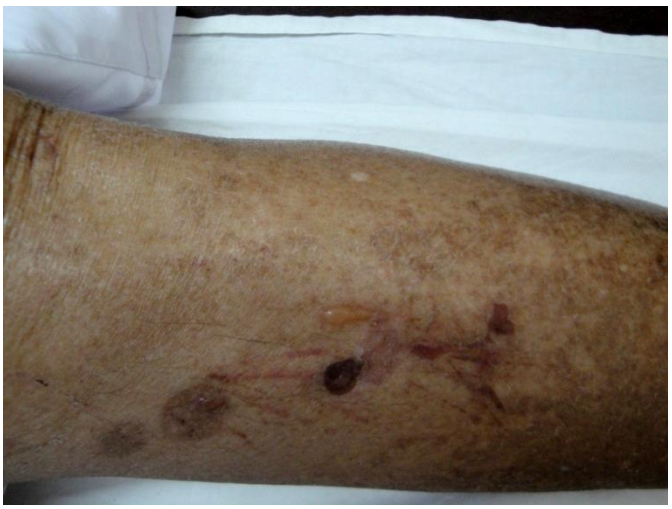
Photograph 2: KOH examination positive for fungal filaments



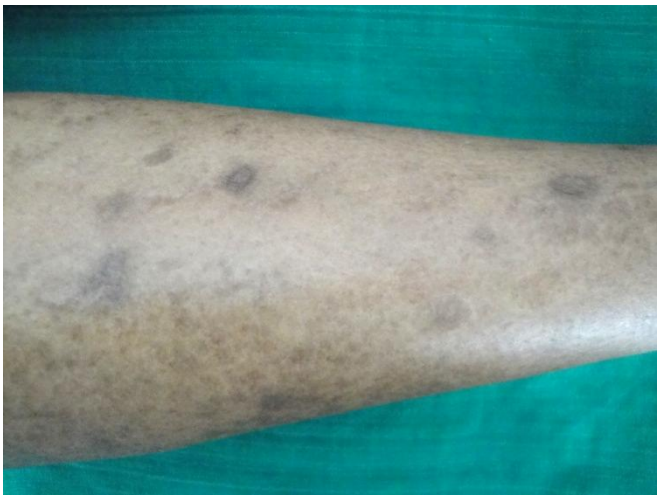
Photograph 3: Ecthyma gangrenosum



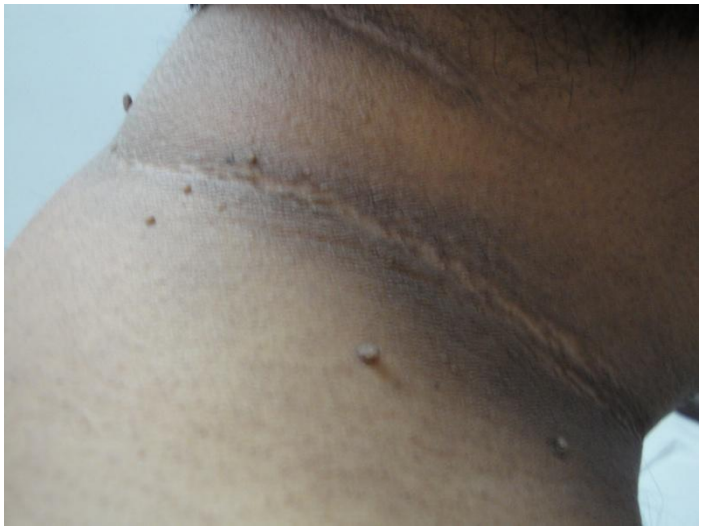
Photograph 4: Vulvovaginal candidiasis



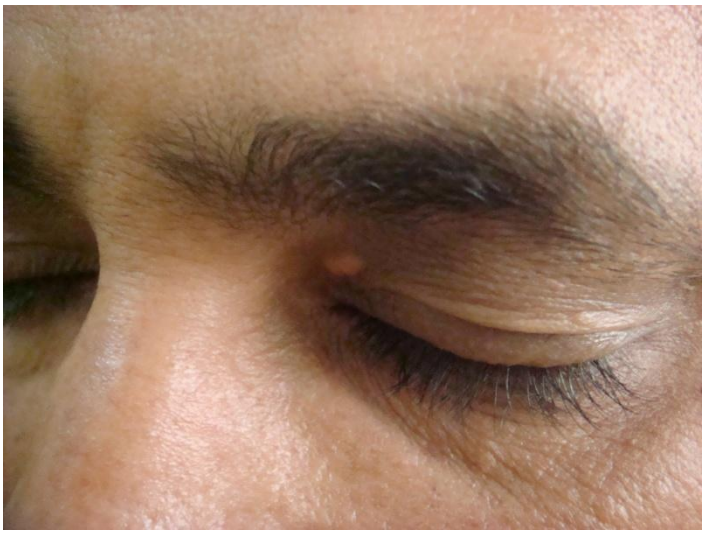
Photograph 5: Diabetic bullae



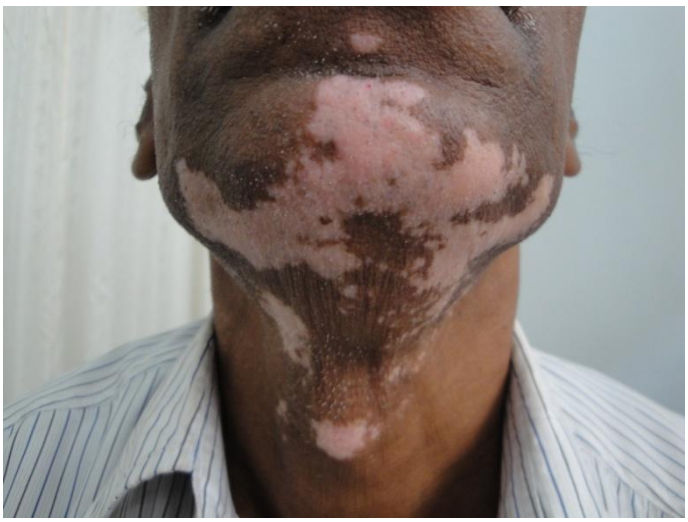
Photograph 6: Diabetic dermopathy



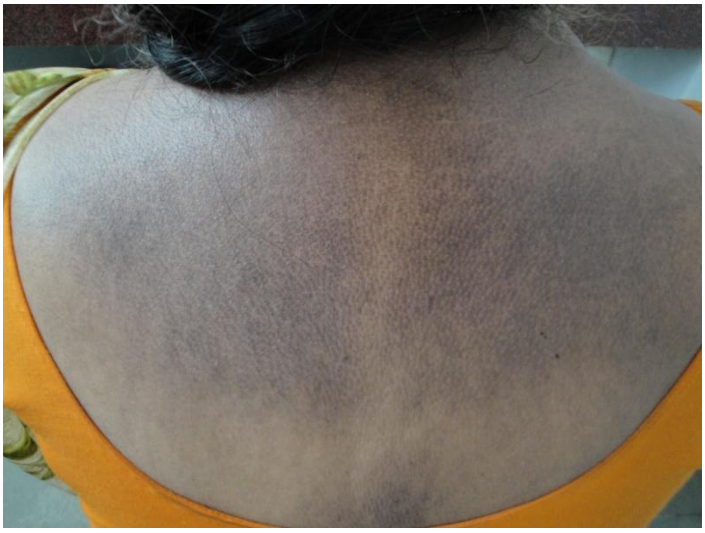
Photograph 7: Acanthosis nigricans with skin tags



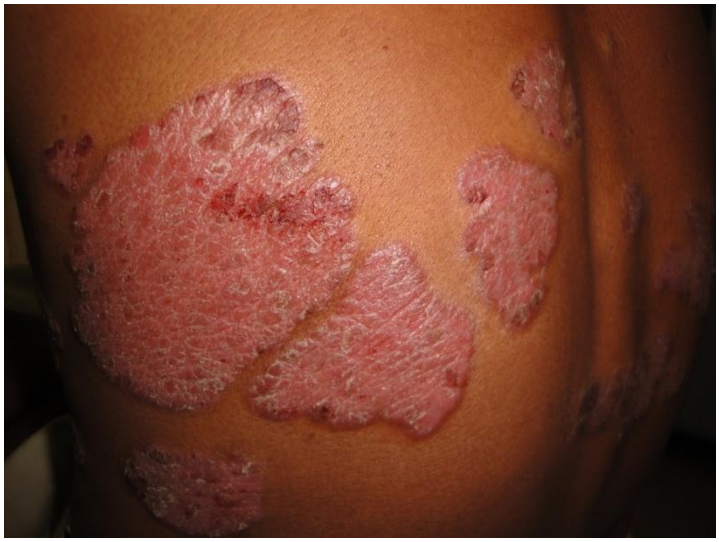
Photograph 8: Xanthelasma palpebrerum



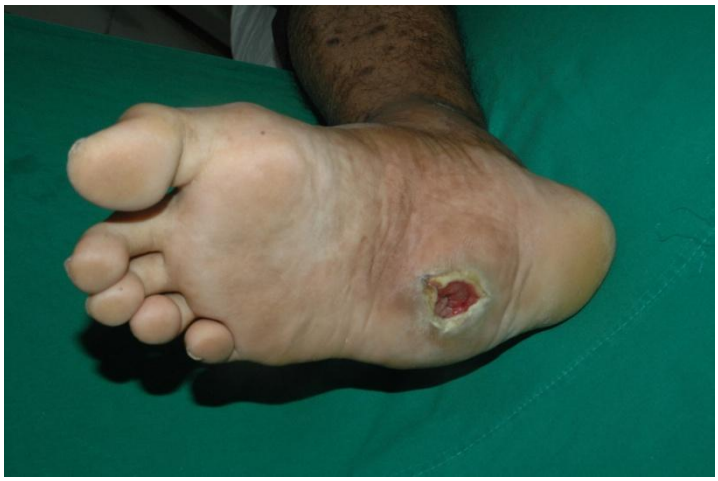
Photograph 9: Vitiligo vulgaris



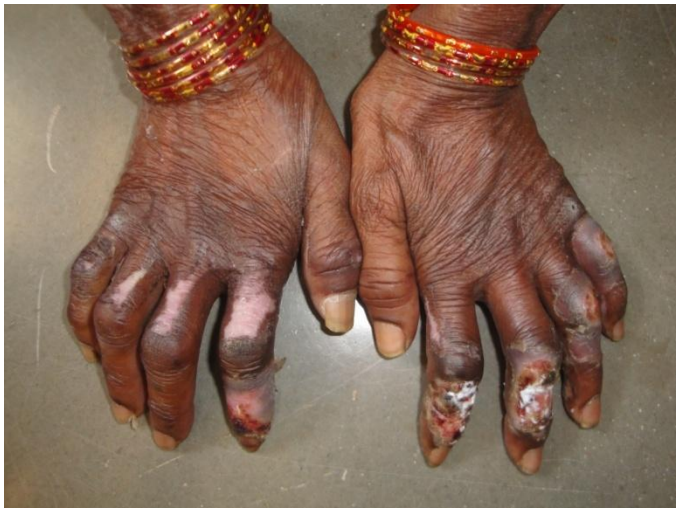
Photograph 10: Macular amyloidosis



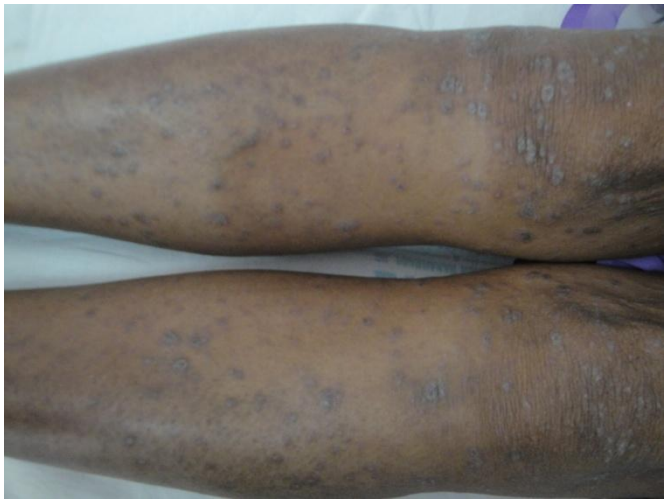
Photograph 11: Chronic plaque psoriasis



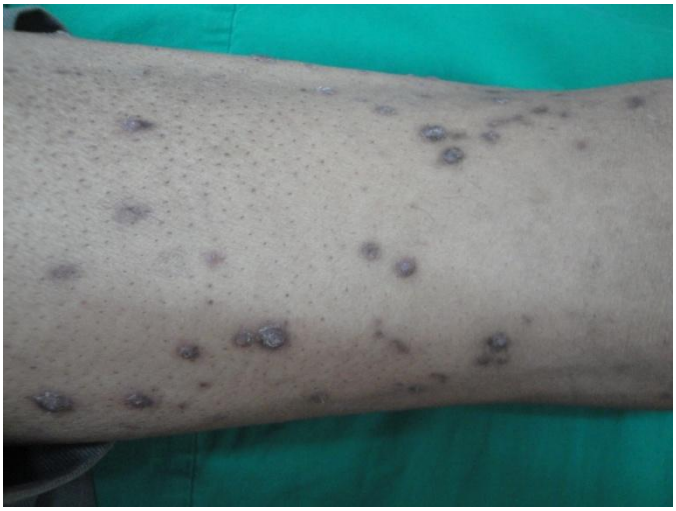
Photograph 12: Diabetic foot



Photograph 13: Arterial ulcers over the digits



Photograph 14: Lichen planus



Photograph 15: Perforating folliculitis

KEY TO MASTER CHART

HTN= Hypertension

IHD= Ischemic Heart Disease

CVD=Coronary Vascular Disease

UKB= Urine Ketone Bodies

HPF= High Power Field

Alb= Albumin

WBC= White Blood Cell

RBC= Red Blood Cell

NAD= No Abnormality Detected

DPN=Dermatosis Papulosa Nigra

AN=Acanthosis Nigricans

TVD=Triple vessel Disease

M=Male

F=Female

Occ= Occasional

Epi= Epithelial Cells

CRF= Chronic Renal Failure

ANNEXURE – V: MASTER CHART

Sl. No	IP/OP No	Age	Sex	Duration of DM	Type of DM	Duration of skin disease	Treat ment	Dermatological diagnosis	Associated Medical disorder	RBS	HbA1c	Gram stain	KOH	Culture	Urine	Biopsy
1	641776	50	M	7 years	Type II	3-4 days	Yes	Pruritus sec to Xerosis with Tinea cruris	Nil	107mg/dl	14.50%	-	+ve	-	4-6WBC/HPF, Alb+	-
2	345235	58	M	8 months	Type II	1 year	Yes	Psoriasis with DPN with Sebaceous cyst	Hypertriglycer idemia	130mg/dl	11.40%	-	-	-	UKB -ve, sugar ++++,calcium oxalate crystals +	-
3	696094	44	F	3 years	Type II	2 months	Yes	Pruritus sec to xerosis	HTN, Gastritis	198mg/dl	8%	-	-	-	NAD	-
4	1100655	46	F	6 months	Type II	2 months	Yes	Verruca vulgaris with DPN with abscess	Nil	169 mg/dl	6.30%	-	-	-	NAD	-
5	345259	72	F	8 years	Type II	6 months	Yes	Pemphigus vegetans	HTN	130mg/dl	6.80%	-	-	staph aureus isolated	sheets of WBCs, 8-10 RBCs/HPF	Done
6	781918	72	F	3 years	Type II	20 days	No	Pruritus sec to Xerosis	HTN	181mg/dl	7.20%	-	-	-	NAD	-
7	898532	55	M	2 years	Type II	1 month	Yes	Candidial balanophosthitis with Xerosis	Nil	260 mg/dl	9.20%	done	+ ve	-	sugar +++	-
8	1214423	56	M	8 years	Type II	3 years	No	Asteototic eczema with gangrene with tinea cruris	HTN	186mg/dl	9.10%	-	-	-	Sugar-yellow ppt,albumin-absent	-
9	1244744	82	M	40 years	Type II	2 days	Yes	Diabetic bulla with xerosis with acrochordons with Schamberg's disease with gangrene	Nil	107 mg/dl	8.60%	-	-	-	Albumin + ,5-6 WBC/HPF	Done
10	349244	69	M	7 years	Type II	1 year	Yes	Asteototic eczema	Osteoarthritis	132mg/dl	7.50%	-	-	-	NAD	-
11	348435	77	M	18 years	Type II	6 months	Yes	Pruritus sec to Xerosis with folliculitis	IHD with CVD	124mg/dl	8.30%	-	-	-	Albumin-traces,WBC-3-4/HPF	-
12	349356	52	M	10 years	Type II	1 month	Yes	Tinea corporis	Nil	300mg/dl	10.60%	-	+ve	-	Sugar-yellow ppt,WBCs-plenty, RBCs-2-	-

															3/HPF,Albumin +	
13	583184	43	M	8 years	Type II	3 days	No	Acrochordons with AN with candidial intertrigo	Hypertriglyceridemia	232mg/dl	9.20%	done	+ve	-	NAD	-
14	1261880	70	M	15 years	Type II	5 years	Yes	Recurrent furunculosis with seborrheic keratosis with fissure feet with acrochordons	Nil	144mg/dl	7.30%	done	-	-	NAD	-
15	1262218	61	M	15 years	Type II	6 months	Yes	Pruritus sec to xerosis with Pityriasis versicolor	HTN	280mg/dl	8.60%	-	+ve	=	NAD	-
16	350221	20	F	12 years	Type I	3 months	Yes	Scabies with Asteototic eczema	Nil	144mg/dl	10.40%	-	-	-	UKB +	-
17	1248056	60	M	3 years	Type II	8 months	No	Vitiligo vulgaris with folliculitis	Hypothyroidism	201mg/dl	7.80%	-	-	-	WBC-3-5/HPF,Sugar-orange ppt, Albumin-traces	-
18	1249227	55	M	20 years	Type II	5 years	Yes	Chronic eczema with Acrochordons	IHD, HTN	392mg/dl	14.50%	-	-	-	Sugar-orange, Albumin +, WBC-6-8/hpf	-
19	591679	33	F	4 years	Type II	2 months	No	Allergic contact dermatitis with macular amyloidosis with Tinea cruris	Nil	128mg/dl	7%	-	+ve	-	NAD	-
20	1087376	56	F	6 years	Type II	4 years	Yes	Vitiligo vulgaris	Bronchial asthma,HTN	230mg/dl	8.80%	-	-	-	Albumin-traces,Epi cells +, WBC-2-3/hpf	-
21	353489	60	M	10 years	Type II	1 year	Yes	Pruritus sec to xerosis with AN	Chronic myeloproliferative disorder,HTN	159mg/dl	8%	-	-	-	NAD	-

22	352342	64	F	12 years	Type II	2 weeks	Yes	Diabetic dermopathy	HTN	170mg/dl	8.20%	-	-	-	NAD	done
23	351544	53	F	15 years	Type II	15 days	Yes	Tinea corporis with Abscess	HTN	134mg/dl	9%	-	+ve	-	Albumin-traces, WBC-6-8/hpf, epi cells++	-
24	604193	50	M	1.5 years	Type II	3 years	Yes	Tinea cruris with Acrochordons with Candidial intertrigo	Nil	158mg/dl	7.80%	done	+ve	-	NAD	-
25	593373	70	M	12 years	Type II	7 years	Yes	Chronic eczema with fissure feet	Nil	129mg/dl	6.60%	-	-	-	NAD	-
26	583486	43	F	13 years	Type II	15 days	Yes	Polymorphous light eruption	HTN	209mg/dl	8.90%	-	-	-	NAD	-
27	729670	46	M	12 years	Tyoe II	I month	Yes	Subacute eczema with id reaction with candidial intertrigo	Nil	126mg/dl	6.90%	done	+ve	-	NAD	-
28	356685	48	M	8 days	Type II	4 years	Yes	Tinea corporis with tinea cruris	Nil	198mg/dl	9.70%	-	+ve	-	Albumin-traces	-
29	1285989	64	M	16 years	Type II	6 months	Yes	Asteototic eczema with follicutitis with keloid with cherry angiomas	HTN	172mg/dl	8%	-	-	-	WBC-5-6 /hpf	-
30	602627	63	F	18 years	Type II	15 days	Yes	Folliculitis with DPN	HTN	178mg/dl	8.40%	-	-	-	NAD	-
31	593939	58	M	12 years	Type II	8 years	Yes	Chronic plaque psoriasis	Nil	318mg/dl	7.70%	-	-	-	Sugar-orange, WBC-2-3/hpf	done
32	353082	60	M	12 years	Type II	2 months	Yes	Parapsoriasis	HTN	148mg/dl	12.70%	-	-	-	NAD	done
33	1310317	66	M	14 years	Type II	2 days	Yes	Diabetic dermopathy with folliculitis	HTN,IHD	160mg/dl	7.30%	done	-	-	NAD	-
34	645395	82	M	30 years	Type II	3 years	Yes	Chronic paronychia	HTN	170mg/sl	8.40%	-	-	-	Albumin-traces	-
35	1314630	50	F	7 years	Type II	20 days	Yes	Scabies with Seborrheic keratosis with xerosis with tinea axillaris	HTN	146mg/dl	12.20%	-	-	-	NAD	-
36	1497372	46	M	4 years	Type II	6 months	No	Asteototic eczema	TVD	403mg/dl	12.10%	-	-	-	Sugar-brick red	-
37	359622	45	M	4 years	Type II	2 years	Yes	Pityriasis versicolor	HTN,IHD	103mg/dl	9.10%	-	+ ve	-	Sugar-orange, WBC-occ	-

38	358072	56	M	7 years	Type II	6 months	Yes	Chronic eczema with xerosis	HTN,Hypothyroidism	253mg/dl	8.30%	-	-	-	NAD	-
39	356833	49	M	7 months	Type II	1 month	Yes	Erythroderma sec to psoriasis	HTN	335mg/dl	12.10%	-	-	-	Albumin -traces, sugar-orange, WBC-2-3/hpf	done
40	355373	56	M	2 years	Type II	2 months	Yes	Erythroderma sec to psoriasis	Nil	186mg/dl	10.30%	-	-	-	Albumin-traces	done
41	1336138	75	M	8 years	Type II	1 year	Yes	Diabetic dermopathy	HTN	120mg/dl	6.70%	-	-	-	NAD	done
42	1345441	25	M	6 years	Type I	5 years	Yes	Alopecia universalis	Nil	414mg/dl	7.30%	-	-	-	WBC-5-6/hpf	-
43	602785	45	F	6 years	Type II	20 days	No	Herpes zoster	Nil	180mg/dl	9.70%	-	-	-	NAD	-
44	665677	65	M	4 years	Type II	1 week	Yes	Pruritus sec to xerosis	HTN, Epilepsy,Chronic kidney disease	176mg/dl	10.80%	-	-	-	Albumin- ++++, WBC-plenty/hpf, RBC-sheets	-
45	366592	45	F	8 months	Type II	1 month	Yes	Lichen planus	Nil	146mg/dl	8.70%	-	-	-	Albumin-traces, WBC-1-2/hpf	done
46	373881	58	M	3 years	Type II	2 months	Yes	Diabetic foot	Nil	177mg/dl	8.30%	-	-	-	UKB,Sugar-Absent	-
47	366067	60	M	8 years	Type II	6 months	Yes	Extensive Tinea corporis with Tinea cruris with AN	OP poisoning	198mg/dl	8%	-	+ve	-	Albumin-traces,WBC-6-8/hpf, UKB+	-
48	367229	48	M	4 years	Type II	I month	No	Recurrent furunculosis with Seborrheic dermatitis	Pancreatitis	253mg/dl	12.30%	done	-	-	NAD	-
49	366835	83	M	9 years	Type II	3 months	Yes	Diabetic foot with xerosis with senile purpura	HTN	175mg/dl	6.00%	-	-	-	Albumin-traces, WBC-10-15/hpf, RBC-4-5/hpf	-
50	1335390	49	M	7 years	Type II	2 years	Yes	Diabetic dermopathy with onychomycosis	Hypertriglyceridemia	246mg/dl	9.90%	-	-	-	Albumin-traces	done
51	371723	63	M	3 years	Type II	1 year	Yes	Pityriasis versicolor	CAD, TVD, HTN,Hypothyroidism	175mg/dl	7.70%	-	+ve	-	Sugar-brick red, Alb,UKB-absent	-
52	1288839	40	F	1 month	Type II	6 months	Yes	Pemphigus vulgaris	Nil	144mg/dl	6.00%	-	-	-	Albumin-traces, WBC-3-4/hpf	done

53	358324	65	M	6 years	Type II	2 years	Yes	Pruritus sec to xerosis with tinea corporis with tinea cruris	HTN,IHD	156mg/dl	7.80%	-	-	-	Sugar-green,Albumin-ab	-
54	370557	68	M	10 years	Type II	10 years	No	Seborrheic keratoses with Senile spots with DPN with Cherry angiomas	IHD-AWMI	152mg/dl	6.90%	-	-	-	Sugar-orange, WBC-2-3/hpf	-
55	360159	60	F	6 years	Type II	2 months	No	Tinea axillaris with Intertrigo	HTN	148 mg/dl	6.80%	-	+ve	-	Albumin+, WBC- 10-15/hpf	-
56	342357	63	M	12 years	Type II	20 days		Diabetic foot	Nil	154mg/dl	6.40%	-	-	-	NAD	-
57	1156095	60	M	3years	Type II	6months	No	Xanthelesma	HTN	108mg/dl	8.20%	-	-	-	Sugar-brick red	-
58	380158	50	F	15 years	Type II	1 year	Yes	Diabetic dermopathy with Malar melasma with Recurrent furunculosis	Mixed dyslipidemia, Mild NPDR	182mg/dl	10.30%	-	-	-	Sugar-green, Albumin-traces	done
59	383042	38	M	7years	Type II	6 months	Yes	Tinea cruris with onychomycosis	Nil	145mg/dl	8.60%	-	+ve	-	Albumin-traces	-
60	1399508	43	M	8months	Type II	4 years	Yes	Xanthelesma with Acrochordons	HTN	180mg/dl	10%	-	-	-	Sugar-green ppt	-
61	1177853	70	M	12 years	Type II	1 year	Yes	Extensive Tinea corporis with Tinea cruris	HTN	164mg/dl	6.10%	-	+ve	-	NAD	-
62	381649	56	F	5 years	Type II	5 days	Yes	Furunculosis	IHD	326mg/dl	9.50%	done	-	-	NAD	-
63	377521	55	F	10years	Type II	8 days	Yes	Erythema multiforme sec to NSAIDs	Nil	125mg/dl	8.10%	-	-	-	Epithelial cells-4-5/hpf	-
64	388386	64	F	4 years	Type II	6months	No	Intertrigo with Seborrheic keratoses	HTN, CRF	133mg/dl	7.20%	-	+ve	-	WBC-4-5/hpf	-
65	581333	68	M	14 years	Type II	3 years	Yes	Pruritus sec to xerosis with tinea corporis	Nil	161mg/dl	7%	-	-	-	NAD	-
66	980712	60	M	14 years	Type II	4days	Yes	Acute eczema with id reaction with cellulitis	Nil	178mg/dl	9%	-	-	-	Sugar-green ppt	-
67	1426911	55	M	4 years	Type II	2 years	No	Tinea cruris with herpes zoster	HTN,CAD	180mg/dl	8.10%	-	+ve	-	NAD	-

68	1430055	56	M	8 years	Type II	6 days	Yes	Drug rash sec to Insulin with Skin tags	Nil	172mg/dl	8.60%	-	-	-	NAD	-
69	391357	46	F	5 years	Type II	1 month	Yes	Lichen planus	HTN	164mg/dl	7.40%	-	-	-	Sugar-yellow, Albumin-traces, WBC-3-5/hpf	done
70	394548	42	M	12 years	Type II	15 days	Yes	Ecthyma gangrenosum with tinea cruris	Nil	184mg/dl	9.80%	-	-	Strep pyogenes isolated	Sugar-orange, Albumin-traces	-
71	772819	67	M	15 years	Type II	10 years	Yes	Chronic eczema with xerosis	HTN	124mg/dl	6.70%	-	-	-	NAD	-
72	594917	63	F	8years	Type II	6 months	Yes	Asteototic eczema	HTN,Dyslipidemia, Fatty liver	195mg/dl	6.40%	-	-	-	NAD	-
73	621306	42	F	7years	Type II	2 years	Yes	Cumulative Irritant contact dermatitis with onychomycosis	Nil	135mg/dl	8.00%	-	-ve	-	Albumin-traces, WBC-5-6/hpf	-
74	1243571	57	M	14 years	Type II	2 years	Yes	Mucosal vitiligo	Nil	167mg/dl	7.50%	-	-	-	NAD	-
75	1433248	53	M	10 years	Type II	13 years	Yes	Unstable vitiligo vulgaris	HTN	135mg/dl	8.60%	-	-	-	Sugar-orange	-
76	390580	73	M	10 years	Type II	10 years	Yes	Gangrene with xerosis with senile comedones with seborrheic keratoses	HTN	228mg/dl	9.40%	-	-	-	Albumin-traces, WBC-3-4/hpf	-
77	1412939	53	M	12 years	Type II	1 month	Yes	Pruritus sec to xerosis with Furunculosis	HTN, Acute Renal Failure	98mg/dl	10.60%	-	-	-	WBC-4-5/hpf	-
78	1434986	48	M	6 years	Type II	1 year	No	Chronic eczema with LSC with Tinea cruris with furunculosis	HTN	142 mg/dl	7.60%	-	+ve	-	Albumin-traces, WBC-3-4/hpf	-
79	1430297	78	F	15 years	Type II	15 days	Yes	Tine corporis with Tinea cruris with resolving furunculosis	HTN, Hypercholesterolemia	167mg/dl	8.00%	-	+ve	-	Sugar- orange, Albumin-traces	-
80	1431741	55	F	2 years	Type II	2 months	No	PPK sec to eczema with Cellulitis	Nil	132mg/dl	8.60%	-	-	-	Sugar-brick red, Albumin-traces	-
81	392476	60	F	16 years	Type II	6 years	Yes	Progressive pigmented purpura	HTN	364mg/dl	10.10%	-	-	-	Albumin++, WBC-plenty, EC-4-5/hpf	-

82	392701	55	M	8 years	Type II	6 months	Yes	Tinea corporis with tinea cruris	Fatty liver, CRF	537mg/dl	9.40%	-	+ve	-	Albumin+, WBC-20-25/hpf, RBC-1-2/hpf	-
83	390713	61	M	6 years	Type II	2 years	No	Pruritus sec to xerosis with Scalp psoriasis	HTN, IHD	174mg/dl	7.90%	-	-	-	NAD	-
84	1504314	70	M	3 years	Type II	1.5 months	Yes	Subacute eczema with sec infection with tinea corporis	Nil	112mg/dl	7.80%	-	-	-	NAD	-
85	1453739	45	F	8 months	Type II	4 months	Yes	Tinea corporis with Acrochordons with filliform warts with seborrheic keratoses	Nil	146mg/dl	8.90%	-	+ve	-	Albumin-traces	-
86	396368	65	M	7 years	Type II	2 years	Yes	Pruritus sec to xerosis	HTN, IHD-AWMI	224mg/dl	8.30%	-	-	-	Sugar-green, Albumin++, WBC-7-8/hpf	-
87	381316	57	F	12 years	Type II	2 years	No	Diabetic dermopathy with xerosis	HTN, Dyslipidemia	178mg/dl	10.60%	-	-	-	WBC-plenty/hpf, Albumin+	-
88	1333359	55	M	6months	Type II	1 week	Yes	Generalised pustular psoriasis	Nil	292mg/dl	9.40%	done	-	NOGC	WBC-6-8/hpf, Albumin+	done
89	383704	13	M	8months	Type I	2 days	Yes	Acute urticaria with xerosis	Nil	324mg/dl	15.40%	-	-	-	UKB +	-
90	594435	56	M	4 years	Type II	2 months	Yes	Tinea corporis	HTN, Hypertriglyceridemia	137mg/dl	9.70%	-	+ve	-	Sugar-orange ppt, WBC-2-3/hpf	-
91	1198764	32	F	20 years	Type I	2 months	Yes	Livedo reticularis with Kyrle's disease with xerosis	End stage Renal disease	239mg/dl	9.30%	-	-	-	Albumin- +++, WBC-8-10/hpf, RBC-3-4/hpf	-
92	404232	40	M	6 months	Type II	2 years	No	Chronic plaque psoriasis with AN	Nil	224mg/dl	11.20%	-	-	-	Albumin-+, WBC-6-8/hpf, EC-2-3/hpf	done
93	417063	66	M	12 years	Type II	1 month	Yes	Extensive dermatophytosis with carbuncle	Nil	170mg/dl	11.50%	-	+ve	MRSA isolated	Albumin-traces, WBC-8-20/hpf	-
94	415805	50	M	1 year	Type II	6 months	Yes	Xerosis with onychomycosis with furunculosis	HTN	251mg/dl	13%	-	-	-	Albumin-traces, sugar-orange	-

95	416490	48	M	8 years	Type II	3 months	Yes	Diabetic dermopathy with Diabetic foot with fissure feet	Hypertriglyceridemia	248mg/dl	8.30%	-	-	-	Albumin-+	-
96	408308	48	M	25 years	Type II	1 year	Yes	Cellulitis with fissure feet	Nil	483mg/dl	12.20%	-	-	-	Sugar-green	-
97	413145	60	M	25 years	Type II	2 years	Yes	Perforating folliculitis	HTN,IHD, TVD	214mg/dl	8.30%	-	-	-	NAD	-
98	418185	35	M	6 years	Type II	I month	Yes	Kyrle's disease	Nil	198mg/dl	9.10%	-	-	-	WBC-6-8/hpf	done
99	403888	50	F	4 years	Type II	1.5 months	Yes	Digital ulcers with dry gangrene	Nil	345mg.dl	10.40%	-	-	-	NAD	-
100	426088	60	F	3 years	Type II	2 months	Yes	Vulvovaginal candidiasis with Tinea cruris	Nil	210mg/dl	9	done	+ve	-	WBC-8-10/hpf	-