

**RUNNING PHARMACY EDUCATION SERIES:  
DIABETES AND ITS COMPLICATIONS –  
A REVIEW**

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## **Introduction and History**

Diabetes is an age old disease, the mention of which is made since long time in the history of mankind and the knowledge in the field is enormous and done since long time back. Diabetes is mentioned in Ebers Papyrus, an Egyptian compilation of 150 BC. Its chief symptom, of passing excess of urine is mentioned in Syshrus in 500 BC. The name diabetes was introduced by Roman Physician, Areatus, in 1<sup>st</sup> century AD. Benedict discovered test for glucose in urine and blood. In Ayurveda (Charak Samhita 600BC and Sushrut Samhita 400BC), there is discussion on Prameh and Madhume. Symptoms like lack of energy and tending to sleep, dryness of throat, sweet taste in mouth, burning sensation in hands and feet and swarming of ants on urine are discussed there. Complains like boils, carbuncles and gangrene are also mentioned. Instructions like sugar, fats and oil restrictions and need for exercise too are given in them (1).

Although diabetes has been recognized since antiquity, and treatments of various efficacy have been known in various regions since the Middle Ages, and in legend for much longer, pathogenesis of diabetes has only been understood experimentally since about 1900 (2). The discovery of a role for the pancreas in diabetes is generally ascribed to Joseph von Mering and Oskar Minkowski, who in 1889 found that dogs whose pancreas was removed developed all the signs and symptoms of diabetes and died shortly afterwards (3). In 1910, Sir Edward Albert Sharpey-Schafer suggested that people with diabetes were deficient in a single chemical that was normally produced by the pancreas—he proposed calling this substance insulin, from the Latin *insula*, meaning island, in reference to the insulin-producing islets of Langerhans in the pancreas (2).

The endocrine role of the pancreas in metabolism, and indeed the existence of insulin, was not further clarified until 1921, when Sir Frederick Grant Banting and Charles Herbert Best repeated the work of Von Mering and Minkowski, and went further to demonstrate they could reverse induced diabetes in dogs by giving them an extract from the pancreatic islets of Langerhans of healthy dogs (4). Banting, Best, and colleagues (especially the chemist Collip) went on to purify the hormone insulin from bovine pancreases at the University of Toronto. This led to the availability of an effective treatment insulin injections and the first patient was treated in 1922. For this, Banting and laboratory director MacLeod received the Nobel Prize in Physiology or Medicine in 1923; both shared their Prize money with others in the team who were not recognized, in particular Best and Collip. Banting and Best made the patent available without charge and did not attempt to control commercial production. Insulin production and therapy rapidly spread around the world, largely as a result of this decision.

The distinction between what is now known as type 1 diabetes and type 2 diabetes was first clearly made by Sir Harold Percival (Harry) Himsworth, and published in January 1936 (5). Despite the availability of treatment, diabetes has remained a major cause of death. For instance, statistics reveal that the cause-specific mortality rate during 1927 amounted to about 47.7 per 100,000 populations in Malta (6). Other landmark discoveries include: identification of the first

of the sulfonylureas in 1942 the determination of the amino acid order of insulin (by Sir Frederick Sanger, for which he received a Nobel Prize) the radioimmunoassay for insulin, as discovered by Rosalyn Yalow and Solomon Berson (gaining Yalow the 1977 Nobel Prize in Physiology or Medicine) (6) the three-dimensional structure of insulin Dr Gerald Reaven's identification of the constellation of symptoms now called metabolic syndrome in 1988 Demonstration that intensive glycemic control in type 1 diabetes reduces chronic side effects more as glucose levels approach 'normal' in a large longitudinal study, (7) and also in type 2 diabetics in other large studies identification of the first thiazolidinedione as an effective insulin sensitizer during the 1990s

### **What is Diabetes ?**

Diabetes is a chronic disease that occurs when the pancreas does not produce enough insulin, or alternatively, when the body cannot effectively use the insulin it produces. Insulin is a naturally occurring hormone in the blood that is necessary for provide our cells with energy to function. When glucose cannot enter our cells, it builds up in the blood (Hyperglycaemia) or raised blood sugar, is a common effect of uncontrolled diabetes and over time leads to serious damage of organs including the eyes and kidneys, or damage of blood vessels and nerves. Diabetes can lead to serious complications and premature death, but people with diabetes can take steps to control the disease and lower the risk of complications.

Patients with type I diabetes mellitus (DM) also known as insulin-dependent DM (IDDM) or Juvenile-onset diabetes, may develop diabetic ketoacidosis (DKA), Patient with type II also DM also known as non-insulin dependent DM (NIDDM) may develop non-ketonic hyperglycemic-hyperosmolar coma (NKHHC). People with Type 1 diabetes need insulin injection and close monitoring to control their blood sugar levels (8).

### **Epidemiology of Diabetes**

India leads the world with largest number of diabetic subject earning the dubious distinction of being termed the “diabetes capital of the world”. The most disturbing trend is the shift in the age of onset of diabetes to a younger age in the recent years. This could have long lasting adverse effect on nation's health and economy. As per WHO, India will be the nation with higher number of diabetics in the world by 2030 followed by China and then USA. This is an alarming sound as far as the health system of India is concerned (Table1). All the corners of health system viz: Doctors, Pharmacists, Nurses, Government, NGOs etc. have to realize this fact and plan accordingly to tackle this situation (9).

Assuming that age-specific prevalence remains constant, the number of people with diabetes in the world is expected to approximately double between 2000 and 2030, based solely upon demographic changes. The greater relative increase will occur in the Middle Eastern Crescent, Sub-Saharan Africa, and India, while the greatest absolute increase in the number of

people with diabetes will be in India. The most striking demographic change in global terms will be the increase in the proportion of the population > 65 years of age.

**Table 1: India's Status at 2030 as per WHO**

Ranking	Country	People with Diabetes (Millions)	
		2000	2030
1	India	31.7	79.4
2	China	20.8	42.3
3	USA	17.7	30.3

In developing countries, the majority of people with diabetes are in 45 to 64 year range, similar to the finding reported previously. In contrast, the majority of people with diabetes in developed countries are > 64 years of age. 2030, it is estimated that the number of people with diabetes > 64 years of age will be > 682 million in developing countries and > 48 million in developed countries. India being one of the fastest developing country, and youth being force for it, which will be hampered at the most is not a good sign. Proper patient education and general awareness about the disease can help in reducing the extent of this damage (10).

### Classification of Diabetes Mellitus

Based on etiology diabetes mellitus is classified as follow

- I Type 1 diabetes** ( $\beta$ -cell destruction, usually leading to absolute insulin deficiency)
  - a. Immune mediated
  - b. Idiopathic
- II Type 2 diabetes** (may range from predominantly insulin resistance with relative insulin deficiency to a predominantly insulin secretory defect with insulin resistance)
- III Other specific types**
  1. Genetic defects of  $\beta$ -cell function
    - a. Chromosome 20q, Hepatocyte Nuclear Transcripeter Factor HNF-4 $\alpha$  (MODY1)
    - b. Chromosome 7p, glucokinase (MODY2)
    - c. Chromosome 12q, HNF-1 $\alpha$  (MODY3)
    - d. Chromosome 13q, insulin promoter factor (MODY4)
    - e. Chromosome 17q, HNF-1 $\beta$  (MODY5)
    - f. Chromosome 2q, Neurogenic differentiation 1/b-cell e-box transactivator 2 (MODY 6)



6. Infections
  - a. Congenital rubella
  - b. Cytomegalovirus
  - c. Others
7. Uncommon forms of immune-mediated diabetes
  - a. "Stiff-man" syndrome
  - b. Anti-insulin receptor antibodies
  - c. Others
8. Other genetic syndromes sometimes associated with diabetes
  - a. Down's syndrome
  - b. Klinefelter's syndrome
  - c. Turner's syndrome
  - d. Wolfram's syndrome
  - e. Friedreich's ataxia
  - f. Huntington's chorea
  - g. Laurence-Moon-Bieldel syndrome
  - h. Myotonic dystrophy
  - i. Porphyria
  - j. Prader-Willi syndrome
  - k. Others

#### **IV. Gestational Diabetes-Mellitus (GDM)**

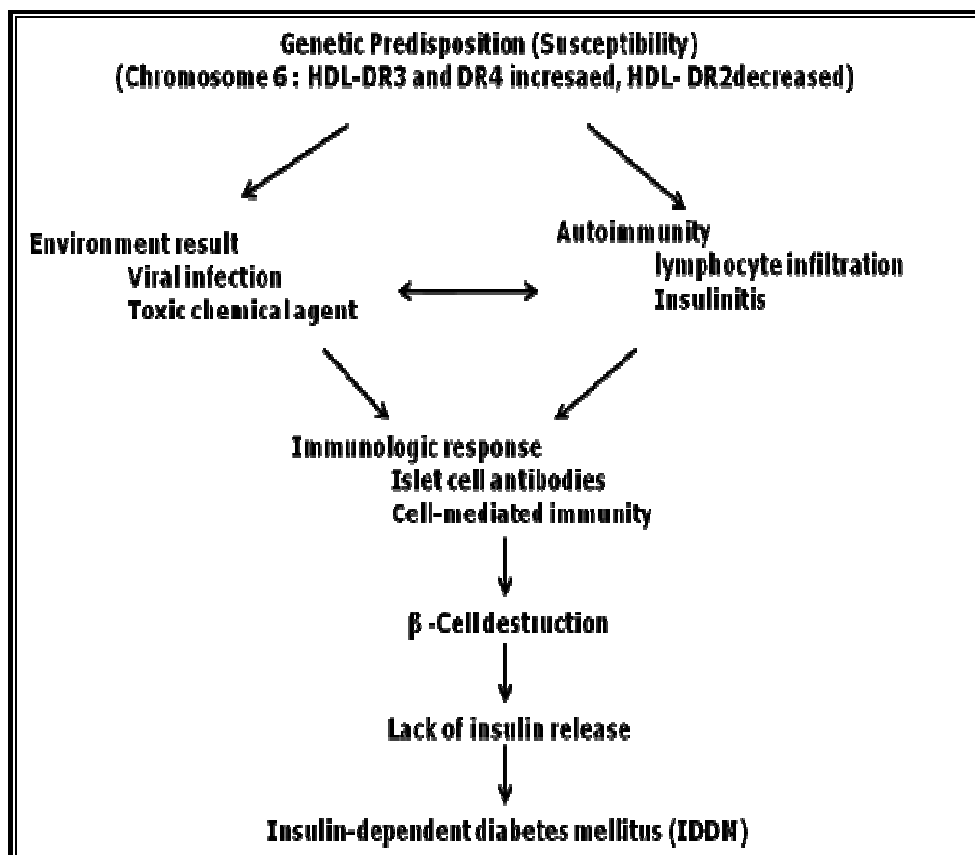
##### **Type 1 Diabetes Mellitus**

Type 1A (immune mediated) diabetes mellitus is defined as immune mediated diabetes mellitus. It can become manifest with hyperglycemia presenting in the first days of life or in adults over the age of 60. Current estimates indicate that immune mediated diabetes represents approximately 5 to 10% of the diabetes developing in adults and that approximately, as many individuals develop this form of diabetes as adults as do children (11). In the United States the great majority (>90%) of Caucasian children developing diabetes have type 1A diabetes while approximately 50% of African American and Hispanic American children developing diabetes lack the autoantibody and immunogenetic markers of typical type 1A diabetes. When an individual presents with type 1A diabetes it indicates that they and their relatives have an increased risk of having or developing a series of autoimmune disorders (12). Risk factors for type 1 diabetes may be autoimmune, genetic, or environmental. There is no known way to prevent type 1 diabetes. Several clinical trials of methods of the prevention of type 1 diabetes are currently in progress or are being planned.

The damage to the insulin-producing cells in type 1 diabetes occurs over a period of years. However, the symptoms of type 1 diabetes may occur over a period of days to weeks.

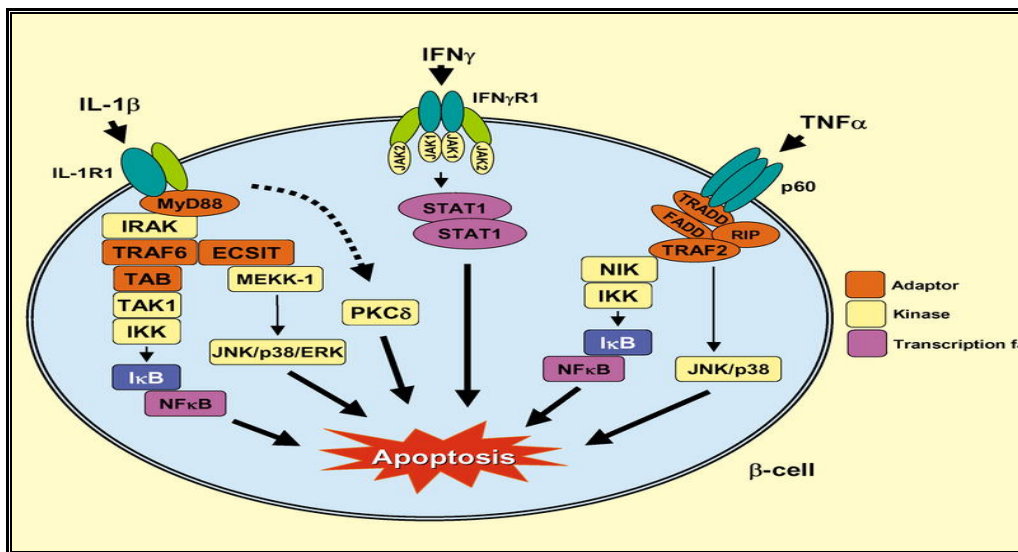
Type 1 diabetes most commonly starts in people under the age of 20, but may occur at any age. Type 1 diabetes is a catabolic disorder in which circulating insulin is virtually absent, glucagon levels are elevated, and pancreatic beta cells fail to respond to all insulin-producing stimuli. One of the actions of insulin is the inhibition of lipolysis (i.e., fat breakdown) and release of free fatty acids (FFA) from fat cells. In the absence of insulin, ketosis develops when these fatty acids are released from fat cells and converted to ketoacids in the liver. Because of the loss of beta function and complete lack of insulin, all people with type 1A diabetes require exogenous insulin replacement to reverse the catabolic state, control blood glucose levels, and prevent ketosis.

Type 1 diabetes is thought to result from genetic predisposition (i.e., diabetogenic genes), a hypothetical triggering event that involves an environmental agent that incites an immune response and the production of autoantibodies that destroy beta cells. These autoantibodies may exist for years before the onset of hyperglycemia. Certain inherited human leukocyte antigens (HLA) are strongly associated with the development of type 1 diabetes. About 95% of persons with the disease have either HLA-DR3 or HLA-DR4. Before diabetes develops, patients generally lose the early insulin secretory response to glucose and may secrete relatively large amount of proinsulin (Fig. 1)



**Figure 1 Pathogenesis of Type I diabetes mellitus**

These methods include the identification of genetically susceptible persons and early intervention in persons with newly diagnosed type 1 diabetes. After the diagnosis of type 1 diabetes, there often is a short period of beta cell regeneration, during which symptoms of diabetes disappear and insulin injections are not needed. This is sometimes called the honeymoon period. Immune interventions designed to interrupt the destruction of beta cells before development of type 1 diabetes are being investigated in the Diabetes Prevention Trial, which is trying to find a way to prevent complete and irreversible beta cell failure.

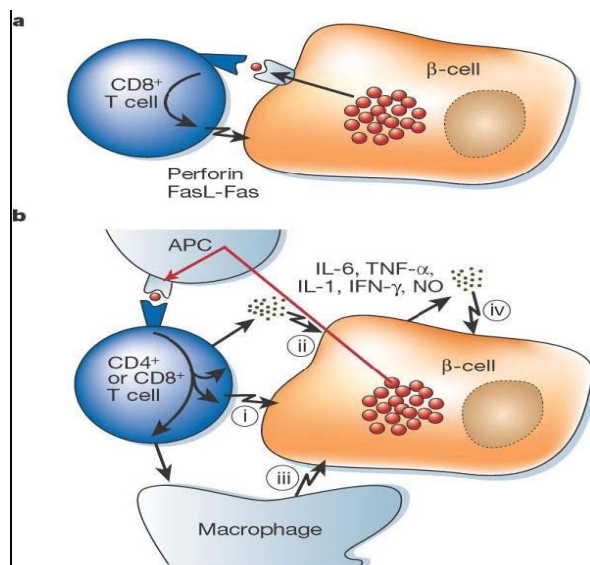


**Figure 2 Overview of cytokine signaling leading to  $\beta$ -cell apoptosis**

Three main cytokines most likely act in synergy during the immune infiltration of the pancreas to induce  $\beta$ -cell damage and apoptosis in type 1 diabetes: IL-1  $\beta$ , TNF  $\alpha$  and interferon (IFN) $\gamma$ . IL-1  $\beta$  is secreted by activated macrophages and, paradoxically, under some circumstances by  $\beta$ -cells (13). TNF  $\alpha$  is solely produced and secreted by macrophages, whereas IFN $\gamma$  is secreted by T-helper cells. In vitro, IL-1  $\beta$  is the most  $\beta$ -cell cytotoxic cytokine sufficient to cause inhibition of  $\beta$ -cell function and often sufficient to promote an apoptotic response.

However, massive induction of apoptosis in  $\beta$ -cells usually requires a combination of IL-1  $\beta$  plus IFN $\gamma$  and/or TNF $\alpha$ . Whether IL-1  $\beta$  alone is sufficient to evoke apoptosis in human  $\beta$ -cells is controversial. Nevertheless, several studies have pointed to the fact that IL-1  $\beta$  alone does induce apoptotic death of human  $\beta$ -cells (Figure 2) (14).

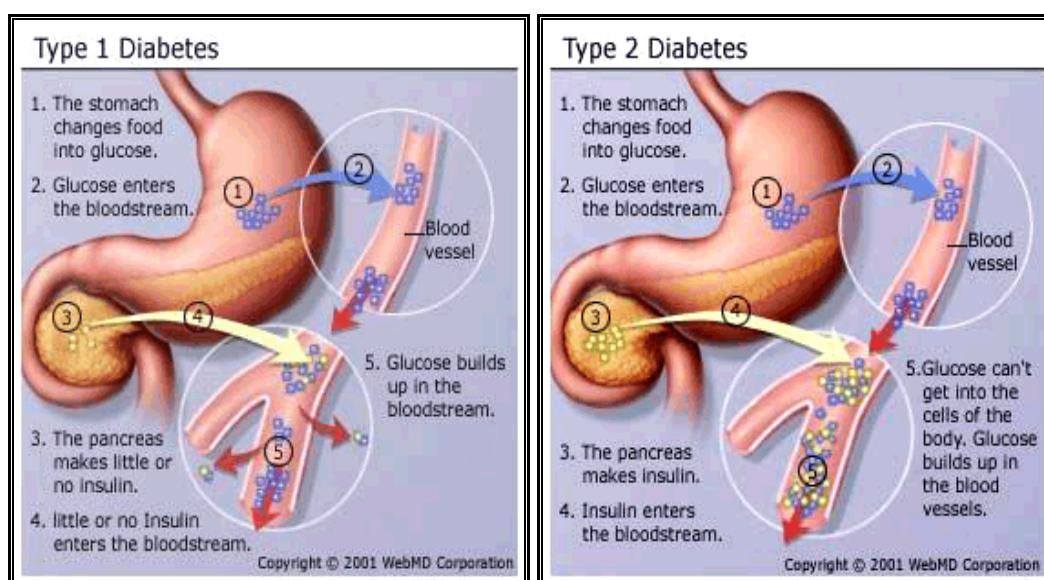
**Figure 3 Proposed model of  $\beta$ -cell death in autoimmune diabetes**





- a) The T-cell is activated by direct recognition of islet  $\beta$ -cell antigens (dots) presented by MHC molecules (in this case class I molecules) on  $\beta$ -cells. Interaction activates the apoptotic machinery via the Perforin or the Fas/FasL pathway.
- b) T-cells recognize the MHC molecules indirectly via antigen presenting cells (macrophages). The resulting activation initiates  $\beta$ -cell death mediated by surface receptors Fas/FasL and TNF-R (i), cytokines (ii), activation of macrophages (iii) and activation of the  $\beta$ -cell and their production of cell death mediators (iv).

Studies of the pathogenesis of type 1 diabetes have blossomed during the past two decades. In terms of summarizing the pathogenesis of this disorder it is convenient to divide the disease into some of stages beginning with genetic susceptibility and ending (from an immunologic standpoint) with complete islet beta cell destruction (15).



**Figure 4 Overview of Type 1 Diabetic and Type 2 Diabetic**

### **Type 2 Diabetes Mellitus**

Type 2 diabetes mellitus is a heterogeneous disorder characterised by multiple defects in the pancreatic  $\beta$ -cell, liver, and peripheral tissues such as skeletal muscle and adipose tissue. There is considerable debate about the primacy of insulin resistance or beta cell failure in the disorder. It is well documented that three major metabolic abnormalities contribute to the development of hyperglycaemia in type 2 diabetes mellitus, including impaired insulin secretion in response to glucose, increased hepatic glucose production, and decreased insulin-dependent glucose uptake in the peripheral tissues. The latter two abnormalities are defined as insulin resistance. Insulin resistance is reversed by enhancing the action of insulin, thereby promoting glucose utilisation in peripheral tissues, suppressing gluconeogenesis in the liver and reducing

lipolysis at the adipocyte. Insulin resistance appears in early stages of the disease. It is a major factor in the progression of the disease, contributing to beta cell exhaustion due to demands on insulin secretion.

The development of type 2 diabetes also depends on the degree to which environmental like viruses (Congenital rubella, mumps and coxsackic  $\beta$  viruses) and genetic factors may contribute, exposure to cow's geography (High in Finland and Sardinia) affect the appearance of type I DM (Fig. 4). At the initial stages of the disease, individuals with type 2 diabetes lose their ability to produce sufficient quantities of insulin to maintain normoglycemia in the face of insulin resistance. Chronic hyperglycemia develops. Furthermore, insulin resistance may cause secondary insulin deficiency, and insulin deficiency tends to lead to insulin resistance. They are reinforcing defects, partly through an effect referred as glucotoxicity (16). Some period of hyperglycemia has a secondary noxious effect that aggravates both insulin resistance and insulin deficiency: Hyperglycemia produces hyperglycemia (17). Before diabetes develops, patients generally lose the early insulin secretory response to glucose and may secrete relatively large amount of proinsulin (Fig. 5).

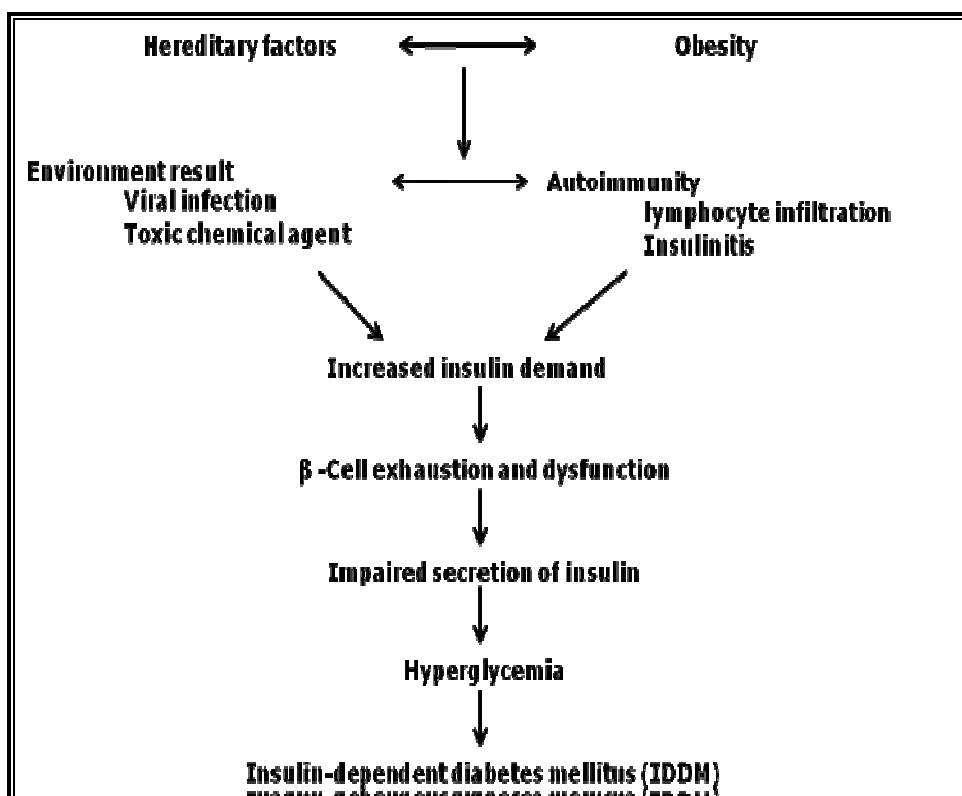
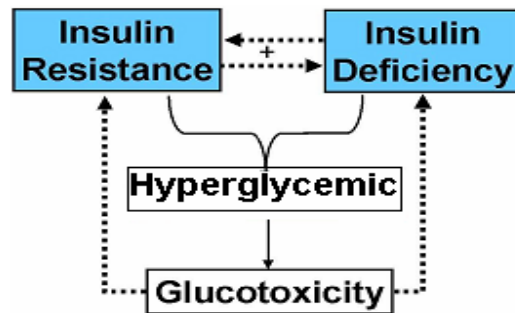


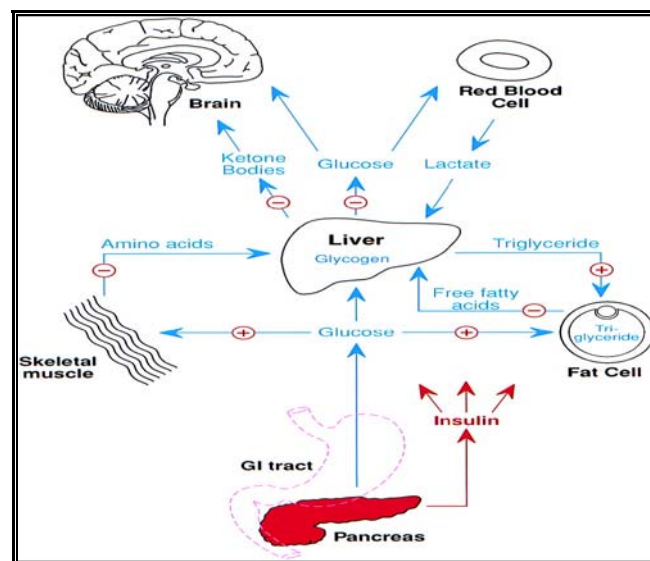
Figure 5 Pathogenesis of Type II diabetes mellitus



**Figure 6** The interrelations of insulin resistance, insulin deficiency, and glucose toxicity that create overall hyperglycemia in type 2 diabetes mellitus are depicted.

### Insulin: the main regulator of energy metabolism

Glucose stimulates pancreatic  $\beta$ -cells and is the main physiological regulator of acute insulin secretion and biosynthesis. Normal glucose regulation (range 3 to 5.5mM) is dependent on closed feedback loop relationship between liver, peripheral tissues (primarily muscle) and pancreatic islets (18).



**Figure 7** Insulin Is the Principal Regulator of Energy Metabolism (19).

When glucose and other nutrients are absorbed from the gastrointestinal tract, this elicits insulin secretion. Insulin regulates the metabolism of multiple fuels (indicated in blue). Selected actions of insulin are indicated in red (+, activation; -, inhibition). Insulin activates transport of glucose into muscle and adipose tissue, and also promotes synthesis of glycogen and triglycerides. Insulin inhibits lipolysis in adipose tissue, ketogenesis in liver, and proteolysis in muscle. Insulin also inhibits hepatic glucose production by inhibiting both glycogenolysis and gluconeogenesis. Insulin does not directly regulate the metabolism of red blood cells which use

glycolysis to provide energy. Although the brain uses glucose in the fed state, it can also use ketone bodies (acetoacetate and 3-hydroxybutyrate) when levels rise high enough (e.g., during fasting). As in type 1 diabetes mellitus, the loss of effective insulin action directly leads to unrestrained hepatic glucose production and inefficient peripheral glucose utilization. Excessive hepatic glucose output largely accounts for elevated fasting plasma glucose (FPG) levels. Resistance to the antilipolytic action of insulin in adipose tissue leads to elevated plasma free fatty acid (FFA) levels and increased FFA delivery to the liver. There, the oxidation of FFA generates energy (ATP) needed to sustain gluconeogenesis. In addition, the latter process is stimulated by FFA metabolites such as acyl coenzyme A (17).

In this indirect manner, insulin resistance also contributes to elevated glucose production in the liver (20). Moreover, the elevation of FFA levels also contributes to insulin resistance in muscle (21). The endocrine pancreas has an enormous capacity to adapt to conditions of higher insulin demand (e.g. pregnancy), as well as to pathological states (e.g. obesity, growth hormone or cortisol excess), by increasing  $\beta$ -cell function and mass (22, 23). These circumstances and increased concentration of hormones that have insulin antagonistic activity mediate insulin resistance, the failure to respond to normal circulating insulin concentrations. Diabetes occurs when  $\beta$ -cells fail to adapt. This is the case in about 10 % of the insulin resistant individuals.

#### Insulin Resistance:

Insulin resistance describes an insufficient action of insulin on target tissues (muscle, liver and adipose tissue) and requires an adaptation by the  $\beta$ -cells to increase insulin production. During digestion, the sugar (glucose) in the food you eat is absorbed into your bloodstream. Insulin from your pancreas escorts glucose into your cells, where it provides energy for your body. Excess glucose is stored in your liver. Type 2 diabetes develops when your pancreas doesn't produce enough insulin or your cells become resistant to insulin.

Insulin resistance triggers the development of type 2 diabetes in most patients. It is present ubiquitously in type 2 diabetic and in obese individuals. In about 90 % of patients with insulin resistance, the  $\beta$ -cell can adapt to this higher insulin demand, but the other 10 % become diabetic with time, a correlation between increasing body mass index and decreasing insulin sensitivity has been demonstrated (24). These results show that insulin resistance in obese diabetic patients is mainly a consequence of obesity. Weight loss can restore normal glucose tolerance in obese individuals with impaired glucose tolerance and prevent progression of diabetes in obese individuals with insulin resistance (25).

There are many individuals, obese and insulin resistant, but non-diabetic, being able to secrete sufficient insulin to compensate for the insulin resistance. The inability to do this may reflect essential genetic defects in those who develop type 2 diabetes, as a defect in the functional capacity of pancreatic  $\beta$ -cells to secrete insulin is undoubtedly necessary for the development of overt hyperglycemia (26). Increased amounts of insulin are needed for glucose

uptake into the muscle. One could imagine that a genetic defect in  $\beta$ -cell function and turnover would prevent an insulin resistant individual from having the appropriate increase in insulin secretion since the  $\beta$ -cell would be unable to compensate for insulin resistance. Under such circumstances the resultant hyperglycemia is the primary risk factor for the further impaired  $\beta$ -cell action.

Type 2 diabetes is characterized by a progressive decrease in insulin action, followed by an inability of the cell to compensate for insulin resistance. Insulin resistance is the first lesion, due to interactions among genes, aging, and metabolic changes produced by obesity. Insulin resistance in visceral fat leads to increased fatty acid production, which exacerbates insulin resistance in liver and muscle. The cell compensates for insulin resistance by secreting more insulin. Ultimately, the cell can no longer compensate, leading to impaired glucose tolerance, and diabetes (Fig. 8).

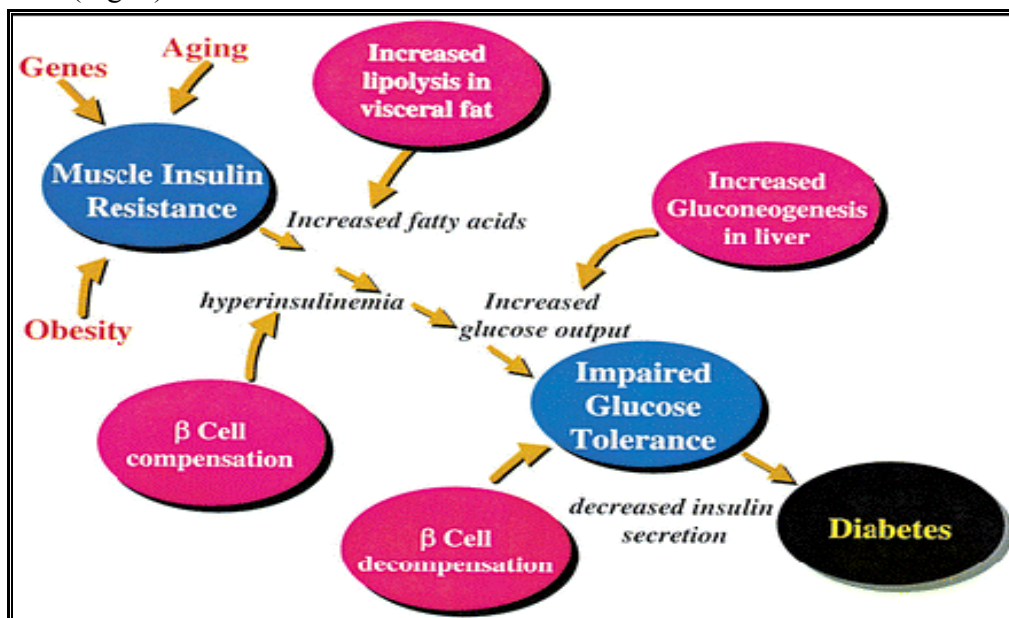


Figure 8 Metabolic Staging of Type 2 Diabetes (27).

### Gestational Diabetes Mellitus (GDM)

Gestational diabetes mellitus (GDM) is defined as glucose intolerance, which is first recognized during pregnancy. In most women who develop GDM, the disorder has its onset in the third trimester of pregnancy. At least 6 weeks after the pregnancy ends, the woman should receive an oral glucose tolerance test and be reclassified as having diabetes, normal glucose tolerance, impaired glucose tolerance, or impaired fasting glucose. Gestational diabetes complicates about 4% of all pregnancies. Gestational diabetes also involves a combination of inadequate insulin secretion and responsiveness, resembling type 2 diabetes in several respects. It develops during pregnancy and may improve or disappear after delivery. Even though it may be

transient, gestational diabetes may damage the health of the fetus or mother, and about 20%–50% of women with gestational diabetes develop type 2 diabetes later in life.

Gestational diabetes mellitus (GDM) occurs in about 2%–5% of all pregnancies. It is temporary and fully treatable but, if untreated, may cause problems with the pregnancy, including macrosomia (high birth weight), fetal malformation and congenital heart disease. It requires careful medical supervision during the pregnancy.

Fetal/neonatal risks associated with GDM include congenital anomalies such as cardiac, central nervous system, and skeletal muscle malformations. Increased fetal insulin may inhibit fetal surfactant production and cause respiratory distress syndrome. Hyperbilirubinemia may result from red blood cell destruction. In severe cases, perinatal death may occur, most commonly as a result of poor placental perfusion due to vascular impairment. Induction may be indicated with decreased placental function. Cesarean section may be performed if there is marked fetal distress or an increased risk of injury associated with macrosomia, such as shoulder dystocia.

**Table 2: Comparison chart between Types I and Type II dependent diabetes mellitus (28).**

	<b>Type I DM</b>	<b>Type II DM</b>
<b>Primary disease</b>	islet cells	Insulin receptor
<b>Presence of genetic factor</b>	Yes	No
<b>Average age at onset</b>	<40	>40
<b>Ketonosis</b>	Common	Hardly encountered
<b>Pancreatic cell antibody</b>	Present	Absent
<b>Insulin treatment</b>	Always required	Not always required
<b>Ketones status</b>	Ketonurea with or without ketoacidosis	Ketones absent/only trace present
<b>Body weight loss</b>	Profound	Minimal
<b>History of symptoms</b>	Abrupt and severe	Gradual and insidious
<b>Frequency</b>	0-20%	80-90%

### **Clinical Features of Diabetes Mellitus (29)**

#### **General symptoms**

- ✓ Polyuria
- ✓ polydipsia
- ✓ polyphagia
- ✓ Nocturia

- ✓ Symptoms of salt and water depletion
- ✓ Tiredness
- ✓ Altered visual activity
- ✓ Symptoms of infection: Purities vulvae, Balanitis, Boils, infection of skin and nails.

### **Clinical features of Type I diabetes**

- ✓ Sudden appearance of weight loss, almost ½ kg per week accompanied by polyurea, nocturea, Polydipsia.
- ✓ Generally appears in young lean subjects typically 10 to 12 years of age.
- ✓ Overwhelming fatigue, pronounced in latter part of day
- ✓ Increased appetite
- ✓ Muscular atrophy in thigh
- ✓ Smell of acetone

### **Clinical features of Type II Diabetes**

- ✓ Usually affects overweight persons (80%)
- ✓ Most are over 40 years of age but now increasingly seen in children
- ✓ Almost 1/3<sup>rd</sup> cases are identified during routine hospital check up or medical problems
- ✓ Common presentations are genital candidiasis (Particularly in women) urinary tract infections/skin infections
- ✓ Generally starts to be 4 to 7 years before diagnosis is made (30)

## **Diagnosis**

Diabetes mellitus is characterized by recurrent or persistent hyperglycemia, and is diagnosed by demonstrating any one of the following: (31)

- ✚ Fasting **plasma glucose** level at or above 126 mg/dL (7.0 mmol/l).
- ✚ plasma glucose at or above 200 mg/dL or 11.1 mmol/l two hours after a 75 g oral glucose load as in a glucose tolerance test.
- ✚ Random plasma glucose at or above 200 mg/dL or 11.1 mmol/l.

A positive result should be confirmed by another of the above-listed methods on a different day, unless there is no doubt as to the presence of significantly-elevated glucose levels. Most physicians prefer measuring a fasting glucose level because of the ease of measurement and the considerable time commitment of formal glucose tolerance testing, which can take two hours to complete. By current definition, two fasting glucose measurements above 126 mg/dL or 7.0 mmol/l is considered diagnostic for diabetes mellitus.

Patients with fasting sugars between 6.1 and 7.0 mmol/l (i.e, 110 and 125 mg/dL) are considered to have "impaired fasting glucose" and patients with plasma glucose at or above

140mg/dL or 7.8 mmol/l two hours after a 75 g oral glucose load are considered to have "impaired **glucose tolerance**". "Prediabetes" is either impaired fasting glucose or impaired glucose tolerance; the latter in particular is a major risk factor for progression to full-blown diabetes mellitus as well as cardiovascular disease.

While not used for diagnosis, an elevated level of glucose irreversibly bound to hemoglobin (termed glycosylated hemoglobin or **HbA1c**) of 6.0% or higher (the 2003 revised U.S. standard) is considered abnormal by most labs; HbA1c is primarily used as a treatment-tracking test reflecting average blood glucose levels over the preceding 90 days (approximately). However, some physicians may order this test at the time of diagnosis to track changes over time. The current recommended goal for HbA1c in patients with diabetes is <7.0%, which as defined as "good glycemic control", although some guidelines are stricter (<6.5%). People with diabetes who have HbA1c levels within this range have a significantly lower incidence of complications from diabetes, including retinopathy and diabetic nephropathy (32),

**Frustramine** is formed by a chemical reaction of glucose with plasma protein and reflects glucose control. It is often helpful when intensive treatment is applied. Test for urine **Ketones** with reagent strips especially for type I Dm who exhibit persistent, rapid and marked fluctuations in their degree of hyperglycemia. To achieve weight reduction is most important in overweight patients with type II DM. If improvement is not achieved with diet, oral drugs should be started.

## **Complications**

The complications of diabetes are far less common and less severe in people who have well-controlled blood sugar levels (33, 34). In fact, the better the control, the lower the risk of complications. Hence patient education, understanding, and participation is vital. Healthcare professionals treating diabetes also often attempt to address health issues that may accelerate the deleterious effects of diabetes. These include smoking (stopping), elevated cholesterol levels (control or reduction with diet, exercise or medication), obesity (even modest weight loss can be beneficial), high blood pressure (exercise or medication if needed), and lack of regular exercise (eschew the remote control).

## **Acute Complications**

### **Diabetic Ketoacidosis**

Diabetic ketoacidosis (DKA) is an acute, dangerous complication and is always a medical emergency. On presentation at hospital, the patient in DKA is typically dehydrated and breathing both fast and deeply. Abdominal pain is common and may be severe. The level of consciousness is typically normal until late in the process, when lethargy (dulled or reduced level of alertness or consciousness) may progress to coma. Ketoacidosis can become severe enough to cause hypotension, shock, and death. Prompt proper treatment usually results in full recovery, though



death can result from inadequate treatment, delayed treatment or from a variety of complications. It is much more common in type 1 diabetes than type 2, but can still occur in patients with type 2 diabetes.

In DKA, the marked hyperglycemia cause osmotic diuresis excessive urinary losses of water, Na, K and volume contraction with acidosis resulting from increase in hepatic ketone body synthesis and release. The major ketone bodies, acetoacetic acid and hydroxybutyric acid, are strong organic acids: the hyperketonemia induces a metabolic acidosis and respiratory compensation, and the marked increased in urinary excretion of acetoacetic acid and hydroxybutyric acid obligate addition losses of Na and K. Acetone deried from the spontaneous decarboxylation of acetoacetic acid accumulates in plasma and is slowly disposed of by respiration; it is a CNS anaesthetic, but the cause of coma in DKA is unknown.

The abnormal ketogenesis in DKA results from the loss of insulin's normal modulating effect on free fatty acid (FFA) released from adipose tissue and on hepatic FFA oxidation and ketogenesis. Plasma FFA levels and FFA uptake by the liver are greatly increased. In the liver, insulin normally regulates FFA oxidation and ketogenesis by indirectly inhibiting the transport of coenzyme A derivatives of long chain FFA across the inner mitochondria, and in DKA the normal opposing effect of insulin is lost. The plasma ratio of hydroxybutyric acid to acetoacetic acid is normally 3:1 and is usually increased in DKA, sometimes reaching 8:1.

Commercially available reagent strips and react with acetoacetic acid but do not react with hydroxybutyric acid. Therefore, reagent strip may significantly underestimate the amount of ketone bodies present.

**Symptoms** and complications may include:

- Nausea and vomiting
- Abnormally deep and rapid breathing with frequent sighing
- Rapid heartbeat
- Smell of acetone
- Dehydration
- If the condition persists, coma and eventually, death, may occur; over the past 20 years, death from DKA has decrease to about 2% of all cases.
- Other serious complication from DKA include aspiration pneumonia and respiratory distress

### **Nonketotic Hyperosmolar Coma**

While not generally progressing to coma, this hyperosmolar nonketotic state (HNS) is another acute problem associated with diabetes mellitus. It has many symptoms in common with DKA, but an entirely different cause, and requires different treatment. In anyone with very high blood glucose levels (usually considered to be above 300 mg/dl (16 mmol/l)), water will be

osmotically drawn out of cells into the blood. The kidneys will also be "dumping" glucose into the urine, resulting in concomitant loss of water, and causing an increase in blood osmolality. If fluid is not replaced (by mouth or intravenously), the osmotic effect of high glucose levels combined with the loss of water will eventually result in very high serum osmolality (ie, dehydration). The body's cells will become progressively dehydrated as water is taken from them and excreted. Electrolyte imbalances are also common, and dangerous. This combination of changes, especially if prolonged, will result in symptoms of lethargy (dulled or reduced level of alertness or consciousness) and may progress to coma. As with DKA urgent medical treatment is necessary, especially volume replacement. This is the 'diabetic coma' which more commonly occurs in type 2 diabetics.

### **Hypoglycemia**

Hypoglycemia, or abnormally low blood glucose, is a complication of several diabetes treatments. It may develop if the glucose intake does not cover the treatment. The patient may become agitated, sweaty, and have many symptoms of sympathetic activation of the autonomic nervous system resulting in feelings similar to dread and immobilized panic. Consciousness can be altered, or even lost, in extreme cases, leading to coma and/or seizures, or even brain damage and death. In patients with diabetes, this can be caused by several factors, such as too much or incorrectly timed insulin, too much exercise or incorrectly timed exercise (exercise decreases insulin requirements) or not enough food (actually an insufficient amount of glucose producing carbohydrates in food). In most cases, hypoglycemia is treated with sugary drinks or food. In severe cases, an injection of glucagon (a hormone with the opposite effects of insulin) or an intravenous infusion of glucose is used for treatment, but usually only if the person is unconscious. In hospital, intravenous dextrose is often used.

#### **Risk Factor for severe Hypoglycemia**

- Patient attempting tight control of blood glucose and HbA1c levels
- Patients who do not comply with treatment (including those who are underinsured, have psychiatric disorders, or who are poorly educated about diabetes)
- Infections such as gastroenteritis or respiratory illnesses

#### **Hypoglycemia symptoms**

Mild symptoms usually occur at moderately low and easily correctable levels of blood glucose. They include :

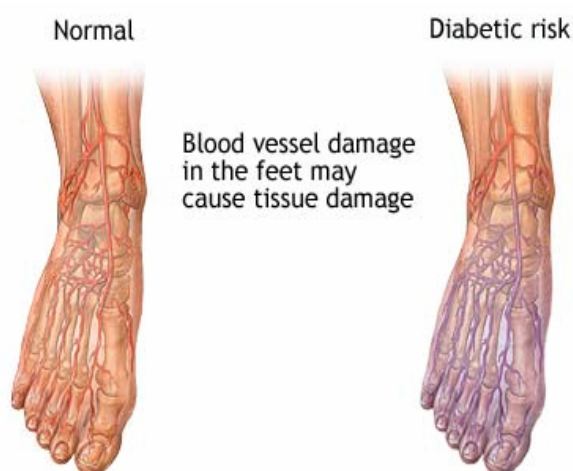
- Sweating
- Trembling
- Hunger
- Rapid heartbeat
- Confusion
- Weakness

- Disorientation
- Combativeness
- In rare and worst cases, coma, seizure, and death

### Foot Ulcer and Amputation

Persons with poorly controlled diabetes often heal slowly, even from small cuts, abrasions, blisters, or separated callus (corns). In such cases, the damage, if unnoticed, left untreated, or failing to heal, can result in an infection. The resulting infection, in extreme cases, can lead to amputation. About 15 % of patient with diabetes with have serious foot problem. They are the leading cause of hospitalizations for these patients. Diabetes is responsible for more than half of all lower limb amputation performed in the U.S. Each year there are about 88,000 non-injury amputations, 50-75 % of them due to diabetes. About 85 % of amputations start with foot ulcers, which develop on about 12 % of people with diabetes. Those most at risk are people with a long history of diabetes, and people with diabetes who are overweight or who smoke. People who have the disease for more than 20 years and are insulin-dependent are at the highest risk. Related conditions that put prople at risk include peripheral neuropathy, peripheral artery disease, foot ulcers develop from infections, such as those resulting from blood vessel injury(Fig. 9). Foot infections often develop from injuries. Even minor infections can develop into severe complications. Numbness from nerve damage, which is common in diabetes, compounds the danger since the patient may not be aware of injuries. About one-third of foot ulcers occur on the big toe.

Diabetic foot, often due to a combination of neuropathy and arterial disease, may cause skin ulcer and infection and, in serious cases, necrosis and gangrene. It is the most common cause of adult amputation, usually of toes and or feet, in the developed world. "Infection, ulceration and/or destruction of deep tissues associated with neurological abnormalities and various degrees of peripheral vascular disease in the lower limb" by WHO.



**Figure 9** Comparison between normal and diabetic foot

## **Pathophysiology of the diabetic foot**

### *Diabetic foot ulcers*

Three broad types:

- neuropathic
- ischaemic
- neuroischaemic

Anatomical distribution: ~50% of ulcers are on the toes; ~30-40% are on the plantar metatarsal head; ~10-15% are on the dorsum of the foot; ~5-10% are on the ankle; up to 10% are multiple ulcers.

Mechanisms of injury that destroy the foot:

- 1) Direct mechanical disruption of tissue (eg patient stepping on nail while barefoot abruptly breaking the skin barrier)
- 2) Small amount of force that is sustained over time that leads to ischaemia (eg tight shoe may lead to breakdown of bunion site)
- 3) Moderate amount of force that is repeated over and over leads to inflammation and enzymatic autolysis of tissue (eg plantar metatarsal ulceration)
- 4) Infection

## **Chronic Complications**

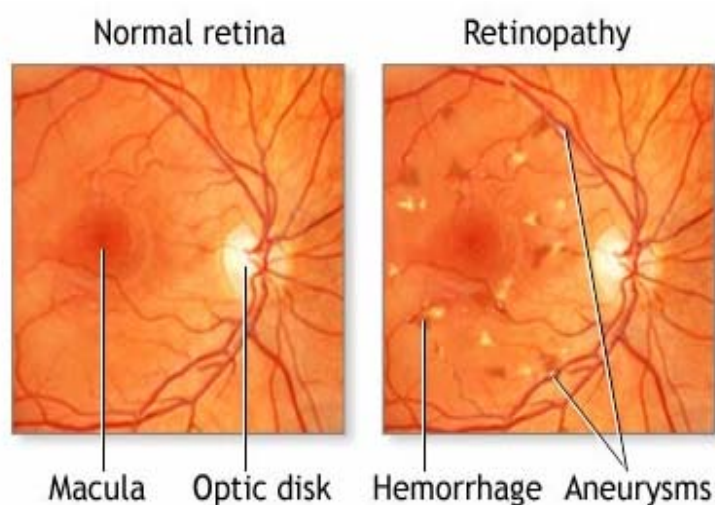
### **Vascular Disease**

Chronic elevation of blood glucose level leads to damage of blood vessels. In diabetes, the resulting problems are grouped under "**microvascular disease**" (due to damage to small blood vessels) and "**macrovascular disease**" (due to damage to the arteries).

### **Microvascular Disease**

#### **Retinopathy And Eye Complication**

In the United States, diabetes is responsible for 8% of legal blindness, making it the leading cause of new cases of blindness in adults 20-74 years of age. Each year, between 12,000 to 24,000 people lose their sight because of diabetes. Diabetes is the fifth-deadliest disease in the United States, and it has no cure. The total annual economic cost of diabetes in 2002 was estimated to be \$132 billion, or one out of every 10 health care dollars spent in the United States. The most common eye disorder in diabetes is retinopathy. The most common eye disorder in diabetes is retinopathy. People with diabetes are also at higher risk for developing cataracts and certain type of glaucoma, such as primary open angle glaucoma (POAG). The risk for POAG is especially high for women with type II diabetes.



**Figure 10 Comparison between normal and diabetic retina**

Diabetic retinopathy, growth of friable and poor-quality new blood vessels in the retina as well as macular edema (swelling of the macula), which can lead to severe vision loss or blindness. Retinal damage (from microangiopathy) makes it the most common cause of blindness among non-elderly adults in the US.

Two basic pathophysiological mechanisms - increased capillary permeability and closure of retinal capillaries vascular leakage retinal oedema and accumulation of lipids seen as hard exudate in the retina and retinal ischaemia (Fig. 10).

### ***Eyesight Insight***

To understand what happens in eye disorders, it helps to understand how the eye works. The eye is a ball covered with a tough outer membrane. The covering in front is clear and curved. This curved area is the cornea, which focuses light while protecting the eye. After light passes through the cornea, it travels through a space called the anterior chamber (which is filled with a protective fluid called the aqueous humor), through the pupil (which is a hole in the iris, the colored part of the eye), and then through a lens that performs more focusing. Finally, light passes through another fluid-filled chamber in the center of the eye (the vitreous) and strikes the back of the eye, the retina. Like the film in a camera, the retina records the images focused on it. But unlike film, the retina also converts those images into electrical signals, which the brain receives and decodes. One part of the retina is specialized for seeing fine detail. This tiny area of extra-sharp vision is called the macula. Blood vessels in and behind the retina nourish the macula. The smallest of these blood vessels are the capillaries.

### ***Glaucoma***

People with diabetes are 40% more likely to suffer from glaucoma than people without diabetes. The longer someone has had diabetes, the more common glaucoma is. Risk also

increases with age. Glaucoma occurs when pressure builds up in the eye. In most cases, the pressure causes drainage of the aqueous humor to slow down so that it builds up in the anterior chamber. The pressure pinches the blood vessels that carry blood to the retina and optic nerve. Vision is gradually lost because the retina and nerve are damaged. There are several treatments for glaucoma. Some use drugs to reduce pressure in the eye, while others involve surgery.

### ***Cataracts***

Many people without diabetes get cataracts, but people with diabetes are 60% more likely to develop this eye condition. People with diabetes also tend to get cataracts at a younger age and have them progress faster. With cataracts, the eye's clear lens clouds, blocking light.

To help deal with mild cataracts, you may need to wear sunglasses more often and use glare-control lenses in your glasses. For cataracts that interfere greatly with vision, doctors usually remove the lens of the eye. Sometimes the patient gets a new transplanted lens. In people with diabetes, retinopathy can get worse after removal of the lens, and glaucoma may start to develop.

### ***Retinopathy***

Diabetic retinopathy is a general term for all disorders of the retina caused by diabetes. There are two major types of retinopathy: **i) nonproliferative**  
**ii) Proliferative.**

**Nonproliferative retinopathy** is the most common form of retinopathy. In nonproliferative retinopathy, capillaries in the back of the eye balloon and form pouches. Nonproliferative retinopathy can move through three stages (mild, moderate, and severe), as more and more blood vessels become blocked. Although retinopathy does not usually cause vision loss at this stage, the capillary walls may lose their ability to control the passage of substances between the blood and the retina. Fluid can leak into the part of the eye where focusing occurs, the macula. When the macula swells with fluid, a condition called macular edema, vision blurs and can be lost entirely. Although nonproliferative retinopathy usually does not require treatment, macular edema must be treated, but fortunately treatment is usually effective at stopping and sometimes reversing vision loss.

In some people, retinopathy progresses after several years to a more serious form called **proliferative retinopathy**. In this form, the blood vessels are so damaged they close off. In response, new blood vessels start growing in the retina. These new vessels are weak and can leak blood, blocking vision, and which is a condition called vitreous hemorrhage. The new blood vessels can also cause scar tissue to grow. After the scar tissue shrinks, it can distort the retina or pull it out of place this is called retinal detachment.

Most people with nonproliferative retinopathy have no symptoms. Even with proliferative retinopathy, the more dangerous form, people sometimes have no symptoms until it is too late to treat them. For this reason, you should have your eyes examined regularly by an eye

care professional. Several factors influence whether you get retinopathy. These include your blood sugar control, your blood pressure levels, how long you have had diabetes, and your genes.

The longer you've had diabetes, the more likely you are to have retinopathy. Almost everyone with type 1 diabetes will eventually have nonproliferative retinopathy. And most people with type 2 diabetes will also get it. But the retinopathy that destroys vision, proliferative retinopathy, is far less common. People who keep their blood sugar levels closer to normal are less likely to have retinopathy or to have milder forms.

### **Vision problems**

#### ***Clinical features:***

- Earliest feature is microaneurysms (small discrete dark red spots near retinal vessels); haemorrhages; hard exudate (appear as spots in perimacular area); soft exudate (appear as cotton wool' spots) venous dilation; new vessel formation
- Presence is best detected with ophthalmoscope through dilated pupils
- Factors associated with worsening diabetic retinopathy:
- Later age of onset of diabetes; poor control of diabetes; longer duration of diabetes; associated hypertension or nephropathy; insulin treatment; pregnancy; smoking.

#### **Factors associated with worsening diabetic retinopathy:**

- Later age of onset of diabetes
- Poor control of diabetes
- Longer duration of diabetes
- Associated hypertension or nephropathy
- Insulin treatment
- Pregnancy
- Smoking

### **Nerve Disorders (Neuropathy)**

Diabetic neuropathy, abnormal and decreased sensation, usually in a 'glove and stocking' distribution starting with the feet but potentially in other nerves, later often fingers and hands. When combined with damaged blood vessels this can lead to diabetic foot. Other forms of diabetic neuropathy may present as mononeuritis or autonomic neuropathy. Nerves send messages to and from your brain about pain, temperature and touch. They tell your muscles when and how to move. They also control body systems that digest food and pass urine. About half of all people with diabetes have some form of nerve damage. It is more common in those who have had the disease for a number of years. Nerve damage from diabetes is called **diabetic neuropathy**. It can lead to many kinds of problems. But if you keep your blood glucose levels on target, you may help prevent or delay nerve damage. There are treatments that can help as well.

There are two common types of nerve damage.

- ✚ The first is sensorimotor neuropathy, also known as **peripheral neuropathy**. This can cause tingling, pain, numbness, or weakness in your feet and hands.
- ✚ The second is called **autonomic neuropathy**. This type can lead to:
  - digestive problems such as feeling full, nausea,
  - vomiting, diarrhea, or constipation
  - problems with how well your bladder works
  - problems having sex
  - dizziness or faintness
  - loss of the typical warning signs of a heart attack
  - loss of the warning signs of low blood glucose
  - increased or decreased sweating
  - changes in how your eyes react to light and dark

People with diabetes can also have what is called focal neuropathy. In this kind of nerve damage, a nerve or a group of nerves is affected, causing sudden weakness or pain. It can lead to double vision, a paralysis on one side of the face called Bell's palsy, or pain in the front of the thigh or other parts of the body. People with diabetes also are at risk for compressed nerves. Something in the body presses against a nerve preventing it from sending a signal. Carpal tunnel syndrome is a common cause of numbness and tingling in the fingers and can lead to muscle pain and weakness as well. Nerve damage can be hard to diagnose because its symptoms can be caused by other conditions. Symptoms can be very mild. Knowing the symptoms to look for and reporting them to your health care team can help. Make a list of your symptoms or use the checklists in this brochure. Your doctor will give you an exam and a number of tests to check for nerve damage.

### **Diabetes And Kidney Failure (Nephropathy)**

Diabetic nephropathy, damage to the kidney which can lead to chronic renal failure, eventually requiring dialysis. Diabetes mellitus is the most common cause of adult kidney failure worldwide in the developed world.

The main job of the kidneys is to remove waste from the blood and return the cleaned blood back to the body. Kidney failure means the kidneys are no longer able to remove waste and maintain the level of fluid and salts that the body needs. One cause of kidney failure is diabetes mellitus, a condition characterised by high blood glucose (sugar) levels. Over time, the high levels of sugar in the blood damage the millions of tiny filtering units within each kidney. This eventually leads to kidney failure. Around 20 to 30 per cent of people with diabetes develop kidney disease (diabetic nephropathy), although not all of these will progress to kidney failure. A person with diabetes is susceptible to nephropathy whether they use insulin or not. The risk is related to the length of time the person has diabetes. There is no cure for diabetic nephropathy,



and treatment is lifelong. Another name for the condition is diabetic glomerulosclerosis. People with diabetes are also at risk of other kidney problems including narrowing of the arteries to the kidneys, called renal artery stenosis or renovascular disease.

### ***Symptoms***

A person can have diabetes without knowing it. This means their unchecked high blood sugar levels may be slowly damaging their kidneys. At first, the only sign is high protein levels in the urine, but this has no symptoms. It may be years before the kidneys are damaged severely enough to cause symptoms.

Some of the symptoms may include:

- Fluid retention (oedema)
- Swollen legs
- Swollen face
- Fatigue
- Headache
- Nausea
- Vomiting.

### ***Kidneys explained***

The human body has two kidneys, one on either side of the spine beneath the lower ribs. Inside each kidney are about one million tiny units called nephrons. Each nephron consists of a small filter (glomerulus) attached to a tubule. Water that contains waste is separated from the blood by the filters and directed into the tubules. Much of the water is returned to the blood by the tubules, while the wastes are concentrated into urine. The urine is collected from the tubules by a funnel-like structure (renal pelvis). From there, the urine flows down a tube (ureter) that joins each kidney to the bladder. Urine leaves the bladder via the urethra, the thin tube that connects to the outside of the body. Kidneys affected by diabetic nephropathy no longer work efficiently, and trace amounts of protein appear in the urine (microalbuminuria). The retained water and salts cause the characteristic fluid retention and, frequently, the blood pressure begins to rise.

### ***The mechanism is unknown***

It is clear that diabetes can lead to kidney disease, but just why high blood sugars should damage the glomeruli is unclear. High blood pressure (hypertension) is a known risk factor for kidney disease and people with diabetes are prone to hypertension. The renin-angiotensin system which helps regulate blood pressure - is also thought to be involved in the development of diabetic nephropathy. Other risk factors include cigarette smoking and family history. Diabetic nephropathy progresses steadily despite medical intervention. However, treatment can significantly slow the rate of damage.

### ***Diagnosis methods***

Diabetic nephropathy is diagnosed using a number of tests including:

- **Urine tests** - to check protein levels. An abnormally high level of protein in the urine is one of the first signs of diabetic nephropathy.
- **Blood pressure** - regular checks for raised blood pressure are necessary. Elevated blood pressure is caused by diabetic nephropathy and also contributes to its progression.
- **Blood tests** - to check the degree of kidney function.
- **Biopsy** - a small tag of tissue is removed from the kidney, via a slender needle, and examined in a laboratory. This is usually only performed when there is doubt about whether kidney damage is due to diabetes or to another cause.
- **Kidney ultrasound** - enables the size of the kidneys to be imaged and allows the arteries to the kidneys to be checked for narrowing that can cause decreased kidney function.

### **Mental Function and Dementia**

Some studies indicate that patient type II diabetes face a higher than average risk of developing dementia caused either by Alzheimer's with diabetes or problem in blood vessels in the brain. Problems in attention and memory can occur even in people under age 55 who have diabetes for a number of years.

### **Infections and Skin Complications**

Diabetes can affect every part of the body, including the skin. As many as one third of people with diabetes will have a skin disorder caused or affected by diabetes at some time in their lives. In fact, such problems are sometimes the first sign that a person has diabetes. Luckily, most skin conditions can be prevented or easily treated if caught early. Some of these problems are skin conditions anyone can have, but people with diabetes get more easily. These include bacterial infections, fungal infections, and itching. Other skin problems happen mostly or only to people with diabetes. These include diabetic dermopathy, necrobiosis lipoidica diabetorum, diabetic blisters, and eruptive xanthomatosis.

**Respiratory infections:** People with diabetes face a higher risk for influenza and its complication, including pneumonia, possibly because the disorder neutralizes the effects of protective proteins on the surface of the lungs. In fact, death among people with diabetes increase by 5-15 % during flu epidemics, and they are six times more likely to be hospitalized with complications from flu than nondiabetic patient who have flu. Everyone with diabetes should have annual influenza vaccinations and a vaccination against pneumococcal pneumonia. Also the diabetic patients are more prone to develop TB treatment. Patient with diabetes are more likely to develop multi drug resistant TB.

**Urinary Tract Infections:** Women with diabetes face a significantly higher risk for urinary tract infections, which are likely to be more complicated and difficulty to treat than in the general population.

### ***Bacterial Infections***

Several kinds of bacterial infections occur in people with diabetes. One common one are styes. These are infections of the glands of the eyelid. Another kind of infection are boils, or infections of the hair follicles. Carbuncles are deep infections of the skin and the tissue underneath. Infections can also occur around the nails. Inflamed tissues are usually hot, swollen, red, and painful. Several different organisms can cause infections. The most common ones are the Staphylococcus bacteria, also called staph. Once, bacterial infections were life threatening, especially for people with diabetes. Today, death is rare, thanks to antibiotics and better methods of blood sugar control. But even today, people with diabetes have more bacterial infections than other people do. Doctors believe people with diabetes can reduce their chances of these infections in several ways. If you think you have a bacterial infection, see your doctor.

### ***Fungal Infections***

The culprit in fungal infections of people with diabetes is often *Candida albicans*. This yeast-like fungus can create itchy rashes of moist, red areas surrounded by tiny blisters and scales. These infections often occur in warm, moist folds of the skin. Problem areas are under the breasts, around the nails, between fingers and toes, in the corners of the mouth, under the foreskin (in uncircumcised men), and in the armpits and groin. Common fungal infections include jock itch, athlete's foot, ringworm (a ring-shaped itchy patch), and vaginal infection that causes itching. If you think you have a yeast or fungal infection, call your doctor. You will need a prescription medicine to cure it.

### ***Itching***

Localized itching is often caused by diabetes. It can be caused by a yeast infection, dry skin, or poor circulation. When poor circulation is the cause of itching, the itchiest areas may be the lower parts of the legs. You may be able to treat itching yourself. Limit how often you bathe, particularly when the humidity is low. Use mild soap with moisturizer and apply skin cream after bathing.

### ***Diabetic Dermopathy***

Diabetes can cause changes in the small blood vessels. These changes can cause skin problems called diabetic dermopathy. Dermopathy often looks like light brown, scaly patches. These patches may be oval or circular. Some people mistake them for age spots. This disorder most often occurs on the front of both legs. But the legs may not be affected to the same degree. The patches do not hurt, open up, or itch. Dermopathy is harmless. You do not need to be treated.

### ***Necrobiosis Lipoidica Diabeticorum***

Another disease that may be caused by changes in the blood vessels is necrobiosis lipoidica diabeticorum (NLD). NLD is similar to diabetic dermopathy. The difference is that the

spots are fewer, but larger and deeper. NLD often starts as a dull red raised area. After a while, it looks like a shiny scar with a violet border. The blood vessels under the skin may become easier to see. Sometimes NLD is itchy and painful. Sometimes the spots crack open. NLD is a rare condition. Adult women are the most likely to get it. As long as the sores do not break open, you do not need to have it treated. But if you get open sores, see your doctor for treatment.

### ***Atherosclerosis***

Thickening of the arteries - atherosclerosis - can affect the skin on the legs. People with diabetes tend to get atherosclerosis at younger ages than other people do. As atherosclerosis narrows the blood vessels, the skin changes. It becomes hairless, thin, cool, and shiny. The toes become cold. Toenails thicken and discolor. And exercise causes pain in the calf muscles because the muscles are not getting enough oxygen. Because blood carries the infection-fighting white cells, affected legs heal slowly when the skin is injured. Even minor scrapes can result in open sores that heal slowly.

People with neuropathy are more likely to suffer foot injuries. These occur because the person does not feel pain, heat, cold, or pressure as well. The person can have an injured foot and not know about it. The wound goes uncared for, and so infections develop easily. Atherosclerosis can make things worse. The reduced blood flow can cause the infection to become severe.

### ***Allergic Reactions***

Allergic skin reactions can occur in response to medicines, such as insulin or diabetes pills. You should see your doctors if you think you are having a reaction to a medicine. Be on the lookout for rashes, depressions, or bumps at the sites where you inject insulin.

### ***Diabetic Blisters (Bullosis Diabeticorum)***

Rarely, people with diabetes erupt in blisters. Diabetic blisters can occur on the backs of fingers, hands, toes, feet, and sometimes, on legs or forearms. These sores look like burn blisters. They sometimes are large. But they are painless and have no redness around them. They heal by themselves, usually without scars, in about three weeks. They often occur in people who have diabetic neuropathy. The only treatment is to bring blood sugar levels under control.

### ***Eruptive Xanthomatosis***

Eruptive xanthomatosis is another condition caused by diabetes that's out of control. It consists of firm, yellow, pea-like enlargements in the skin. Each bump has a red halo and may itch. This condition occurs most often on the backs of hands, feet, arms, legs, and buttocks. The disorder usually occurs in young men with type 1 diabetes. The person often has high levels of cholesterol and fat in the blood. Like diabetic blisters, these bumps disappear when diabetes control is restored.

***Digital Sclerosis***

Sometimes, people with diabetes develop tight, thick, waxy skin on the backs of their hands. Sometimes skin on the toes and forehead also becomes thick. The finger joints become stiff and can no longer move the way they should. Rarely, knees, ankles, or elbows also get stiff. This condition happens to about one third of people who have type I diabetes. The only treatment is to bring blood sugar levels under control.

***Disseminated Granuloma Annulare***

In disseminated granuloma annulare, the person has sharply defined ring-shaped or arc-shaped raised areas on the skin. These rashes occur most often on parts of the body far from the trunk (for example, the fingers or ears). But sometimes the raised areas occur on the trunk. They can be red, red-brown, or skin-colored. See your doctor if you get rashes like this. There are drugs that can help clear up this condition.

***Acanthosis Nigricans***

Acanthosis nigricans is a condition in which tan or brown raised areas appear on the sides of the neck, armpits, and groin. Sometimes they also occur on the hands, elbows, and knees. Acanthosis nigricans usually strikes people who are very overweight. The best treatment is to lose weight. Some creams can help the spots look better.

**Depression**

Diabetes doubles the risk for depression. According to one study, depression, in turn, increases the risk for hyperglycemia and complications of diabetes. Restoring mental health, both through quality of life but may help patient control their blood sugar levels. Feeling down once in a while is normal. But some people feel a sadness that just won't go away. Life seems hopeless. Feeling this way most of the day for two weeks or more is a sign of serious depression.

At any given time, most people with diabetes do not have depression. But studies show that people with diabetes have a greater risk of depression than people without diabetes. There are no easy answers about why this is true. The stress of daily diabetes management can build. You may feel alone or set apart from your friends and family because of all this extra work. If you face diabetes complications such as nerve damage, or if you are having trouble keeping your blood sugar levels where you'd like, you may feel like you're losing control of your diabetes. Even tension between you and your doctor may make you feel frustrated and sad. Just like denial, depression can get you into a vicious cycle. It can block good diabetes self-care. If you are depressed and have no energy, chances are you will find such tasks as regular blood sugar testing too much. If you feel so anxious that you can't think straight, it will be hard to keep up with a good diet. You may not feel like eating at all. Of course, this will affect your blood sugar levels.

**Symptoms**

- **Loss of pleasure** You no longer take interest in doing things you used to enjoy.
- **Change in sleep patterns** You have trouble falling asleep, you wake often during the night, or you want to sleep more than usual, including during the day.
- **Early to rise** You wake up earlier than usual and cannot to get back to sleep.
- **Change in appetite** You eat more or less than you used to, resulting in a quick weight gain or weight loss.
- **Trouble concentrating** You can't watch a TV program or read an article because other thoughts or feelings get in the way.
- **Loss of energy** You feel tired all the time.
- **Nervousness** You always feel so anxious you can't sit still.
- **Guilt** You feel you "never do anything right" and worry that you are a burden to others.

### **Gastroparesis**

The most common cause of gastroparesis is diabetes. People with diabetes have high blood glucose, also called blood sugar, which in turn causes chemical changes in nerves and damages the blood vessels that carry oxygen and nutrients to the nerves. Over time, high blood glucose can damage the vagus nerve.

Some other *causes* of gastroparesis are

- surgery on the stomach or vagus nerve
- viral infections
- anorexia nervosa or bulimia
- medications-anticholinergics and narcotics-that slow contractions in the intestine
- gastroesophageal reflux disease
- smooth muscle disorders, such as amyloidosis and scleroderma
- nervous system diseases, including abdominal migraine and Parkinson's disease
- metabolic disorders, including hypothyroidism

*Signs and symptoms* of gastroparesis are

- heartburn
- pain in the upper abdomen
- nausea
- vomiting of undigested food—sometimes several hours after a meal
- early feeling of fullness after only a few bites of food
- weight loss due to poor absorption of nutrients or low calorie intake
- abdominal bloating
- high and low blood glucose levels
- lack of appetite
- gastroesophageal reflux
- spasms in the stomach area

Eating solid foods, high-fiber foods such as raw fruits and vegetables, fatty foods, or drinks high in fat or carbonation may contribute to these symptoms. The symptoms of gastroparesis may be mild or severe, depending on the person. Symptoms can happen frequently in some people and less often in others. Many people with gastroparesis experience a wide range of symptoms, and sometimes the disorder is difficult for the physician to diagnose.

### **Sexual and Urologic Problems of Diabetes**

Troublesome bladder symptoms and changes in sexual function are common health problems as people age. Having diabetes can mean early onset and increased severity of these problems. Sexual and urologic complications of diabetes occur because of the damage diabetes can cause to blood vessels and nerves. Men may have difficulty with erections or ejaculation. Women may have problems with sexual response and vaginal lubrication. Urinary tract infections and bladder problems occur more often in people with diabetes. People who keep their diabetes under control can lower their risk of the early onset of these sexual and urologic problems.

#### ***Diabetes and Sexual Problems***

Both men and women with diabetes can develop sexual problems because of damage to nerves and small blood vessels. When a person wants to lift an arm or take a step, the brain sends nerve signals to the appropriate muscles. Nerve signals also control internal organs like the heart and bladder, but people do not have the same kind of conscious control over them as they do over their arms and legs. The nerves that control internal organs are called autonomic nerves, which signal the body to digest food and circulate blood without a person having to think about it. The body's response to sexual stimuli is also involuntary, governed by autonomic nerve signals that increase blood flow to the genitals and cause smooth muscle tissue to relax. Damage to these autonomic nerves can hinder normal function. Reduced blood flow resulting from damage to blood vessels can also contribute to sexual dysfunction.

#### ***Erectile Dysfunction***

Erectile dysfunction is a consistent inability to have an erection firm enough for sexual intercourse. The condition includes the total inability to have an erection and the inability to sustain an erection. Estimates of the prevalence of erectile dysfunction in men with diabetes vary widely, ranging from 20 to 75 percent. Men who have diabetes are two to three times more likely to have erectile dysfunction than men who do not have diabetes. Among men with erectile dysfunction, those with diabetes may experience the problem as much as 10 to 15 years earlier than men without diabetes. Research suggests that erectile dysfunction may be an early marker of diabetes, particularly in men ages 45 and younger.

In addition to diabetes, other major causes of erectile dysfunction include high blood pressure, kidney disease, alcohol abuse, and blood vessel disease. Erectile dysfunction may also occur because of the side effects of medications, psychological factors, smoking, and hormonal

deficiencies. Men who experience erectile dysfunction should consider talking with a health care provider. The health care provider may ask about the patient's medical history, the type and frequency of sexual problems, medications, smoking and drinking habits, and other health conditions. A physical exam and laboratory tests may help pinpoint causes of sexual problems. The health care provider will check blood glucose control and hormone levels and may ask the patient to do a test at home that checks for erections that occur during sleep. The health care provider may also ask whether the patient is depressed or has recently experienced upsetting changes in his life.

Treatments for erectile dysfunction caused by nerve damage, also called neuropathy, vary widely and range from oral pills, a vacuum pump, pellets placed in the urethra, and shots directly into the penis, to surgery. All of these methods have advantages and disadvantages. Psychological counseling to reduce anxiety or address other issues may be necessary. Surgery to implant a device to aid in erection or to repair arteries is usually used as a treatment after all others fail.

### ***Retrograde Ejaculation***

Retrograde ejaculation is a condition in which part or all of a man's semen goes into the bladder instead of out the tip of the penis during ejaculation. Retrograde ejaculation occurs when internal muscles, called sphincters, do not function normally. A sphincter automatically opens or closes a passage in the body. With retrograde ejaculation, semen enters the bladder, mixes with urine, and leaves the body during urination without harming the bladder. A man experiencing retrograde ejaculation may notice that little semen is discharged during ejaculation or may become aware of the condition if fertility problems arise. Analysis of a urine sample after ejaculation will reveal the presence of semen. Poor blood glucose control and the resulting nerve damage can cause retrograde ejaculation. Other causes include prostate surgery and some medications.

***Many women*** with diabetes experience sexual problems. Although research about sexual problems in women with diabetes is limited, one study found 27 percent of women with type 1 diabetes experienced sexual dysfunction. Another study found 18 percent of women with type 1 diabetes and 42 percent of women with type 2 diabetes experienced sexual dysfunction.

Sexual problems may include

- decreased vaginal lubrication, resulting in vaginal dryness
- uncomfortable or painful sexual intercourse
- decreased or no desire for sexual activity
- decreased or absent sexual response

Decreased or absent sexual response can include the inability to become or remain aroused, reduced or no sensation in the genital area, and the constant or occasional inability to reach orgasm. Causes of sexual problems in women with diabetes include nerve damage, reduced blood flow to genital and vaginal tissues, and hormonal changes. Other possible causes include



some medications, alcohol abuse, smoking, psychological problems such as anxiety or depression, gynecologic infections, other diseases, and conditions relating to pregnancy or menopause.

Women who experience sexual problems or notice a change in sexual response should consider talking with a health care provider. The health care provider will ask about the patient's medical history, any gynecologic conditions or infections, the type and frequency of sexual problems, medications, smoking and drinking habits, and other health conditions. The health care provider may ask whether the patient might be pregnant or has reached menopause and whether she is depressed or has recently experienced upsetting changes in her life. A physical exam and laboratory tests may also help pinpoint causes of sexual problems. The health care provider will also talk with the patient about blood glucose control.

### **Macrovascular Disease**

Macrovascular disease leads to cardiovascular disease, to which accelerated atherosclerosis is a contributor: Coronary artery disease, leading to angina or myocardial infarction ("heart attack")

- Stroke (mainly the ischemic type)
- Peripheral vascular disease, which contributes to intermittent claudication (exertion-related foot pain) as well as diabetic foot.
- Diabetic myonecrosis ('muscle wasting')

### **Heart Disease and Stroke**

Heart attacks account for 60 % and strokes for 25 % of death in patient with diabetes. Heart disease mainly occurs in diabetic patients with concurrent hypertension and hyperlipidemia. Diabetes affects the heart in many way both type I and II diabetes speed the progression of atherosclerosis and impaired nerve function. Carotid artery stenosis does not occur more often in diabetes, and there appears to be a lower prevalence of abdominal aortic aneurysm. However, diabetes does cause higher morbidity, mortality and operative risks with these conditions (35).

Diabetes itself is a risk factor for heart disease and stroke. Also, many people with diabetes have other conditions that increase their chance of developing heart disease and stroke. These conditions are called risk factors. One risk factor for heart disease and stroke is **having a family history of heart disease**. If one or more members of your family had a heart attack at an early age (before age 55 for men or 65 for women), you may be at increased risk.

You can't change whether heart disease runs in your family, but you can take steps to control the other risk factors for heart disease listed here:

**Having central obesity.** Central obesity means carrying extra weight around the waist, as opposed to the hips. A waist measurement of more than 40 inches for men and more than 35 inches for women means you have central obesity. Your risk of heart disease is higher because

abdominal fat can increase the production of LDL (bad) cholesterol, the type of blood fat that can be deposited on the inside of blood vessel walls.

- **Having abnormal blood fat (cholesterol) levels.**
  - LDL cholesterol can build up inside your blood vessels, leading to narrowing and hardening of your arteries—the blood vessels that carry blood from the heart to the rest of the body. Arteries can then become blocked. Therefore, high levels of LDL cholesterol raise your risk of getting heart disease.
  - Triglycerides are another type of blood fat that can raise your risk of heart disease when the levels are high.
  - HDL (good) cholesterol removes deposits from inside your blood vessels and takes them to the liver for removal. Low levels of HDL cholesterol increase your risk for heart disease.
- **Having high blood pressure.** If you have high blood pressure, also called hypertension, your heart must work harder to pump blood. High blood pressure can strain the heart, damage blood vessels, and increase your risk of heart attack, stroke, eye problems, and kidney problems.
- **Smoking.** Smoking doubles your risk of getting heart disease. Stopping smoking is especially important for people with diabetes because both smoking and diabetes narrow blood vessels. Smoking also increases the risk of other long-term complications, such as eye problems. In addition, smoking can damage the blood vessels in your legs and increase the risk of amputation.

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