DIABETES EPIDEMIC IN INDIA: RISK FACTORS, SYMPTOMS AND TREATMENT

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ABSTRACT

Diabetes is a metabolism disorder in which the pancreas in the human body fails to produce insulin, or is unable to use the insulin produced in an effective manner. Most of the food we eat is broken into glucose, which is a form of sugar in the blood. When the food we eat is digested, the glucose enters our blood stream and is the main source of energy for the human body. But this glucose cannot enter our cells without sufficient insulin being present in our body. Insulin is a hormone produced by the pancreas and is needed to convert sugar, starch and other food into energy. After eating, the pancreas automatically releases the required amount of insulin to move the glucose present in our blood to our cells to regulate our blood sugar level. Insufficient secretion of insulin by the pancreas results in excess glucose levels in the blood stream, resulting in diabetes, which eventually damages various organs in the body..India has 61 million diabetics between 20-79 years according to the International Diabetes Federation. By 2030, this figure is estimated to go up to 101.1 million. President of the International Diabetes Federation Professor Jean Claude Mbanya said, 'Major number of diabetics are in the middle and low income countries.In fact by 2030, according to the estimates, 8.4 per cent of India's adult population will have diabetes.

Key words: Diabetes, Insulin, Sulfonyl ureas, Biguanides, Thiazolidenediones

INTRODUCTION

Diabetes is a disease in which your blood glucose, or sugar, levels are too high. Glucose comes from the foods you eat. Insulin is a hormone that helps the glucose get into your cells to give them energy. With type 1 diabetes, your body does not make insulin. With type 2 diabetes, the more common type, your body does not make or use insulin well. Without enough insulin, the glucose stays in your blood. Over time, having too much glucose in your blood can cause serious problems. It can damage your eyes, kidneys, and nerves. Diabetes can also cause heart disease, stroke and even the need to remove a limb. Pregnant women can also get diabetes, called gestational diabetes. A blood test can show if you have diabetes. Exercise, weight control and sticking to your meal plan can help control your diabetes. You should also monitor your glucose level and take medicine if prescribed. A person with diabetes has no control over his blood sugar as his body either does not produce enough insulin, or produces no insulin or has cells that do not respond effectively to the insulin produced by the pancreas. This leads to too much glucose level in the blood stream which eventually damages various organs in the body. Persons suffering from diabetes show symptoms like fatigue, hazy vision, excessive thirst, weight loss, frequent urination and increase in appetite**.** Diabetes has emerged as a major healthcare problem in India. According to Diabetes Atlas published by the International Diabetes Federation (IDF), there were an estimated 40 million persons with diabetes in India in 2007 and this number is predicted to rise to almost 70 million people by 2025. The countries with the largest number of diabetic people will be India, China and USA by 2030. It is estimated that every fifth person with diabetes will be an Indian. Due to these sheer numbers, the economic burden due to diabetes in India is amongst the highest in the world. The real burden of the disease is however due to its associated complications which lead to increased morbidity and mortality. WHO estimates that mortality from diabetes, heart disease and stroke costs about $210 billion in India in the year 2005. Much of the heart disease and stroke in these estimates was linked to diabetes. WHO estimates that diabetes, heart disease and stroke together will cost about $ 333.6 billion over the next 10 years in India alone.

2. Current Status of Diabetes: In 2006, according to the World Health Organization, at least 171 million people worldwide suffer from diabetes. Its incidence is increasing rapidly, and it is estimated that by the year 2030, this number will double. Diabetes mellitus occurs throughout the world, but is more common (especially type 2) in the more developed countries. The greatest increase in prevalence is, however, expected to occur in Asia and Africa, where most patients will likely be found by 2030.

The increase in incidence of diabetes in developing countries follows the trend of urbanization and lifestyle changes, perhaps most importantly a "Western-style" diet. This has suggested an environmental (i.e.,

dietary) effect, but there is little understanding of the mechanism(s) at present, though there is much speculation, some of it most compellingly presented. Diabetes is in the top 10, and perhaps the top 5, of the most significant diseases in the developed world, and is gaining in significance there and elsewhere (see big killers). For at least 20 years, diabetes rates in North America have been increasing substantially. In 2005 there are about 20.8 million people with diabetes in the United States alone. According to the American Diabetes Association, there are about 6.2 million people undiagnosed and about 41 million people that would be considered prediabetic. However, the criteria for diagnosing diabetes in the USA means that it is more readily diagnosed than in some other countries. The Centers for Disease Control has termed the change an epidemic.

The National Diabetes Information Clearinghouse estimates that diabetes costs $132 billion in the United States alone every year. About 5%–10% of diabetes cases in North America are type 1, with the rest being type 2. The fraction of type 1 in other parts of the world differs; this is likely due to both differences in the rate of type 1 and differences in the rate of other types, most prominently type 2. Most of this difference is not currently understood. The American Diabetes Association point out the 2003 assessment of the National Center for Chronic Disease Prevention and Health Promotion (Centers for Disease Control and Prevention) that 1 in 3 Americans born after 2000 will develop diabetes in their lifetime. According to the American Diabetes Association, approximately 18.3% (8.6 million) of Americans age 60 and older have diabetes. Diabetes mellitus prevalence increases with age, and the numbers of older persons with diabetes are expected to grow as the elderly population increases in number. The National Health and Nutrition Examination Survey (NHANES III) demonstrated that, in the population over 65 years old, 18% to 20% have diabetes, with 40% having either diabetes or its precursor form of impaired glucose tolerance.

3. General consideration: Diabetes mellitus-often simply diabetes, is a syndrome characterized by disordered metabolism and inappropriately high blood sugar (hyperglycemia) resulting from either low levels of the hormone insulin or from abnormal resistance to insulin's effects coupled with inadequate levels of insulin secretion to compensate. The characteristic symptoms are excessive urine production (polygraph), excessive thirst and increased fluid intake (polydipsia), and blurred vision; these symptoms are likely absent if the blood sugar is only mildly elevated.

Most of the food we eat is broken down by the digestive juices into a simple sugar called glucose. Glucose is the main source of fuel for the body. After digestion, the glucose passes into our bloodstream where it is available for body cells to use for growth and energy. For the glucose to get into the cells, insulin must be present. Insulin is a hormone produced by the pancreas, a large gland behind the stomach.

When we eat, the pancreas is supposed to automatically produce the right amount of insulin to move the glucose from our blood into our cells. If your body doesn't make enough insulin or the insulin doesn't work right, the sugar cannot get into the cells. It stays in the blood. This makes your blood sugar level high, causing you to have diabetes. As a result, glucose builds up in the blood, overflows into the urine, and passes out of the body. Thus, the body loses its main source of fuel even though the blood contains large amounts of glucose. (www.google.com)

The World Health Organization recognizes three main forms of diabetes mellitus**:** type 1, type 2, and gestational diabetes (occurring during pregnancy), which have different causes and population distributions. While, ultimately, all forms are due to the beta cells of the pancreas being unable to produce sufficient insulin to prevent hyperglycemia, the causes are different. Type 1 diabetes is usually due to autoimmune destruction of the pancreatic beta cells. Type 2 diabetes is characterized by insulin resistance in target tissues, this causes a need for abnormally high amounts of insulin and diabetes develops when the beta cells cannot meet this demand. Gestational diabetes is similar to type 2 diabetes in that it involves insulin resistance; the hormones of pregnancy can cause insulin resistance in women genetically predisposed to developing this condition.

Gestational diabetes typically resolves with delivery of the child, however types 1 and 2 diabetes are chronic conditions. All types have been treatable since insulin became medically available in 1921. Type 1 diabetes, in which insulin is not secreted by the pancreas, is directly treatable only with injected or inhaled insulin, although dietary and other lifestyle adjustments are part of management. Type 2 may be managed with a combination of dietary treatment, tablets and injections and, frequently, insulin supplementation. While insulin was originally produced from natural sources such as porcine pancreas, most insulin used today is produced through genetic engineering, either as a direct copy of human insulin, or human insulin with modified molecules that provide different onset and duration of action. Insulin can also be delivered continuously by a specialized pump which subcutaneously provides insulin through a changeable catheter.

Diabetes can cause many complications. Acute complications (hypoglycemia, ketoacidosis or nonketotic hyperosmolar coma) may occur if the disease is not adequately controlled. Serious long-term complications include cardiovascular disease (doubled risk), chronic renal failure, retinal damage (which can lead to blindness), nerve damage (of several kinds), and micro vascular damage, which may cause impotence and poor healing. Poor healing of wounds, particularly of the feet, can lead to gangrene, which may require amputation. Adequate treatment of diabetes, as well as increased emphasis on blood pressure control and lifestyle factors (such as not smoking and keeping a healthy body weight), may improve the risk profile of most aforementioned complications. In the developed world, diabetes is the most significant cause of adult blindness in the non-elderly, the leading cause of non-traumatic amputation in adults, and diabetic nephropathy is the main illness requiring renal dialysis in the United States.

4. Diagnosis: The diagnosis of type 1 diabetes and many cases of type 2, is usually prompted by recent-onset symptoms of excessive urination (polyuria) and excessive thirst (polydipsia), and often accompanied by weight loss. These symptoms typically worsen over days to weeks; about a quarter of people with new type 1 diabetes have developed some degree of diabetic ketoacidosis by the time the diabetes is recognized. The diagnosis of other types of diabetes is usually made in other ways. These include ordinary health screening; detection of hyperglycemia during other medical investigations; and secondary symptoms such as vision changes or unexplainable fatigue. Diabetes is often detected when a person suffers a problem that is frequently caused by diabetes, such as a heart attack, stroke, neuropathy, poor wound healing or a foot ulcer, certain eye problems, certain fungal infections, or delivering a baby with macrosomia or hypoglycemia.

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

- Fasting plasma glucose level at or above 126 mg/dL (7.0 mmol/l).
- Plasma glucose at or above 200 mg/dL (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 (11.1 mmol/l).

A positive result, in the absence of clinical symptoms of diabetes, should be confirmed by another of the above-listed methods on a different day. Most physicians prefer to measure a fasting glucose level because of the ease of measurement and the considerable time commitment of formal glucose tolerance testing, which takes two hours to complete. According to the current definition, two fasting glucose measurements above 126 mg/dL (7.0 mmol/l) are considered diagnostic for diabetes mellitus.

Patients with fasting glucose levels between 110 and 125 mg/dL (6.1 and 7.0 mmol/l) are considered to have impaired fasting glycemia. Patients with plasma glucose at or above 140 mg/dL or 7.8 mmol/l two hours after a 75 g oral glucose load are considered to have impaired glucose tolerance. Of these two pre-diabetic states, 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 is considered 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.

5. Classification of Diabetes: The term ***diabetes***, without qualification, usually refers to diabetes mellitus, which is associated with excessive sweet urine, (known as 'glycosuria') but there are several rarer conditions also named diabetes. The most common of these is diabetes insipidus in which the urine is not sweet (insipidus meaning "without taste" in Latin); it can be caused by either kidney (nephrogenic DI) or pituitary gland (central DI) damage. The principal two idiopathic forms of diabetes mellitus are known as types 1 and 2. The term "type 1 diabetes" has universally replaced several former terms, including childhood-onset diabetes, juvenile diabetes, and insulin-dependent diabetes (IDDM). Likewise, the term "type 2 diabetes" has replaced several former terms, including adult-onset diabetes, obesity-related diabetes, and non-insulin-dependent diabetes (NIDDM). Beyond these two types, there is no agreed-upon standard nomenclature. Various sources have defined "type 3 diabetes"

as, among others, gestational diabetes,. There is also maturity onset diabetes of the young (MODY) which is a single gene disorder with strong family history that presents as type 2 diabetes before 30 years of age.

Type 1 diabetes mellitus: Type 1 diabetes mellitus **is** characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas, leading to a deficiency of insulin. The main cause of this beta cell loss is a T-cell mediated autoimmune attack. There is no known preventative measure that can be taken against type 1 diabetes, which comprises up to 10% of diabetes mellitus cases in North America and Europe (though this varies by geographical location). Most affected people are otherwise healthy and of a healthy weight when onset occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. Type 1 diabetes can affect children or adults but was traditionally termed "juvenile diabetes" because it represents a majority of cases of diabetes affecting children.(K.D.Tripathi, Clinical Pharmacology)

Type 2 Diabetes Mellitus- Type 2 diabetes mellitus is due to insulin resistance or reduced insulin sensitivity, combined with reduced insulin secretion. The defective responsiveness of body tissues to insulin almost certainly involves the insulin receptor in cell membranes. In the early stage the predominant abnormality is reduced insulin sensitivity, characterized by elevated levels of insulin in the blood. At this stage hyperglycemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver. As the disease progresses the impairment of insulin secretion worsens, and therapeutic replacement of insulin often becomes necessary.

There are numerous theories as to the exact cause and mechanism in type 2 diabetes. Central obesity (fat concentrated around the waist in relation to abdominal organs, but not subcutaneous fat) is known to predispose individuals for insulin resistance. Abdominal fat is especially active hormonally, secreting a group of hormones called adipokines that may possibly impair glucose tolerance. Obesity is found in approximately 55% of patients diagnosed with type 2 diabetes. Other factors include aging (about 20% of elderly patients in North America have diabetes) and family history (type 2 is much more common in those with close relatives who have had it). In the last decade, type 2 diabetes has increasingly begun to affect children and adolescents, likely in connection with the increased prevalence of childhood obesity seen in recent decades in some places.

Gestational diabetes: Gestational diabetes mellitus (GDM) resembles type 2 diabetes in several respects, involving a combination of inadequate insulin secretion and responsiveness. It occurs in about 2%–5% of all pregnancies and may improve or disappear after delivery. Gestational diabetes is fully treatable but requires careful medical supervision throughout the pregnancy. About 20%–50% of affected women develop type 2 diabetes later in life.

Even though it may be transient, untreated gestational diabetes can damage the health of the fetus or mother. Risks to the baby include macrosomia (high birth weight), congenital cardiac and central nervous system anomalies, 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 profusion due to vascular impairment. Induction may be indicated with decreased placental function. A cesarean section may be performed if there is marked fetal distress or an increased risk of injury associated with macrosomia, such as shoulder dystocia.

Other types: There are several rare causes of diabetes mellitus that do not fit into type 1, type 2, or gestational diabetes; attempts to classify them remain controversial. Some cases of diabetes are caused by the body's tissue receptors not responding to insulin (even when insulin levels are normal, which is what separates it from type 2 diabetes); this form is very uncommon. Genetic mutations (autosomal or mitochondrial) can lead to defects in beta cell function. Abnormal insulin action may also been genetically determined in some cases. Any disease that causes extensive damage to the pancreas may lead to diabetes (for example, chronic pancreatitis and cystic fibrosis). Diseases associated with excessive secretion of insulin-antagonistic hormones can cause diabetes (which is typically resolved once the hormone excess is removed). Many drugs impair insulin secretion and some toxins damage pancreatic beta cells. The ICD-10 (1992) diagnostic entity, ***malnutrition-related diabetes mellitus*** (MRDM or MMDM, ICD-10 code E12), was deprecated by the World Health Organization. (KD.Tripathi, clinical pharmacology, R.S.Satoskar, et.al., pharmacology and pharmacotherapeutics,XIth edition)

6. Signs and Symptoms: The classical triad of diabetes symptoms is polyuria, polydipsia and polyphagia, which are, respectively, frequent urination; increased thirst and consequent increased fluid intake; and increased appetite. Symptoms may develop quite rapidly (weeks or months) in type 1 diabetes, particularly in children. However, in type 2 diabetes the symptoms develop much more slowly and may be subtle or completely absent. Type 1

diabetes may also cause weight loss (despite normal or increased eating) and irreducible fatigue. These symptoms can also manifest in type 2 diabetes in patients whose diabetes is poorly controlled.

When the glucose concentration in the blood is raised beyond the renal threshold, reabsorption of glucose in the proximal renal tubuli is incomplete, and part of the glucose remains in the urine (glycosuria). This increases the osmotic pressure of the urine and inhibits the reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Lost blood volume will be replaced osmotically from water held in body cells, causing dehydration and increased thirst. Prolonged high blood glucose causes glucose absorption, which leads to changes in the shape of the lenses of the eyes, resulting in vision changes. Blurred vision is a common complaint leading to a diabetes diagnosis; type 1 should always be suspected in cases of rapid vision change whereas type 2 is generally more gradual, but should still be suspected.

Patients (usually with type 1 diabetes) may also present with diabetic ketoacidosis DKA), an extreme state of metabolic dysregulation characterized by the smell of acetone on the patient's breath; a rapid, deep breathing known as Kussmaul breathing; polyuria; nausea; vomiting and abdominal pain; and any of many altered states of consciousness or arousal (such as hostility and mania or, equally, confusion and lethargy). In severe DKA, coma may follow, progressing to death. Diabetic ketoacidosis is a medical emergency and requires hospital admission. A rarer but equally severe possibility is hyperosmolar nonketotic state, which is more common in type 2 diabetes and is mainly the result of dehydration due to loss of body water. Often, the patient has been drinking extreme amounts of sugar-containing drinks, leading to a vicious circle in regard to the water loss. (Ramington-19th edition)

7. Pathophysology: Mechanism of insulin release in normal pancreatic beta cells. Insulin production is more or less constant within the beta cells, irrespective of blood glucose levels. It is stored within vacuoles pending release, via exocytosis, which is triggered by increased blood glucose levels. Insulin is the principal hormone that regulates uptake of glucose from the blood into most cells (primarily muscle and fat cells, but not central nervous system cells). Therefore deficiency of insulin or the insensitivity of its receptors plays a central role in all forms of diabetes mellitus. Much of the carbohydrate in food is converted within a few hours to the monosaccharide glucose, the principal carbohydrate found in blood and used by the body as fuel. Some carbohydrates are not so converted. Notable examples include fruit sugar (fructose), usable as cellular fuel but it is not converted to glucose, and which therefore does not participate in the insulin/glucose metabolic regulatory mechanism. Additionally, the carbohydrate cellulose (though it is actually many glucose molecules in long chains) is not converted to glucose, as humans and many animals have no digestive pathway capable of breaking up cellulose.

Insulin is released into the blood by beta cells (β-cells), found in the Islets of Langerhans in the pancreas, in response to rising levels of blood glucose after eating. Insulin is used by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage. Insulin is also the principal control signal for conversion of glucose to glycogen for internal storage in liver and muscle cells. Lowered glucose levels result both in the reduced release of insulin from the beta cells and in the reverse conversion of glycogen to glucose when glucose levels fall. This is mainly controlled by the hormone glucagons which acts in an opposite manner to insulin. Glucose thus recovered by the liver re-enters the bloodstream; muscle cells lack the necessary export mechanism.

Higher insulin levels increase many anabolic ("building up") processes such as cell growth and duplication, protein synthesis, and fat storage. Insulin (or its lack) is the principal signal in converting many of the bidirectional processes of metabolism from a catabolic to an anabolic direction, and vice versa. In particular, a low insulin level is the trigger for entering or leaving ketosis (the fat burning metabolic phase). If the amount of insulin available is insufficient, if cells respond poorly to the effects of insulin (insulin insensitivity or resistance), or if the insulin itself is defective, then glucose will not be absorbed properly by those body cells that require it nor will it be stored appropriately in the liver and muscles. The net effect is persistent high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as acidosis. (Remington 19th Ed.)

8. Diabetic Complication: Diabetes is associated with long-term (developing over many years) complications that affect almost every major part of the body. Diabetes causing stiffening and narrowing of very small blood vessels carrying oxygen to body cells and organs. Diabetes contributes to:

- blindness
- heart disease
- strokes
- kidney failure

- amputations
- nerve damage

Uncontrolled diabetes can complicate pregnancy, and birth defects are more common in babies born to women with diabetes. Class of diabetic complication can be categorized as follows;

Acute complications:

Diabetic ketoacidosis: Diabetic ketoacidosis (DKA) is an acute and dangerous complication that is always a medical emergency. Lack of insulin causes the liver to turn fat into ketone bodies, a fuel mainly used by the brain. Elevated levels of ketone bodies in the blood decrease the blood's pH, leading to most of the symptoms of DKA. On presentation at hospital, the patient in DKA is typically dehydrated and is breathing rapidly and deeply. Abdominal pain is common and may be severe. The level of consciousness is typically normal until late in the process, when lethargy may progress to coma. Ketoacidosis can become severe enough to cause hypotension, shock, and death. Analysis of the urine reveals significant levels of ketone bodies present (which spill over from the blood when the kidneys filter blood). Prompt proper treatment usually results in full recovery, though death can result from inadequate or delayed treatment, or from complications. Ketoacidosis is much more common in type 1 diabetes than type 2.

Nonketotic hyperosmolar coma: The hyperosmolar nonketotic state (HNS) is an acute complication with many symptoms in common with DKA, but an entirely different cause and different treatment. In a person with very high blood glucose levels (usually considered to be above 300 mg/dl (16 mmol/l)), water is drawn out of cells into the blood by osmosis and the kidneys dump glucose into the urine. This results in loss of water and 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 lead to dehydration. The body's cells become progressively dehydrated as water is taken from them and excreted. Electrolyte imbalances are also common and dangerous. As with DKA, urgent medical treatment is necessary, especially volume replacement. Lethargy may ultimately progress to a coma, which is more common in type 2 diabetes than type 1.

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, 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 or incorrectly timed exercise (exercise decreases insulin requirements) or not enough food (specifically glucose-producing carbohydrates). 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.

Chronic complications

Vascular disease: Chronic elevation of blood glucose level leads to damage of blood vessels (angiopathy). The endothelial cells lining the blood vessels take in more glucose than normal, since they don't depend on insulin. They then form more surface glycoproteins than normal, and cause the basement membrane to grow thicker and weaker. In diabetes, the resulting problems are grouped under "micro vascular disease" (due to damage to small blood vessels) and "macro vascular disease" (due to damage to the arteries).

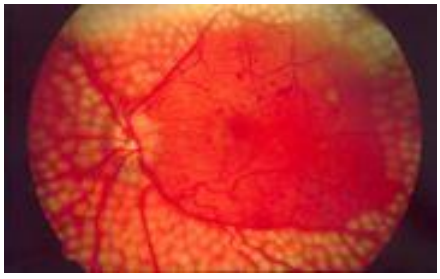

Image of fundus showing scatter laser surgery for diabetic retinopathy

The damage to small blood vessels leads to a microangiopathy, which can cause one or more of the following:

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.(Ramington-19th ed.)

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. Diabetic amyotrophy is muscle weakness due to neuropathy.(Ramington-19th ed.)

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.

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 leg and foot pain) as well as diabetic foot. Diabetic myonecrosis ('muscle wasting')

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 why diabetics are prone to leg and foot infections and why it takes longer for them to heal from leg and foot wounds. It is the most common cause of adult amputation, usually of toes and or feet, in the developed world.

9. Treatment and management: Diabetes mellitus is currently a chronic disease, without a cure, and medical emphasis must necessarily be on managing/avoiding possible short-term as well as long-term diabetes-related problems. There is an exceptionally important role for patient education, dietetic support, sensible exercise, self glucose monitoring, with the goal of keeping both short-term blood glucose levels, and long term levels as well, within acceptable bounds. Careful control is needed to reduce the risk of long term complications. This can be achieved with combinations of diet, exercise and weight loss (type 2), various oral diabetic drugs (type 2 only), and insulin use (type 1 and increasingly for type 2 not responding to oral medication).

Insulin: Insulin is the main hormone controlling intermediary, having actions on liver, muscle and fats. Its overall effect is to conserve fuel by facilitating the uptake and storage of glucose, amino acids and fats after a meal. Actually, it reduces blood sugar. Consequently a fall in plasma insulin increases blood glucose. Insulin is essential for the treatment of type-1 diabetes. Diet is the corner stone, combined with increase exercise. Oral agents are used to control symptoms from hyperglycemia, as well as to limit microvascular complications. Insulin is often needed as increasing age. Dietary measures to prevent atheromatous disease (specially limitations of saturated fat consumption) are crucial. Insulin for clinical use was once either porcine or bovine but is now almost entirely human made by recombinant DNA technology.

Preparation of Insulin: Diabetes mellitus may be managed from a choice of four types of insulin (animal or human) preparations, having :(db, ins, oada, obes)

- Short duration of action (and rapid onset): soluble insulin (natural insulin). The most recent addition to this class of insulin, insulin lispro (Humalog), is modified human insulin in which the reversing of two amino acids has resulted in a very rapid onset of action (within 15 mins. Of injection). Insulin aspart is similar.
- Intermediate duration of action (and slower onset): Isophane Insulin, a suspension with protamine; Insulin Zinc suspensions, amorphous or a mixture and crystalline.
- Longer duration of action: Insulin Zinc suspension, crystalline or Protamine Zinc Insulin (Insulin in suspension with both Zinc and Protamine).
- A mixture of soluble and isophane insulin, officially called biphasic insulin.

Mechanism of Action: Insulin binds to specific receptor on the surface of its target cells. Receptor is a large transmembrane glycoprotein complex consisting of two α- and two β-subunits. The α-subunits are entirely Extra cellular and each carries an insulin binding site, where as the β-subunits are transmembrane proteins with tyrosine kinase activity. This activity is suppressed by the α-subunits, but insulin binding causes a conformational change that depresses (activates) the tyrosine kinase activity of the β-subunits, which act on each other (autophosphorylation) and on other target proteins. At concentration of insulin that produces maximum effects, less than 10 percent of receptors are occupied. Occupied receptors aggregate into clusters, which are sub sequentially vesicles, resulting in down regulation. Internalized receptor is degraded in lysozomes, but the receptors are recycled to the plasma membrane.

Adverse effects: The main undesirable effect of insulin is hypoglycemia. This is common and, if very severe, can cause brain damage. Rebound hyperglycemia ('Somogyi effect') can fallow insulin-induced hypoglycemia, because of the release of counter regulatory hormones. Allergy to human insulin is unusual but can occur. It may take the form of local or systemic reaction. Insulin resistance as a consequence of antibody formation is rare.(Rang&Dale,2003)

Oral Hypoglycemic Agents

Sulfonylureas:

Mechanism of Action: Sulfonylureas cause hypoglycemia by stimulating insulin release from pancreatic β cells. Their effects in the treatment of diabetes, however, are more complex. The acute administration of sulfonylurea to type 2 diabetes mellitus patients increases insulin release from the pancreas. Sulfonylureas also my further increase insulin levels by reducing hepatic clearance of the hormone. In the initial months of the sulfonylurea treatment, fasting plasma insulin level and insulin responses to oral glucose challenges are increased. With chronic administration, circulating insulin levels decline to those that existed before treatment, but, despite this reduction in insulin levels, reduced plasma glucose levels are maintained. The effects of the sulfonylurea are initiated by binding to and blocking an ATP-sensitive K^+ conductance causes membrane depolarization and influx of Ca^{2+} through voltage sensitive Ca^{2+} channels.

Adverse Reactions: Adverse effects of sulfonylurea are infrequent, occurring in about 4% of patients taking first-generation drugs and perhaps slightly less often in patients receiving second-generation drugs. Not unexpectedly, sulfonylurea my cause hypoglycemic reactions, including coma. Other side effects of sulfonylurea may include nausea, vomiting, cholestatic jaundice, hemolytic anemias and dermatological reactions.(Goodman&Gilman,10^{th} ed.)

Other Drugs that Stimulate Insulin Secretion: Several other drugs that lack the sulphonylureas urea moiety but stimulate insulin secretion have recently been developed. This includes repaglinide and nateglinide. This act, like the sulphonylureas, by blocking the sulphonylureas receptors on K_{ATP} channels in pancreatic β-cell membranes.

II. Biguanides: Metformin is the only drug of this class presently available.

Mechanism of Action: Biguanides lower blood glucose. Their mechanisms are complex and incompletely understood. They increase glucose uptake and utilization in skeletal muscle (there by reducing insulin resistance) and reduce hepatic glucose production (gluconeogenesis). Metformin, as well as lowering blood glucose, additionally reduces low density and very low-density lipoproteins (LDL and VLDL respectively).

Adverse Effects: The commonest unwanted effects of metformin are dose related gastrointestinal disturbances (e.g. anorexia, diarrhea, nausea). Lactic acidosis is a rare but potentially fatal toxic effect. (Goodman&Gilman, 10^{th} Ed.)

III. Thiazolidenediones (Glitazones): Thiazolidenediones reduce hepatic output and increase glucose uptake in muscle, enhancing the effectiveness of endogenous insulin and reducing the amount of exogenous insulin needed to maintain given level of blood glucose by approximately 30%. The reduction in blood glucose level often accompanied by reductions in circulating insulin and free fatty acids (FFA). Triglycerides may decline, while LDL and HDL are either unchanged or slightly increased with little alteration in LDL to HDL ratio. The Proportion of small dense LDL particles is reduced.

Mechanism of Action: Thiazolidenediones bind to nuclear receptor called the Peroxisome Proliferator-activated receptor-gamma (PPARγ), which is complexed with retinoid X recepor. PPARγ occurs mainly in adipose tissue, but also in muscle and liver. I mediates differrentiation of adipocytes, increase lipogenesis, and enhance uptake of fatty acids and glucose. Thiazolidenedions are exogenous agonist. They change the PPARγ-RXR complex so that it binds DNA and promotes transcription of several genes with products that are important in insulin signaling, including lipoprotein lipase, fatty acids transporter protein, adipocytes fatty acid-binding protein, Glut-4, Phosphoenolpyruvate carboxykinase, malic enzyme and others.

Adverse Effects: Serious hepatotoxicity is associated with ciglitazones. The commonest unwanted effects of roziglitazones and piogliatzones are weight gain and fulid retention. Fluid retention is a substantial concern since it can precipitate heart failure, which contraindicates their use. Symptoms of uncertain cause including headache, fatigue, which contraindicates their use. Symptoms of uncertain cause including headache, fatigue, and gastrointestinal disturbances have also been reported. Thizolidinediones are contraindicated in pregnant and breast-feeding women and in children. (Charles R. Craig, modern pharmacology 4^{th} Ed.)

IV. α-Glucosidase Inhibitors: Acarbose, an inhibitor of intestinal α-glucosidase, is used in type 2 patients inadequately controlled by diet with or without other agents. It delays carbohydrates absorption, reducing

postprandial increase in blood glucose. The commonest adverse effects are related to its main action and consist of flatulence, loose stools or diarrhoea and abdominal pain and bloating.

Potential new antidiabetic drugs: Several agents are currently being studied including ά antagonists and inhibitors of fatty acid oxidation. Lipolysisin fat cell is controlled by adrenoreceptors of β_3 subtype. The possibility of using selective β_{3-} agonists, currently in development, in the treatment of obese patients with type 2 diabetes is being investigated. There is great interest in inhibitors of protein kinase C (e.g. LY33353, a specific inhibitor specific for the β Isofrom), because of evidence implicating activation of this pathway in the development of vascular complications.(Rang & Dale)

10. Current Diabetes Research:

In recent years, advances in diabetes research have led to better ways to manage diabetes and treat its complications. Major advances include:

- New forms of purified insulin, such as human insulin produced through genetic engineering.
- Better ways for doctors to monitor blood glucose levels and for people with diabetes to test their own blood glucose levels at home.
- Development of external and implantable insulin pumps that deliver appropriate amounts of insulin, replacing daily injections.
- Laser treatment for diabetic eye disease, reducing the risk of blindness.
- Successful transplantation of kidneys in people whose own kidneys fail because of diabetes.
- Better ways of managing diabetic pregnancies, improving chances of successful outcomes.
- New drugs to treat type 2 diabetes and better ways to manage this form of diabetes through weight control.
- Evidence that intensive management of blood glucose reduces and may prevent development of microvascular complications of diabetes.
- Demonstration that antihypertensive drugs called ACE-inhibitors prevents or delay kidney failure in people with diabetes.

Government agencies that sponsoring diabetes programs, as well as collecting and analyzing statistics about diabetes, include the National Institute of Diabetes and Digestive and Kidney Diseases (NIDDK), the Centers for Disease Control and Prevention (CDC), the Indian Health Service, the Health Resources and Services Administration, the Bureau of Veterans Affairs, and the Department of Defense. University research centers and hospitals throughout the United States are also involved in diabetes research.

Many organizations outside of the Government support diabetes research and education activities. These organizations include the American Diabetes Association, the Juvenile Diabetes Foundation International, and the American Association of Diabetes Educators.

11. Potential Future Treatments: In the future, it may be possible to administer insulin through nasal sprays or in the form of a pill or patch. Devices that can "read" blood glucose levels without having to prick a finger to get a blood sample are also being developed.

Researchers continue to search for the cause or causes of diabetes and ways to prevent and cure the disorder. Scientists are looking for genes that may be involved in type 2 diabetes and type 1 diabetes. Some genetic markers for type 1 diabetes have been identified, and it is now possible to screen relatives of people with type 1 diabetes to see if they are at risk for diabetes.

Transplantation of the pancreas or insulin-producing beta cells offers the best hope of cure for people with type 1 diabetes. Some pancreas transplants have been successful. However, people who have transplants must take powerful drugs to prevent rejection of the transplanted organ. These drugs are costly and may eventually cause serious health problems.

Scientists are working to develop less harmful drugs and better methods of transplanting pancreatic tissue to prevent rejection by the body. Using techniques of bioengineering, researchers are also trying to create artificial islet cells that secrete insulin in response to increased sugar levels in the blood.

For type 2 diabetes, the focus is on ways to prevent diabetes. Preventive approaches include identifying people at high risk for the disorder and encouraging them to lose weight, exercise more, and follow a healthy diet. The Diabetes Prevention Program, another new NIDDK project, will focus on preventing the disorder in high-risk populations.

CONCLUSION

The World Health Organisation (WHO) estimates that nearly 200 million people all over the world suffer from diabetes and this number is likely to be doubled by 2030. Even as nations prepare to mark World Diabetes Day on November 14, WHO says about 80% of the diabetes deaths occur in middle-income countries.In India, there are nearly 50 million diabetics, according to the statistics of the International Diabetes Federation. As the incidence of diabetes is on the rise, doctors say, there is a proportionate rise in the complications that are associated with diabetes. They point out that it is a very crucial stage and awareness on the part of people and administration about diabetes is very essential, adding that people should be made aware and educated about their health and fitness level to reduce the number of patients in India.

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