A Basic Review on Diabetes Mellitus

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Author's contribution

The sole author designed, analyzed and interpreted and prepared the manuscript.

Review Article

ABSTRACT

Diabetes mellitus (DM) is a metabolic disorder characterized by excessive glucose levels and less insulin or absent of insulin hormone in the blood circulation. Diabetes mellitus is classified into four types, namely type 1 diabetes mellitus, type 2 diabetes mellitus, gestational diabetes mellitus and juvenile diabetes mellitus. Type one diabetes mellitus is also called insulin dependent diabetes mellitus (IDDM). This diabetes mellitus is failed to produce insulin from beta cells of pancreas. Type two diabetes mellitus is also called non insulin diabetes mellitus (NIDDM). This diabetes mellitus decreases insulin secretion from beta cell of pancreas or insulin resistance. Juvenile diabetes mellitus occurs in children and gestational diabetes which occurs during pregnancy. Long standing diabetes mellitus cause formed macro and micro vascular complications. Diabetes mellitus can be managed with antidiabetic drugs, both oral and parenteral routes.

Keywords: Diabetes mellitus; pathophysiology; management.

1. INTRODUCTION

Diabetes Mellitus (DM) is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both [1]. Lack of insulin affects the metabolism of carbohydrates, protein and fat and

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cause a significant disturbance of water and electrolyte homeostasis. Death may result from acute metabolic decompensation while long standing metabolic derangement is frequently associated with permanent and irreversible functional and structural changes in the cells of the body, with those of the vascular system being particularly susceptible. These changes lead to the development of well defined clinical entities, the so called 'complications of diabetes'. The effects of diabetes mellitus include long term damage, dysfunction, failure of various organs especially the eyes, kidneys, heart and blood vessels [2] and also occur blindness, stroke and amputations [3]. Diabetes may present with characteristic symptoms such as thirst, polyuria, blurring of vision, weight loss and polyphagia and its most severe forms with ketoacidosis or nonketotic hyperosmolarity which in the absence of effective treatment leads to stupor, coma and death.

Often symptoms are not severe or may even be absent. Hyperglycemia sufficient to cause pathologic functional changes may quite often be present for a long time before the diagnosis is made. Diabetes often is discovered because of abnormal results from a routine blood or urine glucose test or because of the presence of a complication. During the evolution of type 1diabetes, for example immunologic disturbances such as islet cell or other antibodies are present and these may precede clinically apparent disease by months or even years [4].

In some families it is possible to recognize certain gene mutations that are strongly associated with certain forms of diabetes such as variations in the glucokinase gene or hepatic nuclear factor genes that cause youth or early adult onset diabetes [5]. The majority of cases of diabetes fall in to two broad etiopathologenetic categories now called Type 1 and Type 2 Diabetes mellitus [6,7]. But the extent of heterogeneity among these types remains uncertain. Because of the increasing number of forms of diabetes for which a specific aetiology can be recognized the current clinical classification proposed by the American Diabetes Association (ADA) in 1997. Type 2 Diabetes mellitus can be manage with diet and lifestyle modification [8,9]. The present review is that to know more about diabetes mellitus, its history, aetiology, pathophysiology, clinical features, investigations, complications and management of diabetes mellitus.

2. EPIDEMIOLOGY

Diabetes mellitus, a chronic metabolic noncommunicable disease (NCD), has attained epidemic proportions worldwide. As of 2018, over 400 million adults have diabetes mellitus, and this number is estimated to increase to 600 million by 2030. An estimated 16 million people in the United States are known to have diabetes, of which 1.4 million have type1 diabetes mellitus and approximately 4.5 million have type 2 diabetes mellitus [10]. The remainder numbered only in the thousands, comprise a third group that was designated as "other specific type" by American Diabetes Association [11]. These other types include disorder for which cause are known. Among these are the rare monogenic defects of either B cell function or of insulin action, primary disease of the exocrine pancreas, endocrinopathies and drug induced diabetes [12].

In India age group between 30 to 80 years are suffering from Diabetes Mellitus approximately 285 million people in worldwide (6.6%). 438 million people (7.8%) will get suffered by 2030 in India. In India more prone to gets Diabetes Mellitus in urban than rural due to lack of physical activity and dietary patterns [13-15].

3. ETIOLOGIC CLASSIFICATION OF DIABETES MELLITUS

Diabetes mellitus is classified into four types, namely gestational diabetes mellitus, juvenile diabetes mellitus, type 1 diabetes mellitus and type 2 diabetes mellitus.

3.1 Gestational Diabetes

Gestational diabetes, defined as hyperglycemia diagnosed for the first time in pregnancy, is a common problem [16,17] . It occurs in individuals who have an inherited predisposition to develop diabetes and may take the form of either type one and type two diabetes mellitus. A screening procedure for gestational diabetes mellitus involving the measurement of true venous plasma glucose concentration one hour after a 50 g oral glucose load, followed by a formal 3 hours 100 g oral glucose tolerance test in suspicious cases, has been validated but is complicated. An accurate laboratory measurement of the basal prevailing venous true plasma glucose concentration can be recommended for the following reasons:

- It is a simple test which avoids the need for special preparation and can be incorporated readily as part of routine antenatal care, thus encouraging assessment two or three times during pregnancy in all pregnant women.
- It is more physiological and relevant to the clinical problem since the prevailing maternal blood glucose concentration is the important things as far as the fetus is concerned.

Although measurements of glycated serum proteins may be more useful than Glycated haemoglobin in pregnancy.

3.2 Juvenile Diabetes

It is a chronic condition in which the pancreas produces little or no insulin. Although the percentage of cases of diabetes in children and adolescents caused by type 2 diabetes has risen in the past 1 to 2 decades, type 1 diabetes remains the most common form of diabetes mellitus in children. In the United States, the prevalence of type 1 diabetes at 18 years of age is approximately 2 to 3 per 1,000. Type 1 diabetes typically has its onset in childhood, although it can present at any age from infancy to adulthood. Recent studies have documented an increase in the incidence, both in the United States and in other western countries, with the incidence in the United States approaching 20 cases per 100,000. There are small peaks in incidence at 2 and 4 to 6 years of age and a larger peak at 10 to 14 years of age. The disease is hereditarily transferable but that does not guarantee one will or will not get the disease. An individual could carry the highest risk susceptibility genes, but any number of environmental factors could possibly offer protection or increased risk at any given time.

This classification differs considerably from the previously type one and two, which used the terms insulin dependent diabetes mellitus and non insulin dependent diabetes mellitus. These terms, however were frequently misused and at best classified patients based on treatment needs rather than on etiologic characteristics. The term type one and type two diabetes mellitus have been adopted for the most common forms of diabetes mellitus.

3.3 Type 1 Diabetes Mellitus (T1DM)

Type 1 diabetes mellitus results from autoimmune beta cell destruction, which leads to insulin deficiency. Individuals with type 1 diabetes mellitus lack immunologic markers indicative of an autoimmune destructive process of the beta cells. However, they develop insulin deficiency by unknown mechanisms and are ketosis prone. Relatively few patients with type 1 diabetes mellitus are in the type 1B idiopathic category; many of these individuals are either African American or Asian in heritage. Type 1 diabetes mellitus most commonly develops before the age of 30, an autoimmune beta cell destructive process can develop at any age. It is estimated that between 5 and 10% of individuals who develop diabetes mellitus after age 30 have type 1 diabetes mellitus [8].

3.4 Type 2 Diabetes Mellitus (T2DM)

Type 2 diabetes mellitus is a heterogeneous group of disorders characterized by variable degrees of insulin resistance, impaired insulin secretion, and increased glucose production. Distinct genetic and metabolic defects in insulin action and/or secretion give rise to the common phenotype of hyperglycemia in type 2 diabetes mellitus. Distinct pathogenic processes in type 2 diabetes mellitus have important potential therapeutic implications, as pharmacologic agents that target specific metabolic derangements have become available. Type 2 diabetes mellitus is preceded by a period of abnormal glucose homeostasis classified as impaired fasting glucose (IFG) or impaired glucose tolerance (IGT). Type 2 diabetes mellitus more typically develops with increasing age, but it also occurs in children, particularly in obese adolescents [9].

4. PATHOPHYSIOLOGY OF DIABETES MELLITUS

Type 2 diabetes mellitus is characterized by inadequate insulin secretion and insulin resistance form beta cells of pancreas. This cause increase in the breakdown of fat and decrease glucose levels in circulation, liver, muscle cells and fat cells.[18,19]

Pathophysiology of diabetes mellitus is insufficient insulin to form reduced tissue up take glucose. It formed intra cellular hypoglycaemia and extracellular hyperglycaemia. Intracellular hypoglycaemia formed the glucogenesis and gluconeogensis and break down of fats, high levels of ketones and diabetic ketoacidosis. Decrease protein synthesis are cachexia, lethargy, polyphagia, decrease gamma globulins, susceptibility to infections, impaired wound

healing. Extracellular hyperglycaemia formed hyperosomtic plasma – dehydration of cells – hyperglycaemic coma. Again extracellular hyperglycaemia – blood glucose > renal threshold – glucosuria/ urine has a high SG and osmotic dieresis (polyuria, polydipsia, hypokalaemia, hyponatraemia) [20].

4.1 Pathogenesis of Gestational Diabetes Mellitus

The endocrinology of human pregnancy involves endocrine and metabolic changes that result from physiological alterations at the boundary between mother and fetus, known as the feto placental unit (FPU), this interface is a major site of protein and steroid hormone production and secretion. Many of the endocrine and metabolic changes that occur during pregnancy can be directly attributed to hormonal signals originating from the FPU. During early pregnancy, glucose tolerance is normal or slightly improved and peripheral (muscle) sensitivity to insulin and hepatic basal glucose production is normal. These could be caused by the increased maternal estrogen and progesterone in early pregnancy which increase and promote pancreatic ß cell hyperplasia (expansion of beta cell mass in response to pregnancy) causing an increased insulin release. This explains the rapid increase in insulin level in early pregnancy, in response to insulin resistance. In the second and third trimester, the continuous increase in the feto placental factors will decrease maternal insulin sensitivity, and this will stimulate mother cells to use sources of fuels (energy) other than glucose as free fatty acids, and this will increase supply of glucose to the fetus. In the normal physiological conditions, the fetal blood glucose is 10-20% less than maternal blood glucose allowing the transport of glucose in the placenta to the fetal blood by the process of simple diffusion and facilitated transport. Therefore, glucose is the main fuel required by the developing fetus, whether as a source of energy for cellular metabolism or to provide energy for the synthesis of protein, lipids, and glycogen. During pregnancy, the insulin resistance of the whole body is increased to about three times the resistance in the non pregnant state. In general, the resistance to insulin can be characterized as pre-receptor (insulin antibodies) as in autoimmune diseases, receptor (decreased number of receptors on the cell surface) as in obesity, or post-receptor (defects in the intracellular insulin signaling pathway). In pregnancy, the decreased insulin sensitivity is best characterized by a post receptor defect resulting in the decreased ability of insulin to bring about SLC2A4 (GLUT4) mobilization from the interior of the cell to the cell surface. This could be due to increase in the plasma levels of one or more of the pregnancy associated hormones. Although, pregnancy is associated with increase in the beta cell mass and increase in insulin level throughout pregnancy but certain pregnant women are unable to up-regulate insulin production relative to the degree of insulin resistance, and consequently become hyperglycemic, developing gestational diabetes.

4.2 Pathogenesis of Type 1 Diabetes Mellitus

Type 1 diabetes mellitus develops as a result of the synergistic effects of genetic, environmental, and immunologic factors that ultimately destroy the pancreatic beta cells. The temporal development of type1 diabetes mellitus is shown schematically as a function of beta cell mass. Individuals with a genetic susceptibility have normal beta cell mass at birth but begin to lose beta cells secondary to autoimmune destruction that occurs over months to years. This autoimmune process is thought to be triggered by an infectious or environmental stimulus and to be sustained by a beta cell specific molecule. In the majority of individuals, immunologic markers appear after the triggering event but before diabetes becomes clinically overt. Beta cell mass then begins to decline, and insulin secretion becomes progressively impaired, although normal glucose tolerance is maintained. The rate of decline in beta cell mass varies widely among individuals, with some patients progressing rapidly to clinical diabetes and others evolving more slowly. Features of diabetes do not become evident until a majority of beta cells are destroyed (80%). At this point, residual functional beta cells still exist but are insufficient in number to maintain glucose tolerance. The events that trigger the transition from glucose intolerance to frank diabetes are often associated with increased insulin requirements, as might occur during infections or puberty. After the initial clinical presentation of type 1 diabetes mellitus, a "honeymoon" phase may ensue during which time glycemic control is achieved with modest doses of insulin or rarely, insulin is not needed. However, this fleeting phase of endogenous insulin production from residual beta cells disappears as the autoimmune process destroys the remaining beta cells, and the individual becomes completely insulin deficient [20].

4.3 Pathogenesis of Type 2 Diabetes Mellitus

Type 2 diabetes melllitus characterized by three pathophysiologic abnormalities: impaired insulin secretion, peripheral insulin resistance, and excessive hepatic glucose production. Obesity, particularly visceral or central (as evidenced by the hip waist ratio), is very common in type 2 diabetes mellitus. Adipocytes secrete a number of biologic products (leptin, TNF, free fatty acids, resistin, and adiponectin) that modulate insulin secretion, insulin action, and body weight and may contribute to the insulin resistance. In the early stages of the disorder, glucose tolerance remains normal, despite insulin resistance, because the pancreatic beta cells compensate by increasing insulin output. As insulin resistance and compensatory hyperinsulinemia progress, the pancreatic islets in certain individuals are unable to sustain the hyperinsulinemic state. IGT, characterized by elevations in postprandial glucose, then develops. A further decline in insulin secretion and an increase in hepatic glucose production lead to overt diabetes with fasting hyperglycemia. Ultimately, beta cell failure may ensue. Markers of inflammation such as IL-6 and C-reactive protein are often elevated in type 2 diabetes mellitus [20].

5. CLINICAL FEATURES

The clinical features of the two main types of diabetes mellitus are thirst, polyuria, nocturia and rapid weight loss are prominent in type 1 diabetes mellitus, but are often absent in patients with type 2 diabetes mellitus, many of whom are asymptomatic or have non specific complaints such as chronic fatigue and malaise. Uncontrolled diabetes is associated with an increased susceptibility to infection and patients may present with skin sepsis and genital candidiasis and complain of pruritus vulvae or balanitis.

Patients with type 1 diabetes mellitus often have no physical signs attributable to diabetes, but weight loss is common. In the fulminating case with ketoacidosis, the striking features are those of salt and water depletion with loss of skin, turgor, furred tongue and cracked lips, tachycardia, hypotension and reduced intraocular pressure. Breathing may be deep and sighing.

Physical signs in patients with type 2 diabetes mellitus at diagnosis depend on the mode of presentation. More than 70% are overweight and obesity may be central. Hypertension is present in 50% of patients with type 2 diabetes mellitus. Although hyperlipidaemia also common, skin lesions such as xanthelasma and eruptive xanthomata are relatively rare. Sometimes patients present with one or more of the long terms complications of diabetes mellitus. Patients may complain of paraesthesia, pain and muscle weakness in the legs with signs of peripheral neuropathy foot ulceration. Signs of macrovascular disease are common and may include diminished or impalpable pulses in the feet, bruits over the carotid or femoral arteries and ischaemic toes.

A few young people have a form of type 2 diabetes mellitus designated maturity onset diabetes of the young (MODY) while some middle aged and elderly patients present with typical autoimmune type 1 diabetes mellitus. Some patients with apparent type 2 diabetes have evidence of autoimmune activity against pancreatic beta cells and may have a slowly evolving variant of type 1 diabetes. Insulin deficient forms of type 2 diabetes mellitus in middle aged patients may be difficult to identify at diagnosis and classification of the type of diabetes can be difficult.

Table 1. Comparative clinical features of type 1 and type 2 diabetes mellitus

	Type 1	Type 2
Age of onset	< 40 years	> 50 years
Body weight	Normal/ low	Obese
Duration of symptoms	Weeks	Months to years
Ketonuria	Yes	No
Rapid death without treatment with insulin	Yes	No
Autoantibodies	Yes	No
Family history of diabetes	No	Yes
Diabetes complications at diagnosis	No	20%
Other autoimmune disease	Yes	No

6. COMPLICATIONS

Hypoglycaemia occurs often in diabetic patients treated with insulin but relatively infrequently in those taking a sulphonylurea drug. Morbidity of severe hypoglycaemia in diabetic patients are coma, convulsions, brain damage, impaired cognitive function, intellectual decline, vascular events transient ischaemic attack, stroke, cardiac arrhythmias, myocardial ischaemia, hypothermia and vitreous haemorrhage [21,22].

6.1 Hypoglycaemia Symptoms

Hypoglycemia is most commonly the result of taking drugs used to treat diabetes mellitus or other drugs, including alcohol. However, a number of other disorders, including end stage organ failure and sepsis, endocrine deficiencies, large mesenchymal tumors, insulinoma, and inherited metabolic disorders are also associated with hypoglycemia. Hypoglycemia is sometimes defined as a plasma glucose level 2.5 to 2.8 mmol/L (45 to 50 mg/dL). However, glucose thresholds for hypoglycaemia induced symptoms and physiologic responses vary widely, depending on the clinical setting. Therefore, an important framework for making the diagnosis of hypoglycemia is *Whipple's triad*: (1) symptoms consistent with hypoglycemia, (2) a low plasma glucose concentration, and (3) relief of symptoms after the plasma glucose level is raised. Hypoglycemia can cause significant morbidity and can be lethal, if severe and prolonged; it should be considered in any patient with confusion, altered level of consciousness or seizures.

(a) Causes: Hypoglycemia is traditionally classified as postprandial or fasting. However, in the clinical setting, hypoglycemia is most commonly a result of diabetes treatment. This topic is therefore addressed before considering the other causes of hypoglycaemia.

(b) Frequency and Impact:

Juvenile Diabetes Mellitus: Hypoglycemia is a common clinical problem in neonates, while it is less common in infants and toddlers, and is rare in older children. It can be caused by various conditions. The most common cause of mild or severe hypoglycemia in childhood is insulin treated type 1 diabetes, when there is a mismatch among food, exercise, and insulin. Many of the etiologies of hypoglycemia may carry the same consequences, complicating the causal distinction. Infants and children with asymptomatic hypoglycemia have been shown to have neurocognitive defects at the time of hypoglycemia, including impaired auditory and sensory evoked responses and impaired test performance. Long term consequences of hypoglycemia include decreased head size, lowered IQ, and specific regional brain abnormalities [23].

Type 1 Diabetes Mellitus: Were it not for hypoglycemia, diabetes would be rather easy to treat by administering enough insulin (or any effective drug) to lower plasma glucose concentrations to, or below, the normal range. Because current insulin replacement regimens are imperfect, individuals with type 1 diabetes are at ongoing risk for periods of relative hyperinsulinemia with resultant hypoglycemia. Those attempting to achieve near normal glycemic control may experience several episodes of asymptomatic or symptomatic hypoglycemia each week. Plasma glucose levels may be 2.8 mmol/L (50 mg/dL) as often as 10% of the time. Such patients suffer an average of one episode of severe, temporarily disabling hypoglycemia, often with seizure or coma, in a given year. Although seemingly complete recovery from the latter is the rule, the possibility of persistent cognitive deficits has been raised, but permanent neurologic defects are rare. About 2 to 4% of deaths associated with type 1 diabetes are estimated to be a result of hypoglycemia. Fear of hypoglycemia can also lead to disabling psychosocial morbidity.

Lack of glucagon response in type 1: For unexplained reasons, patients with type one lose their glucagon responses to hypoglycemica within a year or so after developing diabetes. These patients then rely predominantly on the sympathetic nervous system to counterregulate hypoglycemia and are at special risk in later years when aging, autonomic neuropathy or frequent hypoglycemic episodes blunt their sympathetic responses [24].

Type 2 Diabetes Mellitus: Hypoglycemia is a less frequent problem in type 2 diabetes but still occurs in those treated with insulin or sulfonylureas. Transient, mild hypoglycemia may be seen with the shorter acting sulfonylureas and repaglinide or nateglinide, which also act by enhancing insulin secretion. Patients who take the long acting sulfonylureas, chlorpropamide and glybenclamide, may experience episodes of

severe hypoglycemia that last between 24 and 36 h [25].

(c) Conventional risk factors: Insulin excess is the primary determinant of risk from iatrogenic hypoglycemia. Relative or absolute insulin excess occurs when: (1) insulin (or oral agent) doses are excessive, ill timed, or of the wrong type;(2) the influx of exogenous glucose is reduced (e.g., during an overnight fast or following missed meals or snacks);(3) insulin independent glucose utilization is increased (e.g., during exercise); (4) insulin sensitivity is increased (e.g., with effective intensive therapy, in the middle of the night, late after exercise, or with increased fitness or weight loss); (5) endogenous glucose production is reduced (e.g., following alcohol ingestion); and (6) insulin clearance is reduced (e.g., in renal failure). However, analyses of the Diabetes Control and Complications Trial (DCCT) indicate that these conventional risk factors explain only a minority of episodes of severe iatrogenic hypoglycemia; other causes are involved in the majority of episodes.

Hypoglycemic reactions, the most common complication of insulin therapy, may result from delay in taking a meal or unusual physical exertion. With more type one patients attempting "tight" control, this complication has become even more frequent. More rapid development of hypoglycemia from the effects of regular insulin causes signs of autonomic hyperactivity, both sympathetic (tachycardia, palpitations) and parasympathetic (nausea), that may progress to coma and convulsions. Symptoms are trembling, pounding heart, hunger, anxiety, confusion, drowsiness, speech difficulty, inability to concentrate, in coordination, tiredness and headache.

(d) Prevention and treatment of hypo-glycemia: Because of the potential danger of insulin induced reactions, the diabetic patient should carry packets of table sugar or a candy roll at all times for use at the onset of hypoglycemic symptoms. Tablets containing 3 g of glucose are available (Dextrose). The educated patient soon learns to take the amount of glucose needed and avoids the excess that may occur with eating candy or drinking orange juice, causing very high hyperglycemia.

All of the manifestations of hypoglycemia are rapidly relieved by glucose administration. If more severe hypoglycemia has produced unconsciousness or stupor, the treatment is 50 ml of 50% glucose solution by rapid intravenous infusion. If intravenous therapy is not available, 1 mg of glucagon injection intramuscularly will usually restore the patient to consciousness within 15 minutes to permit ingestion of sugar. If the patient is stuporous and glucagon is not available, small amounts of honey or syrup or glucose gel (15 g) can be inserted within the buccal pouch, but, in general oral feeding is contraindicated in unconscious patients. Rectal administration of syrup 930 ml per 500 ml of warm water) has been effective [26].

6.2 Microvascular Complications

6.2.1 Ocular complications

Diabetic cataracts: In diabetic cataracts occur in diabetic patients and seem to correlate with both the duration of diabetes and the severity of chronic hyperglycemia. Non enzymatic glycostylation of lens protein is twice as high in diabetic patients as in age matched non diabetic person and may contribute to the premature occurrence of cataracts [27].

(a) Diabetic retinopathy: It is three main stages of retinopathy.

Stage 1: Background or simple retinopathy: This means that tiny bulges (microaneurysms) have appeared in the blood vessels the retina, which may leak small amounts of blood. This is very common in people with diabetes.

Stage 2: Preprofliferative retinopathy: This means that more severe and widespread changes are seen in the retina, including bleeding into the retina, with arteriolar ischemia manifested as cotton wool spots and proliferative or malignant, retinopathy, consisting of newly formed vessels.

Stage 3: Proliferative retinopathy: It is a leading cause of blindness in India, particularly since it increases the risk of retinal detachment [28].

(b) Glaucoma: Glaucoma occurs in approximately 6% of persons with diabetes. It is responsive to the usual therapy for open angle diseases. Neovascularisation of the iris in diabetics can predispose to closed angle glaucoma, but this is relatively uncommon except after cataract extraction, when growth of new vessels has been known to progress rapidly,

involving the angle of the iris and obstructing outflow.

6.2.2 Diabetic nephropathy

It is as many as 3000 cases of end stage renal disease occurring each year among diabetic people in India. This is about 1/3rd of all patients being treated for end stage renal disease and represents a considerable national health expense. The cumulative incidence of nephropathy differs between the two major types of diabetes. Patients with type 1 diabetes mellitus have a 30 – 40% chance of having nephropathy after 20 years in contrast to the much lower frequency in type 2 diabetes mellitus patients [29].

(a) **Microalbuminuria:** Using sensitive radio-immunoassay methods of detecting small amounts of urinary albumin have permitted detection of microgram concentrations in contrast to the less sensitive dipstick strips, whose minimal detection limit is 0.3 – 0.5%. Progressive diabetic nephropathy consists of proteinuria of varying severity occasionally leading to nephritic syndrome with hypoalbuminemia, oedema and an increase in circulating LDL cholesterol as well as progressive azotemia [29].

(b) **End stage renal disease (ESRD):** End stage renal disease represents a clinical state or condition in which there has been an irreversible loss of endogenous renal function, of a degree sufficient to render the patient permanently dependent upon renal replacement therapy (dialysis or transplantation) in order to avoid life threatening uremia. Uremia is the clinical and laboratory syndrome, reflecting dysfunction of all organ systems as a result of untreated or undertreated acute or chronic renal failure. Given the capacity of the kidneys to regain function following acute injury, the vast majority (90%) of patients with end stage renal disease have reached this state as a result of chronic renal disease.

6.2.3 Diabetic neuropathy

It is peripheral and autonomic neuropathy, The two most common chronic complications of diabetes are poorly understood. Peripheral neuropathy is distal symmetric polyneuropathy: This is the most common form of diabetic peripheral neuropathy where loss of function appears in a stocking glove pattern and is due to an axonal neuropathic process. Sensory involvement usually occurs first and is generally bilateral, symmetric and associated with dulled perception of vibration, pain and temperature, particularly in the lower extremities [30].

(a) **Peripheral neuropathy:** Peripheral neuropathy and autonomic neuropathy, the two most common chronic complications of diabetes mellitus.

Polyneuropathy/Mononeuropathy: The most common form of diabetic neuropathy is distal symmetric polyneuropathy. It most frequently presents with distal sensory loss. Hyperesthesia, paresthesia, and dysesthesia also occur. Any combination of these symptoms may develop as neuropathy progresses. Symptoms include a sensation of numbness, tingling, sharpness, or burning that begin in the feet and spread proximally.

Neuropathic pain develops in some of these individuals, occasionally preceded by improvement in their glycemic control. Pain typically involves the lower extremities, is usually present at rest, and worsens at night. Both an acute (lasting 12 months) and a chronic form of painful diabetic neuropathy have been described. As diabetic neuropathy progresses, the pain subsides and eventually disappears, but a sensory deficit in the lower extremities persists. Physical examination reveals sensory loss, loss of ankle reflexes, and abnormal position sense.

Mononeuropathy (dysfunction of isolated cranial or peripheral nerves) is less common than polyneuropathy in DM and presents with pain and motor weakness in the distribution of a single nerve. A vascular etiology has been suggested, but the pathogenesis is unknown. Involvement of the third cranial nerve is most common and is heralded by diplopia. Physical examination reveals ptosis and opthalmoplegia with normal pupillary constriction to light. Sometimes cranial nerves IV, VI, or VII (Bell's palsy) are affected. Peripheral mononeuropathies or simultaneous involvement of more than one nerve (mononeuropathy multiplex) may also occur.

Isolate peripheral neuropathy: It is the involvement of the distribution of only one nerve (mononeuropathy) or of several nerves (mononeuropathy multiplex) characterized by sudden onset with subsequent recovery of all or most of the function. This neruopathlolgy has been attributed to vascular ischemia or traumatic

damage. Spontaneous resolution of these ischemic neuropathies generally occurs in 6-12 weeks.

Painful diabetic neuropathy: It is hyper-sensitivity to light touch and occasionally severe burring pain, particularly at night, which can become physically and emotionally disabling. Amitriptyline, 25-75 mg at bed time has been recommended for pain associated with diabetic neuropathy.

(b) Autonomic neuropathy: In autonomic neuropathy, there is evidence of postural hypotension, decreased cardiovascular response to valsalvas maneuver, gastroparesis, alternating bouts of diarrhoea and constipation, inability to empty the bladder and impotence. Diabetic coma may lead to ketoacidemia or other complications of diabetes mellitus [30].

6.3 Macro Vascular Complication

6.3.1 Cardiovascular disease

Cardiovascular disease is increased in individuals with type 1 or type 2 diabetes mellitus. The Framingham Heart Study revealed a marked increase in peripheral arterial disease, congestive heart failure, coronary artery disease, myocardial infarction (MI), and sudden death (risk increase from one to fivefold) in diabetes mellitus. The American Heart Association recently designated diabetes mellitus as a major risk factor for cardiovascular disease (same category as smoking, hypertension, and hyperlipidemia). Type 2 diabetes patients without a prior MI have a similar risk for coronary artery related events as nondiabetic individuals who have had a prior myocardial infarction. Because of the extremely high prevalence of underlying cardiovascular disease in individual with diabetes (especially in type 2 diabetes mellitus), evidence of atherosclerotic vascular disease should be sought in an individual with diabetes who has symptoms suggestive of cardiac ischemia, peripheral or carotid arterial disease, a resting electrocardiogram indicative of prior infarction, plans to initiate an exercise program, proteinuria, or two other cardiac risk factors (ADA recommendations). The absence of chest pain ("silent ischemia") is common in individuals with diabetes, and a thorough cardiac evaluation is indicated in individual undergoing major surgical procedures. The prognosis for individual with diabetes who have coronary artery disease or myocardial infarction is worse than for nondiabetics. Coronary artery disease is more likely to involve multiple vessels in individuals with diabetes mellitus [31].

The central pathological mechanism in macrovascular disease is the process of atherosclerosis, which leads to narrowing of arterial walls throughout the body. Atherosclerosis is thought to result from chronic inflammation and injury to the arterial wall in the peripheral or coronary vascular system. In response to endothelial injury and inflammation, oxidized lipids from LDL particles accumulate in the endothelial wall of arteries. Angiotensin II may promote the oxidation of such particles. Monocytes then infiltrate the arterial wall and differentiate into macrophages, which accumulate oxidized lipids to form foam cells. Once formed, foam cells stimulate macrophage proliferation and attraction of T-lymphocytes. T-lymphocytes, in turn, induce smooth muscle proliferation in the arterial walls and collagen accumulation. The net result of the process is the formation of a lipid rich atherosclerotic lesion with a fibrous cap. Rupture of this lesion leads to acute vascular infarction. In addition to atheroma formation, there is strong evidence of increased platelet adhesion and hypercoagulability in type 2 diabetes. Impaired nitric oxide generation and increased free radical formation in platelets, as well as altered calcium regulation, may promote platelet aggregation. Elevated levels of plasminogen activator inhibitor type 1 may also impair fibrinolysis in patients with diabetes. The combination of increased coagulability and impaired fibrinolysis likely further increases the risk of vascular occlusion and cardiovascular events in type 2 diabetes. Diabetes increases the risk that an individual will develop cardiovascular disease (CVD). Although the precise mechanisms through which diabetes increases the likelihood of atherosclerotic plaque formation are not completely defined, the association between the two is profound. CVD is the primary cause of death in people with either type 1 or type 2 diabetes. In fact, CVD accounts for the greatest component of health care expenditures in people with diabetes. Among macrovascular diabetes complications, coronary heart disease has been associated with diabetes in numerous studies beginning with the Framingham study. More recent studies have shown that the risk of myocardial infarction (MI) in people with diabetes is equivalent to the risk in nondiabetic patients with a history of previous MI. These discoveries have lead to new recommendations by the ADA and American Heart Association that diabetes be

considered a coronary artery disease risk equivalent rather than a risk factor [32,33].

6.3.2 Cerebral Vascular Disease

Cerebral vascular disease occurs due to atherosclerotic changes in cerebral blood vessels. It often involves the formation of an embolus in a different location in the vascular system which then lodges in a cerebral blood vessel. The formed embolus due to blockage of blood flow to any part of the cerebral region can cause transient ischemic attacks and strokes. This pathological situation is complicated in patients with diabetes. In fact, recovery from stroke may be hampered in diabetic individual with extremely high blood glucose concentration at the time of diagnosis. Effective glycemic control is therefore vitally important in the prevention of cerebral vascular disease as a diabetic complication. Diabetes mellitus is an accepted independent risk factor for ischemic stroke, regardless of its mechanism. The prevalence of diabetes mellitus in patients with stroke is between 10% and 20% and has been increasing during the past 20 years, probably in response to rising rates of overweight and obesity in the general population. Diabetes mellitus would be an independent risk factor for the severity of cerebral small artery disease in patients with lacunar strokes [34].

7. DIAGNOSIS

Diagnostic criteria for diabetes mellitus and normality recommended by the World Health Organization (WHO) in 2006. Updated issue was reported in Year 2006*. "* Definition and diagnosis of diabetes mellitus and intermediate hyperglycemia*"* Report of a WHO∕IDF consultation is shown below Table 2. The values are based on the threshold for risk of developing vascular disease. Intermediate readings are classified as impaired glucose tolerance and indicate the need for further evaluation. If the fasting plasma glucose level is ≥7.0 mmol/l or higher on more than one occasion, future evaluation of the patient with glucose challenge is unnecessary. However, when fasting plasma glucose is less than ≥7.0 mmol/l in suspected cases, a standardized oral glucose tolerance test may be done.

7.1 Fasting Blood Glucose

It is a test to determine how much glucose is in a blood sample after an overnight fast. The test is done in the morning, before the person starts eating. The normal range for blood glucose is 70 to 100 mg/dL. Levels between 100 and 126 mg/dl are referred to as impaired fasting glucose or pre diabetes. Diabetes is typically diagnosed when fasting blood glucose levels are 126 mg/dl or higher. The glucose concentrations in whole blood (WB) and plasma (P), both prediluted with distilled water and saline, and in their protein free filtrates, are determined with the Hoffman ferricyanide method. In whole blood prediluted with distilled water the glucose concentration appears to be 13% higher than in whole blood prediluted with saline. In plasma, predilution with distilled water or saline does not result in different glucose values. Plasma glucose is significantly higher than whole blood glucose independent of the method of pretreatment. A direct relationship between the two values exists, which for protein-free filtrates is represented by Glu(P) equals 1.07 Glu(WB) + 0.11. The glucose concentrations in erythrocytes can be calculated and also correlated to plasma glucose values. A good correlation is found when protein free filtrates are used. Apparently, conversion factors from whole blood to plasma glucose may be used only in cases where samples are deproteinized [35].

Table 2. Oral glucose tolerance test: diagnostic criteria

	Plasma glucose venous (capillary)(mmol/l)
Diabetes	
Fasting	≥ 7.0 (or)
2 hours after glucose load	≥11.1
Impaired glucose tolerance	
Fasting	≥7.0 &
2 hours after glucose Load	≥7.8 & <11.1

(a) Level of criteria: In the fasting plasma glucose level is 126 mg/dL or higher on more than one occasion, future evaluation of the patient with a glucose challenge is unnecessary. However, when fasting plasma glucose is less than 126 mg/dL in suspected cases, a standardized oral glucose tolerance test may be done (Table 3). For proper evaluation of the test, the subjects should be normally active and free from acute illness. Medications that may impair glucose tolerance include diuretics, contraceptive drugs, glucocorticoids, niacin and phenytoin.

Table 3. Oral glucose tolerance test

	Normal glucose tolerance	Impaired glucose tolerance	Diabetes mellitus[1]
Fasting plasma glucose (mg/dL)	<110	110-125	≥126
Two hours after glucose load (mg/dL)	<140	≥140 but <200	≥200

[1]*A fasting plasma glucose ≥ 126mg/dL is diagnostic of diabetes if confirmed on a subsequent day*

Because of difficulties in interpreting oral glucose tolerance tests and the lack of standards related to aging, these tests are being replaced by documentation of fasting hyperglycemia [35].

7.2 Glycated Hemoglobin (Hemoglobn A1C)

Glycated hemoglobin is abnormally high in diabetics with chronic hyperglycemia and reflects their metabolic control. It is produced by nonenzymatic condensation of glucose molecules with free amino groups on the beta globin chain of hemoglobin molecule component of hemoglobin. The higher the prevailing ambient levels of blood glucose the higher will be the level of glycated hemoglobin. The major form of glycohemoglobin is termed hemoglobin A1C, which normally comprises only 4 – 6% of the total hemoglobin. The remaining glycohemoglobins (2-4% of the total) consist of phosphorylated glucose or fructose and are termed hemoglobin A1a and hemoglobin A1b. Since glycohemoglobins circulate within red blood cells whose life span lasts up to 120 days, they generally reflect the state of glycemia over the preceding 8 – 12 weeks, thereby providing an improved method of assessing diabetic control. Measurements should be made in patients with either type of diabetes mellitus at 3 to 4 month intervals so that adjustments in therapy can be made if glycohemoglobin is either subnormal or if it is more than 2% above the upper limits of normal for a particular laboratory [36].

(a) Levels of criteria: These two measurements are complementary in that recent intercurrent illnesses may impact the SMBG measurements but not the A1C. Likewise, postprandial and nocturnal hyperglycemia may not be detected by the SMBG of fasting and preprandial capillary plasma glucose but will be reflected in the A1C. In standardized assays, the A1C approximates the following mean plasma glucose values: an A1C of 6% is 7.5 mmol/L (135 mg/ dL), 7% is 9.5 mmol/L (170 mg/dL), 8% is 11.5 mmol/L (205 mg/dL), etc. [A 1% rise in the A1C translates into a 2.0-mmol/L (35 mg/dL) increase in the mean glucose.] In patients achieving their glycemic goal, the ADA recommends measurement of the A1C twice per year. More frequent testing (every 3 months) is warranted when glycemic control is inadequate, when therapy has changed, or in most patients with type 1 DM. The degree of glycation of other proteins, such as albumin, has been used as an alternative indicator of glycemic control when the A1C is inaccurate (hemolytic anemia, hemoglobinopathies). The fructosamine assay (measuring glycated albumin) reflects the glycemic status over the prior 2 weeks. Current consensus statements do not favour the use of alternative assays of glycemic control, as there are no studies to indicate whether such assays accurately predict the complications of diabetes mellitus [36].

(b) Serum Fructosamine: Serum fructosamine is formed by nonenzymatic glycosylation of serum proteins (predominantly albumin). Since serum albumin has a much shorter half life than hemoglobin, serum fructosamine generally reflects the state of glycemic control for only the preceding two weeks. Normal values vary in relation to the serum albumin concentration and are 1.5 – 2.4 mmol/L when the serum albumin level is 5 g/dL [37].

7.3 Other Detected in Diabetes Mellitus

(a) Urinalysis: Testing the urine for glucose is the usual procedure for detecting diabetes, using sensitive glucose specific dipstick methods. If possible, the test for urinary glucose should be performed on urine passed 1-2 hours after a meal since this will detect more cases of diabetes than a fasting urine specimen.

(b) Levels of criteria detected in diabetes ketoacidosis (DKA): Diabetes ketoacidosis is crucial and allows for prompt initiation of therapy. Diabetes ketoacidosis is characterized by hyperglycemia, ketosis, and metabolic

acidosis (increased anion gap) along with a number of secondary metabolic derangements. Occasionally, the serum glucose is only minimally elevated. Serum bicarbonate is frequently 10 mmol/L, and arterial pH ranges between 6.8 and 7.3, depending on the severity of the acidosis. Despite a total body potassium deficit, the serum potassium at presentation may be mildly elevated, secondary to the acidosis. Total body stores of sodium, chloride, phosphorous, and magnesium are also reduced in diabetes ketoacidosis but are not accurately reflected by their levels in the serum because of dehydration and hyperglycemia. Elevated blood urea nitrogen (BUN) and serum creatinine levels reflect intravascular volume depletion. Interference from acetoacetate may falsely elevate the serum creatinine measurement. Leukocytosis, hypertriglyceridemia, and hyperlipoproteinemia are commonly found as well. Hyperamylasemia may suggest a diagnosis of pancreatitis, especially when accompanied by abdominal pain. However, in DKA the amylase is usually of salivary origin and thus is not diagnostic of pancreatitis. Serum lipase should be obtained if pancreatitis is suspected.

The measured serum sodium is reduced as a consequence of the hyperglycemia [1.6 mmol/L (1.6 meq) reduction in serum sodium for each 5.6 mmol/L (100 mg/dL) rise in the serum glucose]. Normal serum sodium in the setting of DKA indicates a more profound water deficit. In "conventional" units, the calculated serum osmolality [2 X(serum sodium+ serum potassium)+ plasma glucose (mg/dL)/18 + BUN/2.8] is mildly to moderately elevated, though to a lesser degree than that found in Hyperosmolar hyperglycemic nonketotic state.

(c) Hyperosmolar: The marked hyperglycemia [plasma glucose may be 55.5 mmol/L (1000 mg/dL)], hyperosmolality (350 mosmol/L), and prerenal azotemia. The measured serum sodium may be normal or slightly low despite the marked hyperglycemia. The corrected serum sodium is usually increased [add 1.6 mEq to measured sodium for each 5.6 mmol/L (100 mg/dL) rise in the serum glucose]. In contrast to DKA, acidosis and ketonemia are absent or mild. A small anion gap metabolic acidosis may be present secondary to increased lactic acid. Moderate ketonuria, if present, is secondary to starvation.

(d) Coma: Glycosuria of 4+ and strong ketonuria with hyperglycemia, ketonemia, low arterial blood pH and low plasma bicarbonate are typical of diabetic ketoacidosis. Serum potassium I soften elevated despite total body potassium depletion resulting from protracted Polyuria or vomiting. Elevation of serum amylase is common but often represents salivary as well as pancreatic amylase. Leukocytosis as high as 25,000/µL with a left shift may occur with or without associated infection (Table 4).

(e) Lipoprotein abnormalities: In type one diabetes mellitus, moderately deficient control of hyperglycemia is associated with only a slight elevation of LDL, cholesterol and serum triglycerides and little if any changes in HDL cholesterol. Once the hyperglycemia is corrected, lipoprotein levels are generally normal. In T1DM or T2DM, the total plasma cholesterol and triglycerides are usually within normal limits when the blood glucose is controlled. Marked hypertriglyceridemia can develop with loss of glycemic control and is often due to superimposed genetic abnormalities in lipoprotein metabolism. Tight control in IDDM usually reduces LDL and VLDL to normal levels and may raise HDL above the normal range. Low HDL cholesterol and mild to moderate elevations of VLDL triglyceride are common in NIDDM if obesity or proteinuria is also present. Both HDL and LDL may be smaller and more dense and may be enriched with triglyceride as compared with cholesterol. These abnormalities may require weight loss for control. The increased incidence of cardiovascular disease in diabetes is unexplained but is amplified by the well defined cardiovascular risk factors. The new American Diabetes Association guidelines call for treatment of high triglycerides and LDL cholesterol to be aggressively reduced. Triglycerides should be under 200 mg/dL and are considered borderline high between 200 and 400 mg/dL, and high when above 400 mg/dL. Low HDL is defined as less than 35 mg/dL. Control of obesity with diet and exercise and reduced intake of saturated fat and cholesterol are important first steps [38].

8. MANAGEMENT

8.1 Diet

A well balanced, nutritious diet remains a fundamental element of therapy. However, in more than half of cases, diabetic patients fail to follow their diet. In prescribing a diet, it is important to relate dietary objectives to the type

Table 4. Laboratory diagnosis of coma in diabetic patients

Related to DM	Glucose	Acetone	Glucose	Bicarbonate	Acetone
Hypoglycemia	0[1]	O or +	Low	Normal	0
DKA	++++	++++	High	Low	++++
Non ketotic					
Hyperglycemic Coma	++++	0	High	Normal or Low	0
Lactic acidosis	0 or +	0 or +	Normal or Low or High	Low	0 or +

[1]Leftover urine in bladder might still contain glucose from earlier hyperglycemia

of diabetes. In obese patients with mild hyperglycemia, the major goal of diet therapy is weight reduction by caloric restriction. Thus, there is less need for exchange lists, emphasis on timing of meals or periodic snacks, all of which are so essential in the treatment of insulin requiring nonobese diabetics. This type of patients represents the most frequent challenge for the clinician. Weight reduction is an elusive goal that can only be achieved by closed supervision and education of the obese patient [39-42].

8.2 ADA Recommendations

The American Diabetes Association releases an annual position statement on medical nutrition therapy that replaces the calculated ADA diet formula of the past with suggestions for an individually tailored dietary prescription based on metabolic, nutritional and life style requirements. The current recommendations for both types of diabetes continue to limit cholesterol to 300 mg daily and advise a daily protein intake of 10 – 20% of total calories [43].

9. Oral Drugs for Treating Hyperglycemia

Various drugs are effective in reducing hyperglycaemia in patients with type 2 diabetes mellitus. Although their mechanism of action is different, most depend upon a supply of endogenous insulin and they therefore have no hypoglycaemic effect in patients with type 1 diabetes. The sulphonylureas and the biguanides have been the mainstay of treatment for many years but novel agents are now available such as the insulin enhancing agents, the thiazolidinediones and the alpha glucosidase inhibitors, which delay carbohydrate digestion and absorption of glucose. Sulphonylureas are mediated through stimulation of the release of insulin from the pancreatic beta cell but they may also exert extra pancreatic effects, particularly in reducing the hepatic release of glucose and diminishing insulin resistance. In the diabetic patients who are requiring increasing dose of a sulphonylurea or biguanide, either alone or in combination the introduction of a single dose of intermediate acting insulin, administered at bedtime, many improve glycaemic control and delay the development of overt pancreatic beta cell failure. Insulin was discovered in 1921 and its clinical application transformed the management of type 1 diabetes mellitus, until then a fatal disorder. Insulin is injected subcutaneously, Centers for Disease Control and Prevention (CDC) recommend sites namely the anterior abdominal wall, upper arms, outer thighs and buttocks. Insulin is administered using a disposable plastic syringe with a fine needle in preference to the traditional glass syringe and metal needle which require repeated sterilization.

Side effects of insulin therapy: A main side effect of insulin therapy is hypoglycaemia, weight gain, peripheral oedema (insulin causes salt and water retention in the short term when started), insulin antibodies (animal insulin), local allergy (rare), lipodystrophy at injection sites. Factors associated with increased mortality and morbidity in diabetic patients is duration of diabetes, early age at onset of disease, high glycated Hb, raised blood pressure, proteinuria, obesity and hyperlipidaemia.

10. CONCLUSION

The review focused on the diabetes mellitus epidemiology, pathophysiology, clinical features, complications, diagnosis. The term Diabetes Mellitus (DM) is characterized by chronic hyperglycemia with disturbances of carbohydrate, fat and protein metabolism resulting from defects in insulin secretion, insulin action or both. Type 1 diabetes mellitus is autoimmune disorder with no longer or deficiency insulin hormone producing from beta cells of pancreas. Type 2 diabetes mellitus is inadequate or lack of insulin hormone producing from beta cells of pancreas or insulin resistance.

Management of diabetes mellitus had two goals. First goal is to replace insulin deficiency with administration of oral medication or injections as well as modification in dietary and regular exercise regarding insulin resistance. Secondary goal is that blood sugar levels under control leads to prevent of diabetes mellitus macro and micro vascular complications. This management methods cause each and every human being can live with joyfully life.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

COMPETING INTERESTS

Author has declared that no competing interests exist.

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