

Diabetes Mellitus: Classification

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Abstract: *Diabetes mellitus (DM) is world's largest growing metabolic disorder and presently affecting a large population around the globe. The growing prevalence of diabetes in societies worldwide is widely recognized as among the greatest threats to global health in the coming century. DM is broadly divided in Type 1 and Type 2. Type 1 is commonly seen in juveniles, characterized by failure to produce insulin due to autoimmune destruction of β -cells of the pancreas while type 2 is usually adult-onset and is associated with insufficient production of insulin and loss of responsiveness by cells to insulin.*

Keywords: *Diabetes mellitus, Type-1 DM and Type-2 DM.*

I. Introduction

Diabetes mellitus is a major public health problem in the developed as well as developing countries. It is ranked seventh among the leading cause of death, and third when its fatal complications are taken in to account [1]. It is estimated that 25% of the world population is affected by this disease. It is predicted to increase and estimated to be 300 million people worldwide by 2025 [2]. Regions with greatest interest are Asia and Africa, where diabetes rates could rise to 2-3 folds than present rates [3]. In India the number is expected to reach about 72 million by 2025 [4]. It is defined as acquired deficiency in production of insulin by the pancreas, or by the ineffectiveness of the insulin produced. The ancient Ayurvedic medicine treatise, 'Charak Samhita' dating to Vedic period (1500 B.C.) of Indian civilization mention this disorder as 'Madhumeha' (honey urine). The word diabetes was coined by 'Aretaeus' (1st century A.D.) of Cappadoica, who described diabetes as 'melting down of flesh and limbs into urine'. The word is taken from Greek diabainein, which literally means "passing through", or "siphon", a reference to one of the major symptoms of excessive urine discharge seen in diabetes. The word becomes "diabetes" from the English adoption of the Medieval Latin diabetes. In 1675 Thomas Willis added mellitus to the name (Greek mel, "Honey sweet") which he noted that a diabetic's urine and blood has a sweet taste [5].

DM is a disorder characterized by chronic hyperglycaemia with disturbances of carbohydrate, proteins and fat metabolism resulting from defects in insulin secretion, insulin action, or both. The characteristic symptoms include such as thirst, polyuria, blurring of vision, and weight loss. In its most severe forms, ketoacidosis or a non-ketotic hyperosmolar state may develop and lead to stupor, coma and, in absence of effective treatment, death. The progressive development of the specific complications of retinopathy with potential blindness, nephropathy that may lead to renal failure, and/or neuropathy with risk of foot ulcers, amputation, charcot joints, and features of autonomic dysfunction, including sexual dysfunction are some of its long term effects. People with diabetes are at increased risk of cardiovascular, peripheral vascular and cerebrovascular disease. Several pathogenic processes include destruction of the β cells of the pancreas with consequent insulin deficiency, and others that result in resistance to insulin action. The abnormalities of carbohydrate, fat and protein metabolism are due to deficient action of insulin on target tissues resulting from insensitivity or lack of insulin.

II. Global Prevalence

The prevalence rates are rising alarmingly among comparatively young and productive persons in the developing world [6]. Although the prevalence of diabetes is higher in developed countries than in developing countries and is expected to remain so until 2025 [7], the developing world will bear the brunt of the escalating epidemic in the future. There are currently more than 194 million people with diabetes worldwide. The estimated global burden of diabetes to be 124 million people, and projected that this would increase to 221 million people by the year 2010 [8]. If nothing is done to slow the epidemic, the number is expected to exceed 333 million by 2050. Now diabetes is the fourth main cause of death in most developed countries.

III. Indian Scenario

The prevalence of diabetes in India is estimated to be 1-5%. Also, the number of diabetics is projected to rise from 15 million in 1995 to 57 million by the year 2025 making it the country with the highest number of diabetics in the world. There have been several studies from various parts of India, revealing a rising trend in the prevalence of type-2 diabetes in the urban population [9]. A multicentre epidemiological study carried out by Indian Council of Medicinal Research (ICMR) in early seventies, reported the prevalence of diabetes to be 2.3%

in the urban and 1.5% in the rural areas [10]. A series of studies from Chennai showed that the percentage of adult urban subject affected had increased from 5.2% in 1984 to 8.2% in 1989, 11.6% in 1995 and 13.9% in 2000 which further increased to 14.3 % in 2004 [11]. A national Indian survey in 2000 showed that the prevalence of diabetes in urban India was 12.1% in subjects aged >20 years [12]. At present there are more than 60 million cases of diabetes in India. Being the second most populated country in the world, it is soon expected to be contributing towards the highest number of diabetic patients.

IV. Classification

4.1 Earlier Classifications

The first widely accepted classification of diabetes mellitus was published by WHO in 1980 and, in modified form, in 1985 [13] as: Insulin dependent diabetes mellitus (IDDM) or Type I diabetes and Non-insulin dependent diabetes mellitus (NIDDM) or Type 2 diabetes

According to WHO in 1985 the terms Type 1 and Type 2 were omitted, but the classes IDDM and NIDDM were retained, and a class of Malnutrition-related Diabetes Mellitus (MRDM) was introduced. These were reflected in the subsequent International Nomenclature of Diseases (IND) in 1991, and the tenth revision of the International Classification of Diseases (ICD-10) in 1992. The 1985 classification was widely accepted and is used internationally. Also in 1997, American Diabetes Association report by expert committee recommended dividing type 1 diabetes into type 1A (immune mediated) and type B (other forms of diabetes with severe insulin deficiency).

4.2 Revised Classification

The classification encompasses both clinical stages and aetiological types of diabetes mellitus and other categories of hyperglycaemia [14]. The clinical staging reflects that diabetes, regardless of its aetiology, progresses through several clinical stages during its natural history.

V. Types Of Diabetes

5.1 Type 1 (B-Cell Destruction, Usually Leading To Absolute Insulin Deficiency)

5.1.1. Autoimmune Diabetes Mellitus

Only 5–10% contributes to this form, known as insulin dependent diabetes, type I diabetes, or juvenile-onset diabetes, results from a cellular-mediated autoimmune destruction of the β -cells of the pancreas. Individuals depend on insulin for survival and at risk for ketoacidosis [15]. There is little or no insulin secretion as manifested by low or undetectable levels of plasma C-peptide [16], the rate of β -cell destruction is quite variable, being rapid (mainly infants and children) and slow (mainly adults). Ketoacidosis may be the first manifestation of the disease in some patients (particularly children and adolescents). While others may have modest fasting hyperglycemia that can rapidly change to severe hyperglycemia and/or ketoacidosis in the presence of infection or other stress. Some may retain residual β -cell function that is sufficient to prevent ketoacidosis for many years. Immune mediated diabetes can occur at any age but commonly occurs in childhood and adolescence. Patients are rarely obese with this type of diabetes, are also prone to other autoimmune disorders such as Hashimoto's thyroiditis, Graves' disease, Addison's disease, celiac sprue, autoimmune hepatitis, vitiligo, myasthenia gravis, and pernicious anemia.

5.1.2. Idiopathic

There are some forms of Type 1 diabetes which have no known aetiology. Some of these patients have permanent insulinopenia and are prone to ketoacidosis, but have no evidence of autoimmunity [17]. This form of diabetes is more common among individual of African and Asian origin. In other form found in Africans, on absolute requirement for insulin replacement therapy insulin affected patients may come and go, and patients periodically develop ketoacidosis.

5.2 Type 2 (Predominantly An Insulin Secretory Defect With/Without Insulin Resistance)

Previously called non-insulin dependent diabetes, or adult onset diabetes, is a term used for insulin dependent who have relative insulin deficiency. People with this type of diabetes frequently are resistant to the action of insulin [18]. This form of diabetes may remain undiagnosed for many years because the hyperglycaemia is often not severe enough to show noticeable symptoms of diabetes. Due to which such patients are at the risk of developing macrovascular and microvascular complications. The majority of patients with this form of diabetes are obese, and obesity itself causes insulin resistance. Initially patients may have normal or elevated insulin levels, in course of time insulin secretion may become defective and insufficient to compensate for insulin resistance. On the other hand, some individuals have essentially normal insulin action, but markedly impaired insulin secretion. The risk of developing Type 2 diabetes increases with age, obesity and

lack of physical activity. It occurs more frequently in women with prior gestational diabetes mellitus (GDM) and in individual with hypertension or dislipidaemia.

5.3 Other Specific Types Of DM

5.3.1. Gestational Hyperglycaemia And Diabetes

Gestational diabetes is carbohydrate intolerance resulting in hyperglycaemia of variable severity with onset or first recognition during pregnancy. In the early part of pregnancy (e.g. first trimester and first half of second trimester) fasting and postprandial glucose concentrations are normally lower than in normal, non-pregnant women. Individuals at high risk of gestational diabetes include older women, those with a history of large gestational age babies, women from certain high-risk ethnic group, and any pregnant women who have elevated fasting, or casual, blood glucose levels [19].

5.3.2. Genetic Defects Of B-Cell Function

Several forms of diabetic state may be associated with monogenic defects in β -cell function, frequently characterized by onset of mild hyperglycaemia at an early age (generally before age 25 years). They are usually inherited in an autosomal dominant pattern and referred to as maturity-onset diabetes of the young (MODY), have impaired insulin secretion with minimal or no defect in insulin action. Abnormalities at four genetic loci: mutation on chromosome 12 in a hepatic nuclear transcription factor referred to as HNF1, mutations in the glucokinase gene on chromosome 7p, mutation in the HNF4^α gene on chromosome 20q [20] and mutations in another transcription factor gene, IPF-1, which in its homozygous form leads to total pancreatic agenesis.

5.3.3. Genetic Defects In Insulin Action

Some unusual causes of diabetes result from genetically determined abnormalities of insulin action. The metabolic abnormalities associated with mutations of the insulin receptors may range from hyperinsulinaemia and modest hyperglycaemia to symptomatic diseases. Some individual with these mutations have acanthosis nigricans. Women may have virilization and have enlarged cystic ovaries. In the past, this syndrome was termed Type A insulin resistance [21]. The two pediatric syndromes Leperchaunism and Rabson-Mendenhall have mutations in the insulin receptor gene with subsequent alteration in insulin receptor function and show extreme insulin resistance. The former has characteristic features while the later is associated with abnormalities of teeth and nails and pineal gland hyperplasia.

5.3.4. Disease Of The Exocrine Pancreas

Any injures to the pancreas can cause diabetes. Acquired processes include pancreatitis, infection, pancreatic carcinoma, trauma, and pancreatectomy. With the exception of cancer, damage to pancreas must be extensive for diabetes to occur. However, adenocarcinomas can also cause diabetes. Fibrocalculus pancreatopathy may be accompanied by abdominal pain radiating to back and pancreatic calcification on X-ray and ductal dilation [22].

5.3.5. Endocrinopathies

Several hormones (e.g. Growth hormone, glucagons, cortisol and epinephrine) antagonize insulin action. Disease associated with excess secretion of these hormones can cause diabetes (eg. Glucagonoma, Acromegaly, Cushing's syndrome and 28 Phaeochromocytoma) [23]. These forms of hyperglycaemia typically resolve when excess hormone is removed. Somatostatinoma, and aldosteronoma induced hypokalaemia, can cause diabetes, at least in part by inhibiting insulin secretion

5.3.6. Drug Or Chemical Induced Diabetes

Many drugs can also disturb insulin secretion. These drugs may not, by themselves, cause diabetes but they may precipitate diabetes in person with insulin resistance. Certain toxins can permanently destroy pancreatic β cells such as Vacor (a rat poison) and pentamidine [24]. Other drugs and hormones like nicotinic acid and glucocorticoids can also impair insulin action.

5.3.7. Infections

Certain viruses have been associated with β -cell destruction. Diabetes occurs in some patients with congenital rubella. In addition, Coxsackie B, cytomegalovirus and other viruses (eg. Adeno virus and mumps) have been used in inducing the disease [25].

5.3.8. Immune Mediated Diabetes Mellitus

Several immunological diseases have been associated with Diabetes. The stiff man syndrome is an autoimmune disorder of the central nervous system, characterized by stiffness of the axial muscles with painful

spasm. Affected people have high titres of the glutamic acid decarboxylase (GAD) autoantibodies and approximately one-half will develop diabetes. In certain instances, severe insulin deficiency occurs in patients receiving interferon alpha associated with islet cell autoantibodies. Anti-insulin receptor antibodies can cause diabetes by binding to the insulin receptor, thereby reducing the binding of insulin to target tissue [26]. However these antibodies also can act as an insulin antagonist after binding to the receptor and can thereby cause hypoglycaemia. As in other stages of extreme insulin resistance, patients with anti-insulin receptor antibodies often have acanthosis nigricans. In the past, this syndrome was termed type B insulin resistance.

VI. Conclusion

Diabetes is likely to remain a significant threat to public health in the years to come. In the absence of effective and affordable interventions for both types of diabetes, the frequency of the disease will escalate worldwide, with a major impact on the population of developing countries. Despite the considerable progress in the understanding and management of diabetes, the disease and the complications related to it continue to increase.

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