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A COMPREHENSIVE REVIEW ON DIABETES MELLITUS: AN OVERVIEW

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ABSTRACT

Diabetes mellitus is worldwide one of the most common non-communicable diseases. Our country faces many challenges in diabetes management, including a rising prevalence in urban and rural areas, lack of disease awareness among the public, limited health care facilities, high cost of treatment, suboptimal glycogenic control and rising prevalence of diabetic complications. The common therapy of Insulin therapy for diabetes is most commonly delivered via subcutaneous injections, up to four times a day. The long-term insulin therapy, compounded by the invasive nature of its administration, has caused problems with patient compliance, ultimately influencing patient outcomes. There is an increase in the prevalence of type- 1diabetes also, but main cause of diabetic epidemic is type-2 diabetes mellitus, which accounts for more than 90 percent of all diabetes cases. Type-2 is the most serious and common chronic disease resulting from a complex inheritance-environment interaction along with other risk factors such as obesity and sedentary lifestyle.

KEYWORDS: Diabetes mellitus, diagnosis, cause and treatment.

INTRODUCTION

Diabetes mellitus (DM), commonly known as diabetes, is a group of metabolic disorders characterized by a high blood sugar level over a prolonged period of time.[1] Symptoms often include frequent urination, increased thirst and increased appetite. If untreated, diabetes can cause many complications. Acute complications can include diabetic ketoacidosis, hyperosmolar hyperglycemic state, or death.[2,3] The serious long-term complications include cardiovascular disease, stroke, chronic kidney disease, foot ulcers, damage to the nerves, damage to the eyes and cognitive impairment.[4,5] Diabetes is due to either the pancreas not

producing enough insulin, or the cells of the body not responding properly to the insulin produced.[6]

Classification of diabetes mellitus

The first mostly accepted classification of diabetes mellitus was published by WHO in the year 1980, and it is modified in the year 1985.[7,8] The most common and important form of Primary or idiopathic diabetes mellitus, which is focus of our discussion. It must be different from secondary diabetes mellitus which includes forms of hyperglycemia associated with identifiable causes in which destruction of pancreatic islets is induced by inflammatory Pancreatic diseases, surgery, tumors, certain drugs, iron overloaded (Hemochromatosis) and certain acquired or genetic endocrinopathies.[9] The classification encompasses both clinical stages and etiological types of diabetes mellitus and other categories of hyperglycemia.[10] Primary diabetes mellitus probably represents a heterogeneous group of disorders that have hyperglycemia as a common feature the new classification of diabetes mellitus contains stages which reflect the various degrees of hyperglycemia in individual subjects with any of the disease processes which may lead to diabetes mellitus.[11-13] The old and new terms of insulin-dependent(IDDM) or non-insulin-dependent (NIDDM) which were proposed by WHO in1980 and 1985 have disappeared and the terms of new classification system identifies four types of diabetes mellitus: type-1 (IDDM), type-2 (NIDDM),"other specific types" and gestational diabetes (WHO Expert Committee 1999). These were reflected in the subsequent International Nomenclature of Diseases (IND) in 1991and the tenth revision of the International classification of Diseases (ICD-10) in 1992.[10] Hence, classification of diabetes mellitus is described as below.

1. Insulin dependent diabetes mellitus (Type1 IDDM)

This type of diabetes mellitus is also called autoimmune diabetes and previously known as juvenile-onset or ketosis-prone diabetes. The individual may also seek with other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, and Addison's disease.[14] Type I diabetes mellitus is also known as insulin- dependent diabetes mellitus (IDDM), this occurs mainly in children and young adults; the onset is usually sudden and can be life threatening.[15] Type 1 is usually characterized by the presence of anti–glutamic acid decarboxylase, islet cell or insulin antibodies which identify the autoimmune processes which leads to beta-cell destruction.[16] Type 1 diabetes (due to the destruction of b-cell which is usually leading to absolute insulin deficiency) (American Diabetes Association, 2014). The rate of destruction of beta-cell is quite variable; it can be occur rapidly in some individuals

and slow in others.[17] There is a severe deficiency or absence of insulin secretion due to destruction of ß-islets cells of the pancreas. Treatment with injections of insulin is required.[15] Markers of immune destruction, including islet cell auto-antibodies, and/or auto antibodies to insulin, and auto antibodies to glutamic acid decarboxylase (GAD) are present in 85-90 % of individuals with Type 1 diabetes mellitus when fasting diabetic hyperglycemia is initially detected.[18] The exact cause of diabetes mellitus is remaining unknown, although, in most people, there is evidence of an autoimmune mechanism involving auto-antibodies that destroy the beta-islet cells.[15]

2. Non-Insulin dependent diabetes mellitus (Type-2/NIDDM)

Adult-onset diabetes is another name of Type-2 diabetes mellitus. The progressive insulin secretary defect on the background of insulin resistance (American Diabetes Association, 2014) People with this type of diabetes frequently are resistant to the action of insulin.[19] The long-term complications in blood vessels, kidneys, eyes and nerves occur in both types and are the major causes of morbidity and death from diabetes. The causes are multifunctional and predisposing factor includes obesity, sedentary lifestyle, increasing age, Genetic factor, such patients are at increased risk of developing macro vascular and micro vascular complications.[20-21]

3. Gestational diabetes mellitus

The glucose intolerance occurring for the first time or diagnosed during pregnancy is referred to as gestational diabetes mellitus (GDM).[22] Women who develop Type1 diabetes mellitus during pregnancy and women with undiagnosed asymptomatic Type 2 diabetes mellitus that is discovered during pregnancy are classified with Gestational Diabetes Mellitus (GDM).[13] Gestational diabetes mellitus (GDM) (diabetes diagnosed during pregnancy that is not clearly over diabetes).[14] The gestational diabetes mellitus may develops during pregnancy and may disappear after delivery; In the longer term, children born to mothers with GDM are at greater risk of obesity and type 2 diabetes in later life, a phenomenon attributed to the effects of intrauterine exposure to hyperglycemia.

4. Other specific type (Monogenic types)

The most common form of monogenic types of diabetes is developed with mutations on chromosome 12 in a hepatic transcription factor referred to as hepatocyte nuclear factor (HNF)1a.They also referred to as genetic defects of beta cells. These forms of diabetes are frequently characterized by onset of hyperglycemia at an early age (generally before age of

25 years). They are also referred to as maturity onset diabetes of the young (MODY).[8] maturity- onset diabetes in youth or with defects of insulin action; persons with diseases of the exocrine pancreas, such as pancreatitis or cystic fibrosis; persons with dysfunction associated with other endocrinopathies (e.g., acromegaly); and persons with pancreatic dysfunction caused by drugs, chemicals or infections.[13] Some drugs also used in the combination with the treatment of HIV/ AIDS or after organ transplantation. Genetic abnormalities that result in the inability to convert proinsulin to insulin have been identified in a few families, and such traits are inherited in an autosomal dominant pattern. They comprise less than 10% of DM cases.[7]

Causes of diabetes mellitus

Disturbances or abnormality in gluco-receptor of ß cell so that they respond to higher glucose concentration or relative ß cell deficiency. In either way, insulin secretion is impaired; may progress to ß cell failure.[23] The theory of principal in micro vascular disease leading to neural hypoxia, and the direct effects of hyperglycemia on neuronal metabolism.[24]

1. Reduced sensitivity of peripheral tissues to insulin: reduction in number of insulin receptors, 'down regulation' of insulin receptors. Many hypersensitive and hyperinsulinemia, but normal glycemic; and have associated dyslipidemia, hyperuricemia, abdominal obesity. Thus there is relative insulin resistance, particularly at the level of liver, muscle and fat. Hyperinsulinemia has been implicated in causing angiopathy.[25]
2. Excess of hyperglycemia hormone (glucagon) etc. obesity; causes relative insulin deficiency the ß cells lag behind. Two theories have demonstrated abnormalities in nitric oxide metabolism, resulting in altered perineural blood flow and nerve damage.[23]
3. Other rare forms of diabetes mellitus are those due to specific genetic defects (type 3) like "maturity onset diabetes of young" (MODY) other endocrine disorders, pancreatectomy and gestational diabetes mellitus (GDM).[25]
4. Due to imbalance of specific receptor can cause diabetes mellitus. Some specific receptors are Glucagon-like peptide-1(GLP-1) receptor, peroxisomes proliferators-activated (γ) receptor (PPARγ), beta3 (ß3) ardent-receptor some enzymes like α glycosidase, dipeptidyl peptidase IV enzyme etc.[25]
5. Current research on diabetic neuropathy is focused on oxidative stress, advanced gyration-end products, protein kinase C and the polyol pathway.[24]

Pathophysiology

Insulin is the principal hormone that regulates the uptake of glucose from the blood into most cells of the body, especially liver, adipose tissue and muscle, except smooth muscle, in which insulin acts via the IGF-1. Therefore, deficiency of insulin or the insensitivity of its receptors play a central role in all forms of diabetes mellitus.[26] The body obtains glucose from three main sources: the intestinal absorption of food; the breakdown of glycogen (glycogenolysis), the storage form of glucose found in the liver; and gluconeogenesis, the generation of glucose from non-carbohydrate substrates in the body. Insulin plays a critical role in regulating glucose levels in the body. Insulin can inhibit the breakdown of glycogen or the process of gluconeogenesis, it can stimulate the transport of glucose into fat and muscle cells, and it can stimulate the storage of glucose in the form of glycogen.[27] 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, typically 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. Lower glucose levels result in decreased insulin release from the beta cells and in the breakdown of glycogen to glucose. This process is mainly controlled by the hormone glucagon, which acts in the opposite manner to insulin.[28]

If the amount of insulin available is insufficient, or if cells respond poorly to the effects of insulin (insulin resistance), or if the insulin itself is defective, then glucose is not absorbed properly by the body cells that require it, and is not stored appropriately in the liver and muscles. The net effect is persistently high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as metabolic acidosis in cases of complete insulin deficiency.[26] When glucose concentration in the blood remains high over time, the kidneys reach a threshold of reabsorption, and the body excretes glucose in the urine (glycosuria).[29] This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production (polyuria) and increased fluid loss. Lost blood volume is replaced osmotically from water in body cells and other body compartments, causing dehydration and increased thirst (polydipsia).[26-29]

Diagnosis

- Diabetes mellitus is characterized by recurrent or persistent high blood sugar, and is diagnosed by demonstrating any one of the following.[65][30]
- Fasting plasma glucose level ≥ 7.0 mmol/L (126 mg/dL)

- Plasma glucose ≥ 11.1 mmol/L (200 mg/dL) two hours after a 75 gram oral glucose load as in a glucose tolerance test (OGTT)
- Symptoms of high blood sugar and casual plasma glucose ≥ 11.1 mmol/L (200 mg/dL)
- Glycated hemoglobin (HbA1C) ≥ 48 mmol/mol (≥ 6.5 DCCT %).[74][31]

A positive result, in the absence of unequivocal high blood sugar, should be confirmed by a repeat of any of the above methods on a different day. It is preferable 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 and offers no prognostic advantage over the fasting test.[32] According to the current definition, two fasting glucose measurements above 7.0 mmol/L (126 mg/dL) is considered diagnostic for diabetes mellitus. Per the WHO, people with fasting glucose levels from 6.1 to 6.9 mmol/L (110 to 125 mg/dL) are considered to have impaired fasting glucose.[78][33] People with plasma glucose at or above 7.8 mmol/L (140 mg/dL), but not over 11.1 mmol/L (200 mg/dL), two hours after a 75 gram oral glucose load are considered to have impaired glucose tolerance. Of these two prediabetic states, the latter in particular is a major risk factor for progression to full-blown diabetes mellitus, as well as cardiovascular disease.[34]

Prevention

There is no known preventive measure for type 1 diabetes. Type 2 diabetes—which accounts for 85–90% of all cases worldwide—can often be prevented or delayed.[35] by maintaining a normal body weight, engaging in physical activity, and eating a healthy diet. Higher levels of physical activity (more than 90 minutes per day) reduce the risk of diabetes by 28%.[36] Dietary changes known to be effective in helping to prevent diabetes include maintaining a diet rich in whole grains and fiber, and choosing good fats, such as the polyunsaturated fats found in nuts, vegetable oils, and fish. Limiting sugary beverages and eating less red meat and other sources of saturated fat can also help prevent diabetes.[37]Tobacco smoking is also associated with an increased risk of diabetes and its complications, so smoking cessation can be an important preventive measure as well.[38] The relationship between type 2 diabetes and the main modifiable risk factors (excess weight, unhealthy diet, physical inactivity and tobacco use) is similar in all regions of the world. There is growing evidence that the underlying determinants of diabetes are a reflection of the major forces driving social, economic and cultural change: globalization, urbanization, population aging, and the general health policy environment.[39]

Management

Diabetes management concentrates on keeping blood sugar levels as close to normal, without causing low blood sugar. This can usually be accomplished with dietary changes, exercise, weight loss, and use of appropriate medications (insulin, oral medications). Learning about the disease and actively participating in the treatment is important, since complications are far less common and less severe in people who have well-managed blood sugar levels.[40-41] Per the American College of Physicians, the goal of treatment is an HbA1C level of 7-8%.[42] Attention is also paid to other health problems that may accelerate the negative effects of diabetes. These include smoking, high blood pressure, metabolic syndrome obesity, and lack of regular exercise.[43] Specialized footwear is widely used to reduce the risk of ulcers in at-risk diabetic feet although evidence for the efficacy of this remains equivocal.[44]

Treatment of diabetes mellitus

The treatment is to overcome the precipitating cause and to give high doses of regular insulin. The insulin requirement comes back to normal once the condition has been controlled[45] the aims of management of diabetes mellitus can be achieved by:

1. To restore the disturbed metabolism of the diabetic as nearly to normal as is consistent with comfort and safety.
2. To prevent or delay progression of the short and long term hazards of the disease.
3. To provide the patient with knowledge, motivation and means to undertake this own enlightened care.

Insulin and Oral hypoglycemic drugs

Insulin therapy should aim to mimic nature, which is remarkably successful both in limiting postprandial hyperglycemia and preventing hypoglycemia between meals.[45] Site of administration of insulin injection is equally important for better and safe action of insulin and can be given by intramuscular or intravenous route. Different preparations of insulin are available such as human insulin, beef insulin, pork insulin. Insulin therapy is no free from complications and adverse effects. The most important adverse effect are weight gain and hypoglycemia when inappropriate dose of insulin is taken and when there is mismatch between meals and insulin injection.[46-47] Weight gain after starting insulin therapy for uncontrolled diabetes is an inevitable consequence and is the result of increased truncal fat and muscle bulk. This is also due to reduced energy losses through glycosuria.[48-49] Sulphonyl urea's such as glibenclamide, glipizide and biguanides such as metformin,

phenformin are oral hypoglycemic drugs. Sulfonylureas cause hypoglycemia by stimulating insulin release from pancreatic ß-cells. They bind to sulfonylurea (SUR) receptors on the ß-cell plasma membrane, causing closure of adenosine triphosphate (ATP)- sensitive potassium channels, leading to depolarization of the cell membrane. This in turn opens voltage gated channels, allowing influx of calcium ions and subsequent secretion of preformed insulin granules. Acute administration of sulfonylureas to type 2 DM patient's increases insulin release from the pancreas and also may further increase insulin levels by reducing hepatic clearance of the hormone. Initial studies showed that a functional pancreas was necessary for the hypoglycemic actions of sulfonylureas.[50] Biguanides such as metformin is antihyperglycemic, not hypoglycemic.[51] It does not cause insulin release from the pancreas and does not cause hypoglycemia, even in large doses.[52] It has been shown to increase peripheral uptake of glucose, and to reduce hepatic glucose output by approximately 20-30% when given orally but not intravenously. Impaired absorption of glucose from the gut has also been suggested as a mechanism of action.[53-55]

Herbal treatment of diabetes

In the last few decades eco-friendly, bio-friendly, cost effective and relatively safe, plant-based medicines have moved from the fringe to the main stream with the increased research in the field of traditional medicine. There are several literature reviews by different authors about anti-diabetic herbal agents, but the most informative is the review by Atta-ar-Rahman who has documented more than 300 plant species accepted for their hypoglycemic properties. This review has classified the plants according to their botanical name, country of origin; parts used and nature of active agents. One such plant is Momordica charantia (Family: Cucurbitaceae).[56] WHO has listed 21,000 plants, which are used for medicinal purposes around the world, Among these 2500 species are in India, out of which 150 species are used commercially on a fairly large scale. India is the largest producer of medicinal herbs and is called the botanical garden of the world.[57]

CONCLUSION

Diabetes mellitus is a serious complication in today life. The lifestyle and day today circumstances are play major role in occurring this type of serious complications. In this review we get some idea regarding diabetes mellitus. The term diabetes mellitus includes several different metabolic disorders that all, if left untreated, result in abnormally high concentration of a sugar called glucose in the blood. Diabetes mellitus type 1 results when the

pancreas no longer produces significant amounts of the hormone insulin, usually owing to the autoimmune destruction of the insulin-producing beta cells of the pancreas. Diabetes mellitus type 2, in contrast, is now thought to result from autoimmune attacks on the pancreas and/or insulin resistance. The pancreas of a person with type 2 diabetes may be producing normal or even abnormally large amounts of insulin. The main goal of diabetes management is, as far as possible, to restore carbohydrate metabolism to a normal state. To achieve this goal, individuals with an absolute deficiency of insulin require insulin replacement therapy, which is given through injections or tablets. Insulin resistance, in contra6st, can be corrected by dietary modifications and exercise. Other goals of diabetes management are to prevent or treat the many complications that can result from the disease itself and from its treatment. By keeping the blood sugar level under control, diabetes can become patient's companion and he/she can enjoy life joyfully.

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