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Diabetes Mellitus: A Review

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ABSTRACT

Diabetes mellitus (DM), or simply diabetes, is a group of metabolic diseases in which a person has high blood sugar, either because the body does not produce enough insulin, or because cells do not respond to the insulin that is produced. This high blood sugar produces the classical symptoms of polyuria (frequent urination), polydipsia (increased thirst) and polyphagia (increased hunger). Conventionally, diabetes has been divided into three types namely: Type 1 DM or insulin-dependent diabetes mellitus (IDDM) in which body fails to produce insulin, and presently requires the person to inject insulin or wear an insulin pump. This is also termed as "juvenile diabetes". Type 2 DM or non insulin-dependent diabetes mellitus (NIDDM), results from insulin resistance, a condition in which cells fail to use insulin properly, with or without an absolute insulin deficiency. This type was previously referred to as or "adult-onset diabetes". The third main type is gestational diabetes which occurs when women without a previous history of diabetes develop a high blood glucose level during her pregnancy. It may precede development of type 2 DM. Currently available pharmacotherapy for the treatment of diabetes mellitus includes insulin and oral hypoglycemic agents. Such drugs acts by either increasing the secretion of insulin from pancreas or reducing plasma glucose concentrations by increasing glucose uptake and decreasing gluconeogenesis. However these current drugs do not restore normal glucose homeostasis for longer period and they are not free from side effects such as hypoglycemia, kidney diseases, GIT problems, hepatotoxicity, heart risk problems, insulinoma and they have to take rest of life. Various herbal drugs have been also proved effective due to their beneficial contents in treatment of diabetes. The present review therefore is an attempt to focus on the physiological aspects of diabetes, its complications, goals of management, and synthetic and herbal treatment of diabetes.

***Key words**: Insulinoma, hyperinsulinemia, adiponectin, Momordica charantia.*

INTRODUCTION

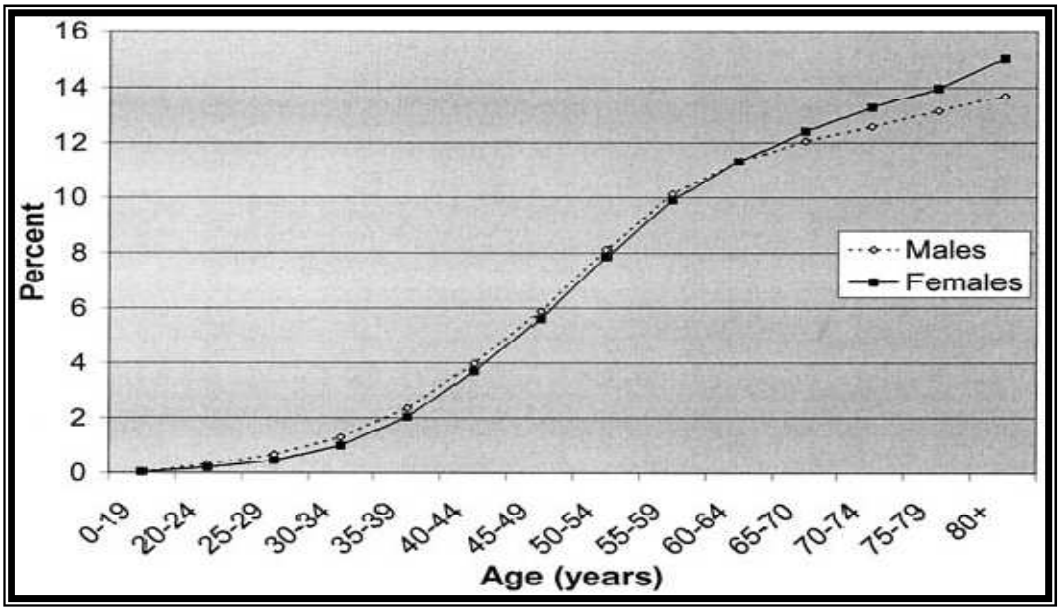
Diabetes mellitus (DM) is commonest endocrine disorder that affects more than 100 million people worldwide (6% population). It is caused by deficiency or ineffective production of insulin by pancreas which results in increase or decrease in concentrations of glucose in the blood. It is found to damage many of body systems particularly blood vessels, eyes, kidney, heart and nerves[1]. Diabetes mellitus has been classified into two types i.e. insulin dependent diabetes mellitus (IDDM, Type I) and non-insulin dependent diabetes mellitus (NIDDM, Type II). Type I diabetes is an autoimmune disease characterized by a local inflammatory reaction in and around islets that is followed by selective destruction of insulin secreting cells whereas Type II diabetes is characterized by peripheral insulin resistance and impaired

insulin secretion[2]. The presence of DM shows increased risk of many complications such as cardiovascular diseases, peripheral vascular diseases, stroke, neuropathy, renal failure, retinopathy, blindness, amputations etc[3]. Drugs are used primarily to save life and alleviate symptoms. Secondary aims are to prevent long-term diabetic complications and, by eliminating various risk factors, to increase longevity. Insulin replacement therapy is the mainstay for patients with type 1 DM while diet and lifestyle modifications are considered the cornerstone for the treatment and management of type 2 DM [4]. Various types of hypoglycemic agents such as *biguanides* and *sulfonylureas* are also available for treatment of diabetes. However none of these medications is ideal due to their toxic side effects and diminution of responses is observed sometimes in their prolonged use [5]. The main disadvantage of currently available drugs is that they have to be given throughout the life and produce side effects[6]. Medicinal plants and their bioactive constituents can be used for treatment of DM throughout the world especially in countries where access to the conventional anti-DM agents is inadequate[3]. Various experimental models are also available to screen antidiabetic activity of plant[7]. The present review therefore is an attempt to know more precisely about diabetes mellitus, its clinical presentation, epidemiological data, complications and current available treatment of diabetes.

Epidemiology

It is estimated that 366 million people had DM in 2011; by 2030 this would have risen to 552 million. The number of people with type 2 DM is increasing in every country with 80% of people with DM living in low- and middle-income countries. DM caused 4.6 million deaths in 2011[8]. It is estimated that 439 million people would have type 2 DM by the year 2030.The incidence of type 2 DM varies substantially from one geographical region to the other as a result of environmental and lifestyle risk factors[9]. It is predicted that the prevalence of DM in adults of which type 2 DM is becoming prominent will increase in the next two decades and much of the increase will occur in developing countries where the majority of patients are aged between 45 and 64 years[10].

Fig. 1: Epidemiology of diabetes: A global view



Diabetes in India

According to recent estimates, approximately 285 million people worldwide (6.6%) in the 20–79 year age group will have diabetes in 2010 and by 2030, 438 million people (7.8%) of the adult population, is expected to have diabetes. India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the "diabetes capital of the world". According to the Diabetes Atlas 2006 published by the International Diabetes Federation, the number of people with diabetes in India currently around 40.9 million is expected to rise to 69.9 million by 2025 unless urgent preventive steps

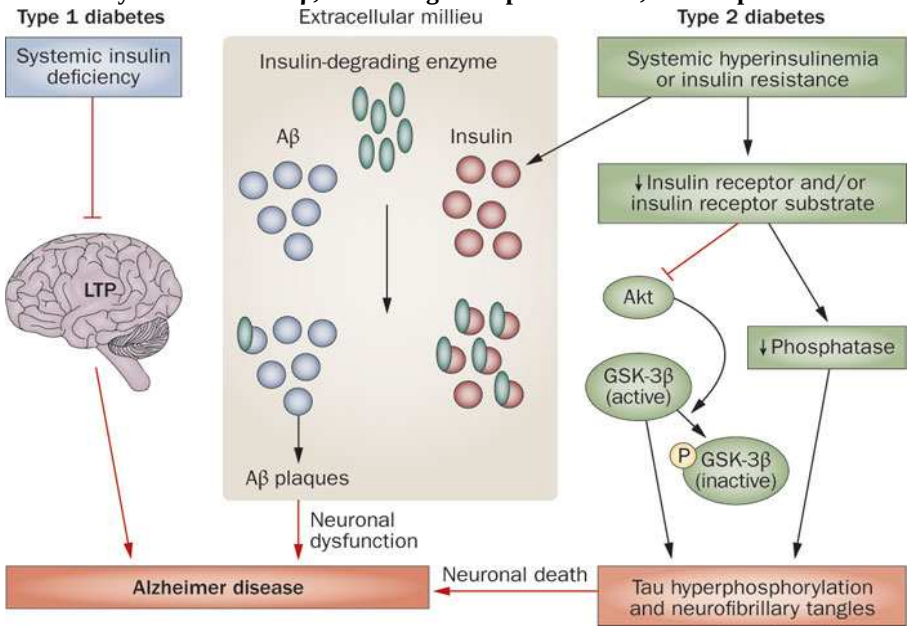
are taken. The "Asian Indian Phenotype" refers to certain unique clinical and biochemical abnormalities in Indians which include increased insulin resistance, greater abdominal adiposity i.e., higher waist circumference despite lower body mass index, lower adiponectin and higher high sensitive C-reactive protein levels. Higher prevalence of diabetes mellitus often results from in changes in dietary patterns and decreased physical activity in the urban population[11]. Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease[12,13]. In 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus followed by China (20.8 million) with the United States (17.7 million) in second and third place respectively. According to Wild et al. the prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India. It is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India, while China (42.3 million) and the United States (30.3 million) will also see significant increases in those affected by the disease[10, 14].

Pathophysiological aspects

Type 2 DM is characterized by insulin insensitivity as a result of insulin resistance, declining insulin production, and eventual pancreatic beta-cell failure. This leads to a decrease in glucose transport into the liver, muscle cells and fat cells. There is an increase in the breakdown of fat with hyperglycemia[15, 16].

Type 1 diabetic patients are usually young (children or adolescents) and not obese when they first develop symptoms. There is an inherited predisposition, with a 10-fold increased incidence in first-degree relatives of an index case, and strong associations with particular histocompatibility antigens (HLA types). Studies of identical twins have shown that genetically predisposed individuals must additionally be exposed to an environmental factor such as viral infection. Viral infection may damage pancreatic B cells and expose antigens that initiate a self-perpetuating autoimmune process. The patient becomes overtly diabetic only when more than 90% of the B cells have been destroyed. In this type, insulin deficiency attenuates long term potentiating and might lead to deficits in learning and memory. Type 2 diabetes is accompanied both by insulin resistance and by impaired insulin secretion, each of which are important in its pathogenesis. Such patients are often obese and usually present in adult life, the incidence rising progressively with age as B-cell function declines. In this insulin resistance leads to both Aβ plaque formation and tau hyperphosphorylation. During hyperinsulinemia, insulin and Aβ competes for insulin-degrading enzyme, leading to Aβ accumulation and plaque formation. A decrease in insulin receptor signaling leads to inhibition of Akt and dephosphorylation (activation) of GSK-3β and results in tau hyperphosphorylation[17, 18].

Fig. 2: Pathophysiology of Type I and Type II diabetes. Abbreviations: Aβ- Amyloid- β, GSK-3β-glycogen synthase kinase 3β, LTP- long term potentiation, P- Phosphate



Complications

As the disease progresses tissue or vascular damage ensues leading to severe diabetic complications such as retinopathy, neuropathy, nephropathy, cardiovascular complications and ulceration. Long standing type 1 DM patients are susceptible to microvascular complications; and macrovascular disease (coronary artery, heart and peripheral vascular diseases)[19,20]. Type 2 DM caries a high risk of large vessel atherosclerosis commonly associated with hypertension, hyperlipidaemia and obesity. Most patients with type 2 diabetes die from cardiovascular complications and end stage renal disease[4].

Diagnosis

According to the *Americal Diabetes Association* (ADA), the fasting glucose concentration should be used in routine screening for diabetes; but postprandial blood sugar, random blood sugar and glucose tolerance test are also used for blood sugar determination. For the diagnosis of diabetes, at least one criterion must apply:

- Symptoms of diabetes (polyurea, polydipsia, unexplained weight loss, etc) as well as casual plasma glucose concentration = 11.1 mmol/L (200 mg/dL).
- Fasting plasma glucose = Its normal range is 70-110 mg/dl with no caloric intake for at least 8 h.

The World Health Organization (WHO) classification includes both clinical stages (normoglycaemia, impaired glucose tolerance/impaired fasting glucose (IGT/IFG), diabetes) and etiological types of diabetes mellitus, identical to the ADA except that WHO group includes classification formerly known as gestational impaired glucose tolerance (GIGT) and GDM: fasting glucose = 7.0 mmol/L (126 mg/dL) and/or 2-h glucose = 7.8 mmol/L (140 mg/dL) after a 75-g OGTT [4].

Goals of management

Primary prevention is the main aim at preventing diabetes from occurring in susceptible individuals or in general population. Regular physical activity is an important component of the prevention and management of type 2 diabetes mellitus. Prospective cohort studies have shown that increased physical activity, independently of other risk factors, has a protective effect against the development of type 2 diabetes[21, 22 and 23]. Dietary and lifestyle modifications are the main goals of treatment and management for type 2 diabetes. The majority of people with type 2 diabetes is overweight and usually has other metabolic disorders of the insulin resistance syndrome, so the major aims of dietary and lifestyle changes are to reduce weight, improve glycemic control and reduce the risk of coronary heart disease (CHD), which accounts for 70% to 80% of deaths among those with diabetes [24]. Insulin replacement therapy is the mainstay for patients with type 1 DM while diet and lifestyle modifications are considered the cornerstone for the treatment and management of type 2 DM. Insulin is also important in type 2 DM when blood glucose levels cannot be controlled by diet, weight loss, exercise and oral medications. Oral hypoglycemic agents are also useful in the treatment of type 2 DM. Oral hypoglycemic agents include sulphonylureas, biguanides, alpha glucosidase inhibitors and thiazolidenediones. Their main goal is to restore normal metabolic disorder such as insulin resistance and inadequate insulin secretion from pancreas. Diet and lifestyle strategies are to reduce weight, improve glycemic control and reduce the risk of cardiovascular complications, which account for 70% to 80% of deaths among those with diabetes[25].

Treatment

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[26]. 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[27, 28]. 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[29,30]. *Sulphonyl ureas* 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[31]. *Biguanides* such as *metformin* is antihyperglycaemic, not hypoglycemic[32]. It does not cause insulin release from the pancreas and does not cause hypoglycemia, even in large doses[33]. 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[34, 35 and 36].

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 hypoglycaemicproperties.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)[37]. 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[38].

CONCLUSION

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 contrast, 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.

Conflict of interest

The authors declare that there is no conflict of interest in publication of this paper.

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