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Diabetes Mellitus and Its Global Menace – A Review

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Abstract

To provide a reviewed report on diabetes mellitus on an ongoing research on the global effects of diabetes mellitus. Reports on diabetes mellitus were extracted from cited journals and articles. Diabetes has been known as disease associated with aberration in glucose metabolism resulting from defects in insulin secretion and/or action. It is a chronic disease that occurs either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces. It is no exaggeration to describe diabetes as one of the major contributors to ill health and premature mortality worldwide. Globally, across all ages, it is est imated that at least 1 in 20 deaths are attributable to diabetes. If the current trend continues it is estimated that by 2030 the number of people with diabetes will more than double. Most of this increase will be due to a 150% increase in developing countries, where the cadre of people affected mostly will be men and women in their economically productive years. It is the fifth leading cause of death worldwide. About 300 million people worldwide were reported by WHO in 2010 to be afflicted with diabetes. This review reports the global state as a result of the metabolic effects of diabetes mellitus.

Keywords: Diabetes,Insulin, Glucose metabolism, Pancreas, Worldwide, WHO

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Introduction

Diabetes mellitus (DM), commonly referred to as diabetes, is a group of metabolic diseases in which there are high blood sugar levels over a prolonged period [1], due to either the inability of pancreas to produce enough insulin or the cells of the body not responding properly to the insulin produced [2]. It thus occurs as a chronic disease either when the pancreas does not produce enough insulin or when the body cannot effectively use the insulin it produces [1]. About 300million people worldwide were reported by WHO in 2010 to be afflicted with diabetes and according to the WHO report [3], it can be ascribed that diabetes as one of the major contributors to ill health and premature mortality worldwide and it is known to be the fifth leading cause of death worldwide [4].

Globally, across all ages, it is estimated that at least 1 in 20 deaths are attributable to diabetes [1] and IDF [5] report says that if the current trend continues, it is estimated that by 2030 the number of people with diabetes will more than double. This increase may be due to a 150% increase in developing countries, where the cadre of people affected mostly will be men and women in their economically productive years [6].

Etymology of Diabetes mellitus

Diabetes

The word diabetes comes from Latin diabētēs, which in turn comes from Ancient Greek which literally means "a passer through [7]. Ancient Greek physician Aretaeus of Cappadocia used that word, to mean "excessive discharge of urine [8]. The word mellitus comes from the classical Latin word mellītus, meaning "mellite" (i.e. sweetened with honey; honey-sweet) [9]. It was Thomas Willis who in 1675 added "mellitus" to the word "diabetes" as a designation for the disease,

when he noticed the urine of a diabetic had a sweet taste (glycosuria) [10]. This sweet taste had been noticed in urine by the ancient Greeks, Chinese, Egyptians, Indians, and Persians [10]. Symptoms of high blood sugar include frequent urination, increased thirst, and increased hunger. If left untreated, diabetes can cause many complications [11]. Acute complications include diabetic ketoacidosis and nonketotic hyperosmolar coma [6]. Serious long-term complications include cardiovascular disease, stroke, kidney failure, foot ulcers and damage to the eyes [11].

In 2014, the International Diabetes Federation (IDF) estimated that diabetes resulted in 4.9 million deaths. The World Health Organization (WHO) estimated that diabetes resulted in 1.5 million deaths in 2012, making it the 8th leading cause of death [12]. The discrepancy between the two estimates is due to the fact that cardiovascular diseases are often the cause of death for individuals with diabetes throughout the world, but is more common (especially type 2) in more developed countries [13].

Symptoms of untreated diabetes

The classic symptoms of untreated diabetes are weight loss, polyuria (frequent urination), polydipsia (increased thirst), and polyphagia (increased hunger) [6]. Symptoms may develop rapidly (weeks or months) in type 1 diabetes, while they usually develop much more slowly and may be subtle or absent in type 2 diabetes [11]. Several other signs and symptoms can mark the onset of diabetes, although they are not specific to the disease [14]. They include blurry vision, headache, fatigue, slow healing of cuts, and itchy skin [11]. Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in its shape, resulting in vision changes [6]. A number of skin rashes that can occur in diabetes are collectively known as diabetic dermadromes [14].

Complications

All forms of diabetes increase the risk of long-term complications [15]. The major long-term complications relate to damage to blood vessels. Diabetes doubles the risk of cardiovascular disease and about 75% of deaths in diabetics are due to coronary artery disease [16]. The primary microvascular complications of diabetes include damage to the eyes, kidneys, and nerves [17]. Damage to the eyes, known as diabetic retinopathy, is caused by damage to the blood vessels in the retina of the eye, and can result in gradual vision loss and blindness [17]. Damage to the kidneys, known as diabetic nephropathy, can lead to tissue scarring, urine protein loss, and eventually chronic kidney disease, sometimes requiring dialysis or kidney transplant [17].

Since 1980, WHO estimates that the worldwide prevalence of obesity has more than doubled, with significant increases seen in every region. In sub-Saharan Africa, the number of overweight children grew from 4 million in 1990 to 10 million in 2012 [45]. Damage to the nerves of the body, known as diabetic neuropathy, is the most common complication of diabetes [17].

Types of diabetes mellitus:

Type 1 Diabetes Mellitus

Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the islets of Langerhans in the pancreas, leading to insulin deficiency [18]. This type can be further classified as immune-mediated or idiopathic [18]. The majority of type 1 diabetes is of the immune-mediated nature, in which a T-cell-mediated autoimmune attack leads to the loss of beta cells and thus insulin [19]. Type 1 diabetes can affect children or adults, but was traditionally termed "juvenile diabetes" because a majority of these diabetes cases were in children [18; 19]. Type 1 diabetes can be accompanied by irregular and unpredictable hyperglycemia, frequently with ketosis, and sometimes with serious hypoglycemia [18].

Type 2 Diabetes Mellitus

Type 2 diabetes mellitus is characterized by insulin resistance, which may be combined with relatively reduced insulin secretion [2]. The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor [20]. However, the specific defects are not known. Type 2 diabetes is the most common type [20]. In the early stage of type 2, the predominant abnormality is reduced insulin sensitivity [2]. At this stage, hyperglycemia can be reversed by a variety of measures and medications that improve insulin sensitivity or reduce glucose production by the liver [2]. Type 2 diabetes is due primarily to lifestyle factors and genetics [20]. A number of lifestyle factors are known to be important to the development of type 2 diabetes, including obesity (defined by a body mass index of greater than thirty), lack of physical activity, poor diet, stress, and urbanization [2; 20]. Dietary factors such as consumption of sugar-sweetened drinks in excess can also influence the risk of developing type 2 diabetes [21].

Gestational Diabetes Mellitus

Gestational diabetes mellitus (GDM) resembles type 2 diabetes in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness [22]. It occurs in about 2–10% of all pregnancies and may improve or disappear after delivery [23]. However, after pregnancy approximately 5–10% of women with gestational diabetes are found to have diabetes mellitus, most commonly type 2 [24].

Gestational diabetes is fully treatable, but requires careful medical supervision throughout the pregnancy. Management may include dietary changes, blood glucose monitoring, and in some cases insulin may be required [22].Though it may be transient, untreated gestational diabetes can damage the health of the fetus or mother [22]. Risks to the baby include macrosomia (high birth weight), congenital cardiac and central nervous system anomalies, and skeletal muscle malformations [24]. Increased fetal insulin may inhibit fetal surfactant production and cause respiratory distress syndrome [24].

Other types of Diabetes Mellitus: Latent autoimmune diabetes of adults (LADA) Prediabetes indicates a condition that occurs when a person's blood glucose levels are higher than normal but not high enough for a diagnosis of type 2 DM. Many people destined to develop type 2 DM spend many years in a state of prediabetes [23]. Latent autoimmune diabetes of adults (LADA) is a condition in which type 1 DM develops in adults. Adults with LADA are frequently initially misdiagnosed as having type 2 DM, based on age rather than etiology [25]. Any disease that causes extensive damage to the pancreas may lead to diabetes (for example, chronic pancreatitis and cystic fibrosis) [26]. Diseases associated with excessive secretion of insulin-antagonistic hormones can cause diabetes. Many drugs impair insulin secretion and some toxins damage pancreatic beta cells. The ICD-10 (1992) diagnostic entity, malnutrition-related diabetes mellitus (MRDM or MMDM, ICD-10 code E12), was deprecated by the WHO when the current taxonomy was introduced in 1999 [12].

Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis-related diabetes, steroid diabetes induced by high doses of glucocorticoids, and several forms of monogenic diabetes [26]. According to the current definition, two fasting glucose measurements above 126 mg/dl (7.0 mmol/l) have been considered diagnostic for diabetes mellitus [27]. Per the World Health Organization 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 [24]. 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 75g oral glucose load are considered to have impaired glucose tolerance [24]. 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 [27]. The American Diabetes Association since 2003 uses a slightly different range for impaired fasting glucose of 5.6 to 6.9 mmol/l (100 to 125 mg/dl) [24]. The rare disease diabetes insipidus has similar symptoms to diabetes mellitus, but without disturbances in the sugar metabolism (insipidus means "without taste" in Latin) and does not involve the same disease mechanisms [28].

History

Diabetes was one of the first diseases described, with an Egyptian manuscript from c. 1500 BCE mentioning "too great emptying of the urine" [29]. The first described cases are believed to be of type 1 diabetes (Laios et al., 2012). Indian physicians around the same time identified the disease and classified it as madhumeha or "honey urine", noting the urine would attract ants (Dubois and Bankauskaite, 2005). The term "diabetes" or "to pass through" was first used in 230 BCE by the Greek Appollonius of Memphis [7]. The disease was considered rare during the time of the Roman Empire, with Galen commenting he had only seen two cases during his career [29]. This is possibly due the diet and life-style of the ancient people, or because the clinical symptoms were observed during the advanced stage of the disease. Galen named the disease "diarrhea of the urine" (diarrhea urinosa) [29]. The earliest surviving work with a detailed reference to diabetes is that of Aretaeus of Cappadocia (2nd or early 3rd century CE). He described the symptoms and the course of the disease, which he attributed to the moisture and coldness, reflecting the beliefs of the "Pneumatic School" [29]. He hypothesized a correlation of diabetes with other diseases and he discussed differential diagnosis from the snakebite which also provokes excessive thirst [30]. His work remained unknown in the West until the middle of the 16th century when, in 1552, the first Latin edition was published in Venice [30].

Type 1 and type 2 diabetes were identified as separate conditions for the first time by the Indian physicians Sushruta and Charaka in 400-500 CE with type 1 associated with youth and type 2 with being overweight [7]. The term "mellitus" or "from honey" was added by the Briton John Rolle in the late 1700s to separate the condition from diabetes insipidus, which is also associated with frequent urination [29]. Effective treatment was not developed until the early part of the 20th century, when Canadians Frederick Banting and Charles Herbert Best isolated and purified insulin in 1921 and 1922 [30]. This was followed by the development of the long-acting insulin NPH in the 1940s [30]. The most common drugs that are currently being used for the experimental induction of Diabetes is alloxan and streptozotocin (STZ) [31].

Global reports

Global impact of diabetic mellitus

Diabetes mellitus is a common and very prevalent disease affecting the citizens of both developed and developing countries [32]. It has been estimated that 25% of the world population is affected by this disease [33]. Diabetes has significant health consequences for individuals, communities and countries. The WHO estimated that about 30 million people suffered from diabetes in 1985 and the number increased to more than 171 million in 2000. Additionally, it has been estimated that the number will increase to over 366 million by 2030 mostly in developing countries, especially in people aged between 45 and 64 years [12].

A large disparity in total health spending for diabetes among the top 80 most populous countries exists, varying from USD 1.3 million to USD 198.0 billion [34]. The country with the highest total expenditure, the United States of America, will spend 52.7% of the global expenditure. India, the country with the largest population of people living with diabetes, will spend an estimated USD 2.8 billion or less than 1% of the world total. The total diabetes spending in the 18 countries in IDF's African Region will be only USD 1.2 billion, 0.3% of the global total [34].

As of 2014, an estimated 387 million people have diabetes worldwide with type 2 diabetes making up about 90% of the cases [35]. This is equal to 8.3% of the adult population, with equal rates in both women and men [36]. In the years 2012 to 2014, diabetes is estimated to have resulted in 1.5 to 4.9 million deaths per year [37]. The global economic cost of diabetes in 2014 was estimated to be $612 billion USD while in the United States, diabetes cost $245 billion in 2012 [38]. Based on the most recent 2015 IDF estimates for South Africa, there were 2.286 (1.1637-4.6206) million adults (20-79 years) with diabetes; the national prevalence was 7.0% (3.6-14.1) with a comparative prevalence of 7.6% (3.1-14.7). Of the 2.3 million people with diabetes, 1.3968 (0.603-2.3944) million (61.1%) were undiagnosed. The mean health expenditure per person with diabetes was USD 918.9 USD (1736.1 international dollars); and there were 57,319 diabetes related deaths [46].

Diabetic mellitus and oxidative stress

Diabetes mellitus is associated with an increased risk of cardiovascular diseases mediated via oxidative stress [39]. Reactive oxygen species can directly damage lipids, proteins or DNA and modulate intracellular signaling pathways, such as mitogen activated protein kinases and redox sensitive transcription factors causing changes in protein expression with irreversible oxidative modifications [40]. Hyperglycaemia-induced mitochondrial dysfunction and endoplasmic reticulum stress has been shown to promote reactive oxygen species (ROS) accumulation, accelerates cellular damage and significantly contributes to the diabetic complications development and progression [41].

Mechanisms of cardiovascular dysfunction in diabetes:

The role of superoxide and peroxynitrite has been discussed. Here, hyperglycaemia induces increased superoxide anion ($O_2^{\bullet-}$) production via activation of multiple pathways including xanthine and NAD(P)H oxidases, cyclooxygenase, uncoupled nitric oxide synthase (NOS), glucose autoxidation, mitochondrial respiratory chain, polyol pathway, and formation of advanced glycation end products (AGE) [42]. Hyperglycaemia-induced increased superoxide generation may also favour an increased expression of nitric oxide synthases (NOS) through the activation of NFκB, which may increase the generation of nitric oxide (NO) [42].

Superoxide anion may quench NO, thereby reducing the efficacy of a potent endothelium-derived vasodilator system [42]. Superoxide can also be converted to hydrogen peroxide (H_2O_2) by superoxide dismutase (SOD) and interact with NO to form a reactive oxidant peroxynitrite ($ONOO^-$), which induces cell damage via lipid peroxidation, inactivation of enzymes and other proteins by oxidation and nitration, and activation of matrix metalloproteinases (MMPs) among others. This figure was adapted from [42].

Hyperglycaemia-induced oxidative stress also mediates endothelial dysfunction which plays a central role in the pathogenesis of micro- and macro-vascular diseases with resultant increase in pro-inflammatory cytokines and induction of apoptosis and impairment of nitric oxide release [43]. Hyperglycaemia induces vascular damage probably through a single common pathway - increased intracellular oxidative stress- linking four major mechanisms, namely the polyol pathway, advanced glycation end-products (AGEs) formation, the protein kinase C (PKC)-diacylglycerol (DAG) and the hexosamine pathways [43]. However, synthetic drugs against diabetes mellitus with avalanche of side effects were reported by [44].

Treatment of Diabetes mellitus

Medications

Type 1 Diabetes Mellitus is typically treated with combinations of regular and NPH insulin, or synthetic insulin analogues [25]. When insulin

is used in type 2 diabetes, a long-acting formulation is usually added initially, while continuing oral medications [25]. Doses of insulin are then increased to effect [25].

Pancreatic transplantation

Diabetes may be identified anywhere along the clinical spectrum: in apparently low-risk asymptomatic individuals who happen to have glucose testing; in those tested based on diabetes risk assessment; and in symptomatic patients. Diabetes can be diagnosed based on the plasma glucose criteria, either the fasting plasma glucose (FPG), the 2-h plasma glucose (2-h PG) value after a 75g oral glucose tolerance test (OGTT), random plasma glucose in symptomatic individuals, or the HbA1c criteria [47]. A pancreas transplant is occasionally considered for people with type 1 diabetes who have severe complications of their disease, including end stage renal disease requiring kidney transplantation [26].

Medicinal plant

Studies on the hypoglycaemic and antidiabetic properties of some selected plants by scientists across the globe has led to the discovery of over 250 000 higher plants that has been screened pharmacologically and very few (usually < 1%) are known to have antidiabetic properties [48].

Conclusion

Diabetes mellitus involves different metabolic disorders that all, if left untreated can cause an abnormally high concentration of the blood sugar. Diabetes mellitus type 1 means 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 while type 2, as a result of the autoimmune attacks on the pancreas and/or insulin resistance. Here, the pancreas can produce normal or even abnormally large amounts of insulin. Diabetes mellitus is known to be a common and very prevalent disease affecting the citizens of both developed and developing countries with a population of about 25% of the world population is affected by this disease, which was estimated to be more than 171 million in 2000. Additionally, it has been estimated that the number will increase to over 366 million by 2030 mostly in developing countries, especially in people aged between 45 and 64 years. Type 1 Diabetes Mellitus is typically treated with combinations of regular and NPH insulin, or synthetic insulin analogues or. When insulin is used in type 2 diabetes, a long-acting formulation is usually added initially, while continuing oral medications. Also, pancreas transplant is occasionally considered for people with type 1 diabetes as well as pharmacologically tested medicinal plants for both type 1 and type 2. 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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