IOSR Journal of Dental and Medical Sciences (IOSR-JDMS)
e-ISSN: 2279-0853, p-ISSN: 2279-0861.Volume 16, Issue 12 Ver. XII (Dec. 2017), PP 08-15
www.iosrjournals.org

Diabetes Mellitus: Management Challenges, and Prevention

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Abstract:*Diabetes mellitus (DM), a chronic metabolic disorder with no known cure. In 2016,422 million people have diabetes worldwide with high mortality.DM is classified into four broad categories:type1,type 2,gestational diabetes and "other specific types".DM is more variable disease than once thought and people may have combinations of forms. Clinical manifestation includes frequent urination.Increasedthirst, and increased hunger. Diabetic effects can range from feeling of unease,sweating, trembling, and increased appetite in mild cases to more serious issues such as confusion, changes in behavior,aggressiveness, seizure, unconsciousness, and rarely permanent brain damage or death in severe cases. Diabetes doubles the risk of cardiovascular disease (CVD), with high mortality. World Health Organization criteria, people with fasting glucose levels from 6.1 to 6.9 mmol/L(110-125mg/dl) are considered to have impaired fasting glucose. Glycatedhemoglobin (HbA_{Ic}) is better than fasting glucose determination. Management concentrates on keeping blood glucose levels as close to normal, without causing low blood glucose. Metformin is the first line treatment for type 2 diabetes, with added agents that decrease absorption of sugar, and make the body more sensitive to insulin. Prevention includes a normal body weight, physical activity, healthy diet, and limiting sugary beverages.*

Keywords:*Diabetes mellitus,Management,Complication,Prevention*

Date of Submission: 21-12-2017 Date of acceptance: 28-12-2017

I. Introduction

Diabetes mellitus(DM),commonly referred to as diabetes, is a group of metabolic disorders in which there are high blood sugar levels over a prolonged period[1].As of 2015,an estimated 415 million people had diabetes worldwide[2],with type 2 DM making up about 90% of the cases[3].This represents 8.3 % of adult population[4],with equal rates in both women and men[5].As of 2014,trends suggested the rate would continue to rise[6].In Malaysia 3.6 million(11,25%) Malaysians out of population of 32 million suffering from diabetes [7].From 2012 to 2015,approximately 1.5 to 5.0 million deaths each year resulted from diabetes[2].The global economic cost of diabetes in 2014 was estimated to be US612 billion[8].In the United States diabetes cost $245 billion in 2012[9].Diabetes is due to either the pancreas not producing enough insulin or the cells in the body not responding to the insulin produced[10].Three main types of diabetes include type 1 DM results from the pancreas's failure to produce enough insulin[11],type 2 DM begins with insulin resistance, a condition in which cells fail to respond to insulin properly[11],and gestational diabetes occurs in pregnant women without previous history of diabetes develop high blood sugar levels[11].Clinical manifestation include frequent urination, increased thirst, and increased hunger[11].Acute complications can include diabetic ketoacidosis, hyperosmolar, hyperglycemic state, or death[12],serious complications, heart disease,kidney failure. Foot ulcers, damage to eyes [11].Treatment and prevention include, insulin, metformin, healthy diet, physical exercise [11].The manuscript reviews the management and prevention of DM.

II. Origin of wordDM andhistory

The word diabetes comes from Latin diabetes, which in turn comes from Greek word which literally means "a passer through; a siphon[13].Ancient Greek physician Aretaeus Cappadocia(first century CE) used the word, with the intended meaning "excessive discharge of urine",as the same name for the disease[14].Ultimately, the word comes from Greek(diabainein),meaning to pass through[13].The word "diabetes" is first recorded in English, in the form *diabete*,in a medical text in 1425[[14].The word mellitus(/ma'lartas/ormehitas/)comes from the classical Latin word *mellitus*,

meaning"mellite"(i.e.sweetenedwith honey[15],honey sweet[16].The Latin word comes from *mell*,which comes from *Mel*, meaning honey [15,16], sweetness [16],pleasant thing[16], and the suffix-*itus*[15],whose meaning is the same as that of English suffix-"ite"[17].It was Thomas Willis who in 1675 added the word "mellitus" to the word "diabetes" as a designation for the disease, when he noticed that urine of a diabetic had sweet taste(glycosuria).this sweet taste had been noticed by the ancient Greeks, Chinese, Egyptians ,Indians, and Persians[17].

History: Diabetes was one of the first diseases described [18],with an Egyptian manuscript fromc.1500 BCE mentioning "too great emptying of the urine"[19].The Ebers papyrus includes a recommendation for a drink to be taken in each cases[20].The first described cases are believed to be of type 1 diabetes[19].Indian physicians around the same time identified the disease and classified it as *madhumeha* or "honey urine ",noting urine would attract ants[19].

The term" diabetes" or "pass through" was first used in 230 BCE by the Greek Apollonius of Memphis[19].The disease was considered rare during the Roman empire with Galen commenting he had only seen two cases during his career[19].This may be due to the diet and lifestyle of the ancients, or because the clinical symptoms were observed during the advanced stage of the disease. Galen named the disease "diarrhea of urine"{diarrhea urinosa)[21].The earlies surviving work with a detailed reference to diabetes is that of Aretaeus of Cappadocia(2^{nd} or 3^{rd} 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". Hehypothesized a correlation of diabetes with other diseases, and he discussed differential diagnosis from the snakebite which also provokes excessive thirst. His work remained unknown in the west until 1552,when the first Latin edition was published in Venice[21].Type 1 and type 2 diabetes were identified as separate conditions for the first time by the Indian physicians Sushkruta and Charaka in 400-500 CE with type 1 associated with youth and type 2 with being overweight[19].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[19].Effective treatment was not developed until early part of the 20^{th}century, when Canadians Fredericks Banting and Charles Herbert Best isolated and purified insulin in 1921[19].This was followed by the development of the long acting NPH in the 1940s[19].

III. Worldwide Prevalence

As of 2016,422 million people have diabetes worldwide [22],up from an estimated 382 million people in 2013[4],and from 108 million in 1980[22].According to the shifting age structure of the global population, the prevalence of diabetes is 8.5% among adults, nearly double the rate of 4.7% in 1980[22].Type 2 makes up about 90% of cases[5].Some data indicate rates are roughly equal in women and men[5], but male excess in diabetes has been found in many populations with higher type 2,possible due to sex- related differences in insulin sensitivity, consequences of obesity and regional body fat deposition, and other contributing factors such as high blood pressure, tobacco smoking and alcohol intake[23].The World Health Organization (WHO) estimates that diabetes mellitus resulted 1.5 million deaths in 2012, making it the 8^{th} leading cause of death[22].However another 2,2 million deaths worldwide were attributed to high blood glucose and increased risk of cardiovascular disease and other associated complications(e.g. Kidney failure),which often lead to premature death and are often listed as the underlying cause on death certificates rather than diabetes[22].For example, in 2014,the International Diabetes Federation(IDF) estimated that diabetes resulted in 4.9 million deaths worldwide[6],using modeling to estimate the total number of deaths that could be directly or indirectly attributed to diabetes[8].Diabetes mellitus occurs throughout the world but is more common(especially type 2) in more developed countries. The greatest increases in rates has however been seen in low and middle- income countries[22],where more than 80% of diabetic deaths occur[24].The fastest prevalence increase is expected to occur in Asia and Africa, where most people with diabetes will live in 2030[25].The increase in rates in developing countries follows the trend of urbanization and lifestyle changes, including increasing sedentary lifestyles, less physical demanding work and the global nutrition transition, marked by increased intake of foods that are high energy-dense but nutrient poor(often high in sugar and saturated fats, sometimes referred to as the "Western-style "diet)[25].

IV. Contributory Factors

Diabetes mellitus is classified into four broad categories: type 1,type 2,gestational diabetes and "other specific types"[10].The "other specific types" are a collection of a few dozen individual causes[10].Diabetes is a more variable disease than once thought and people may have combinations of forms[26].

4.1 Type 1 diabetes

Type 1 diabetes mellitus is characterized by loss of the insulin-producing beta cells of the pancreatic islets, leading to deficiency. This type can be further classified as immune-mediated or idiopathic. The majority of type 1 diabetes is of the immune-mediated nature, in which a T cell-mediated autoimmune attack lead s to the loss of beta cells and thus insulin[27].Type 1 diabetes can affect children or adults, but was traditionally termed "juvenile diabetes" because a majority of these diabetes were in children."Brittle" diabetes, also known as unstable diabetes or labile diabetes, as a term that was traditionally used to describe the dramatic and recurrent swing in glucose levels, often occurring for no apparent reason in insulin- dependent diabetes. This term, however, has no biologic basis ans should not be used[28].Type 1 diabetes is partly inherited, with multiple genes, including HLA(human leucocyte antigen)genotypes, known to influence the risk of diabetes. In genetically susceptible people, the onset of diabetes can be triggered by one or more environmental factors [29],such as a viral infection or diet. Several viruses have been implicated, but to date there is no stringent evidence to support this hypothesis in humans[30].Among dietary factors data suggest that gliadin(a protein present in gluten) my play a role in the development of type-1 diabetes, but the mechanism is not fully understood[30].

4.2 Type 2 Diabetes

Type 2 DM is characterized by insulin, which may be combined with relatively reduced secretion [10].The defective responsiveness of body tissues to insulin is believed to involve the insulin receptor. However, the specific defects are not known. Diabetes mellitus cases due to a known defect are classified separately. Type 2 DM is the most common type of diabetes [11].Type 2 DM is primarily due to lifestyle factors and genetics[31].A number of life style factors are known to be important to the development of type 2 DM, including obesity(BMI > 30),lack of physical activity, poor diet, stress, and urbanization [32,]. Excess body fat is associated with 30% of cases in those of Chinese and Japanese descent, 60-80% of cases in those of European and African descent, and 100% of Pima Indian and Pacific Islanders[10].Often those who are not obese often have a high waist-hip ratio[10].Dietary factors also influence the risk of developing type 2 DM.Consumption of sweetened drinks in excess is associated with an increased risk[33].The type of fat in the diet is also important, with saturated fat and trans fats increasing the risk and polyunsaturated and monosaturated fat decreases the risk[32].Eating lots of white rice may increase the risk of diabetes[34].A lack of physical activity is believed to cause 7% of cases[35].

4.3 Pregnancy - gestational diabetes

Pregnancy or gestational diabetes (GDM) resembles type 2 DM in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness. It occurs in about 2-10% of all pregnancies and may improve or disappear after delivery [36,].However, after pregnancy approximately 5-10% of women with gestational diabetes are found to have diabetes mellitus, most commonly type 2[36].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 [36].

Gestational diabetes though may be transient, untreated can damage the health of the fetus or mother. Risks to the baby include macrosomia (high birth weight), congenital heart and central nervous system abnormalities, and skeletal muscle malformations; increased levels of insulin in a fetus's blood may inhibit fetal surfactant production and cause respiratory distress syndrome. A high blood bilirubin level may result from red blood cell destruction. In severe cases, potential death may occur, most commonly as a result of poor placental perfusion due to vascular impairment. Labor induction may be indicated with decreased placental function. A Caesarean section may be performed if there is marked fetal distress or an increased risk of injury associated with macrosomia such as shoulder dystocia [36].

4.4 OtherTypes of Diabetes

4.5 Maturity onset of diabetes of the young(MODY):MODY is an autosomal dominant inherited form of diabetes, due to one of several single-gene mutations causing defects in insulin production[37].It significantly less common than the three main types. The name of this disease refers to early hypotheses as to its nature. Being due to a defective gene, this disease varies in age at presentation and in severity according to the specific gene defect: thus there are at least 13 subtypes of MODY.People with MODY often can control it without using insulin[37].Prediabeticcondition:Prediabetic condition 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.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 cause. Tissue receptors: Some cases of diabetes are caused by the body's tissue receptors not responding to insulin(even when insulin levels are normal, which is what separates it from type 2 diabetes);this form is very uncommon. Genetic

mutation:Genetic mutations(autosomal or mitochondrial) can lead to defects in beta cell function. Abnormal insulin action may also have been genetically determined in some cases. Any disease that causes extensive damage to pancreas may lead to diabetes(for example, chronic pancreatitis and cystic fibrosis).Diseases associated with excessive secretion of insulin-autogonostic hormones can cause diabetes(which typically resolved once hormone excess is removed)

Drug InducedDiabetes: Many drugs impair insulin secretion and some toxins damage pancreatic beta cels.The ICD-10(1992).diagnostic entity,*malnutrition-related diabetes mellitus*(MRDM or MMDM.ICD-10 code 12) was deprecated by the World Health Organization when the current taxonomy was introduced in 1999[38].Other forms of diabetes mellitus include congenital diabetes, which is due to genetic defects of insulin secretion, cystic fibrosis diabetes, steroid diabetes induced by high doses of glucocorticoid, and several forms of monogenic diabetes. "Type 3 diabetes" has been suggested for Alzheimer's as the underlying process may involve insulin resistance by the brain [39]Other causes of diabetes includes:[40].a)Genetic defects of β cell function, b) Genetic defects in insulin processing or insulin action. c)Exocrine pancreatic defects, d)Endocrinopathies e) Infections, f) Drugs-mainly glucocorticoid,Thyroidhormone,beta-adrenergic agnostic and g)Statins[41].*Statin therapy is associated with a slightly increased risk of development of diabetes, but the risk is low in absolute terms and when compared with reduction in coronary events. Clinical practice in patients with moderate or high cardiovascular risk or existing cardiovascular diseaseshould not change.*

V. Pathophysiology

Insulin is the principal hormone that regulates the uptake of glucose from 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 plays a central role in all forms of diabetes mellitus[42].The body obtains glucose from three main places: the intestinal absorption of food; the breakdown glycogen, the storage form of glucose found in the liver; and gluconeogenesis, the generation of glucose from non-carbohydrate substrates in the body[43].Insulin plays a critical role in balancing glucose levels in the body. Insulin can inhibit the breakdown of glycogen or the process of glycogenesis,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 [43].

Insulin is released into 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 blood for use as fuel, for conversion to other needed molecules, or for storage. Lower glucose levels results 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 [44].If the amount insulin available is insufficient, if cells respond poorly to the effect of insulin(insulin insensitivity or insulin resistance),or if insulin itself is defective, then glucose will not be absorbed properly by the body cells that require it, and it will not be stored appropriately in the liver and muscles. The net effect is persistently high levels of blood glucose, poor protein synthesis, and other metabolic derangement, such as acidosis [43].When the glucose concentration in the blood remains high over time, the kidneys will reach a threshold of reabsorption, and glucose will be excreted in the urine(glycosuria)[45].This increases the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting increased urine production(polyuria) and increased fluid loss. Lost blood volume will be replaced osmotically from water held in body cells and other body compartments, causing dehydration and increased thirst (polydipsia)[43].

VI. Clinical Manifestations

The frequent symptoms of untreated diabetes are weight loss, polyuria (increased urination), polydipsia(increased thirst),and polyphagia(increased hunger)[46]Symptoms may develop rapidly(weeks or months) in type 1 DM,while usually develop more slowly and may be subtle or absent in type 2 DM.Other symptoms include blurry vision, headache, fatigue, slow healing of cuts, and itchy skin. Prolonged high blood glucose can cause glucose absorption in the lens of the eye, which leads to changes in shape in its shape, resulting in vision changes. A number of skin rashes that can occur in diabetes are collectively known as dermadrome [47].

6.1 Emergencies and complications in diabetes

Low blood sugar is common in persons with type 1 and type 2 DM.Most cases are mild and not considered medical emergencies. Effects can range from feelings of unease, sweating, trembling, and increased appetite in mild cases to more serious issues such as confusion, changes in behavior such as aggressiveness,seizure, unconsciousness, and rarely permanent brain damage or death in severe cases[48].Moderate hypoglycemia may easily be mistaken for drunkenness[49],rapid breathing and sweating, cold, pale skin are characteristic of hypoglycemia but not definitive[50].Mild to severe cases are self- treated by eating or drinking something high in sugar. Severe cases can lead to unconsciousness and must be treated with

intravenous glucose or injections with glucagon[50].People with(usually with type 1 DM)may also experience episodes of diabetic a ketoacidosis,a metabolic disturbance characterized by nausea, vomiting and abdominal, pain, the smell of acetone on the breath, deep breathing known a Kussmaul breathing and severe cases a decreased level of consciousness[51].A rare but equally severe possibility is hyperosmolar hyperglycemia state, which is more common in type 2 DM and is mainly the result of dehydration[51].

6.2.Complications:The major long term complications relate to blood vessels. Diabetes doubles the risk of cardiovascular disease [52],and 75% of deaths in diabetes are due to coronary artery disease. Other "macrovascular" diseases are stroke and peripheral artery disease[53].The primary complications of diabetes due to damage to small vessels include damage to the eyes, kidneys, and nerves[54].Damage to the eyes, known as diabetic retinopathy, is caused by damage to blood vessels in the retina of the eye, and can result gradual visual loss and blindness[54].The damage to kidney disease, sometimes require dialysis or kidney transplantation[54].Damage to the nerves of the body, known as a diabetic neuropathy, is most common complication of diabetes[54].The symptoms can include numbness tingling, pain, and altered pain sensation, which can lead to damage to skin. Diabetes –related foot problems (such as diabetic foot ulcers)mayoccur, and can difficult to treat, occasionally requiring amputation. Additionally, proximal diabetic neuropathy causes painful muscle atrophy and weakness [54].There is a link between cognitive deficit and diabetes. Comparted to those without diabetes, those with the disease have a 1.2 to 1,5 greater rate of decline in cognitive function[55,].Being ,diabetic, especially, when on insulin increases the risk of falls in older people[56].

VII. Diagnosis

Diabetes mellitus is characterized by recurrent or persistent high blood sugar, and is diagnosed by demonstrating any one of the following:[38].a).Fasting plasma glucose level ≥ 7.0 mmol/L(126 mg/dl).b).Plasma glucose ≥11.1 mmol/L(200 mg/dl)two hours after 75 g oral glucose load as in glucose tolerance test, c).symptoms of high blood sugar and casual plasma glucose ≥ 11.1mmol/L(200mg)d).Glycated hemoglobin (HbA1c)≥48mmol(≥ 6.5 DCCT%)[57].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 days[58].Per the World Health Organization people with fasting glucose levels from 6.1 to 6.9 mmol/L (110-125mg /dl) are considered to have impaired fasting glucose[59],people with plasma glucose at or above 7.8 mmol/L(140 mg/dl),but not over 11.1/L(200 mg/dl),two hours after 75 g oral glucose load considered to have impaired glucose tolerance. Off course prediabetes states, the latter in particular is a major risk factor for to full-blown diabetes mellitus, as well as cardiovascular disease [60].The American Diabetes Association since 2003 uses a slightly different range for impaired fasting glucose of 5.6 to 6.9mmml/L(100-to 125 mg/dl).[61].Glycated hemoglobin is better than fasting glucose determination risks of cardiovascular disease and death from any cause[62].

VIII. Management and Prevention

Diabetes mellitus is a chronic disease, for which there is no known cure except in very specific situation. Management concentrates on keeping blood sugar levels as close to normal, without causing low blood sugar.[63].Learning about the disease and actively participating in the treatment is important since complications are far less severe in people who have well managed blood sugar levels[64].The goal of the treatment is an HbA_{1C}level of 6.5%,but should not be lower than that, and may be set higher[65].The attention is also paid to other health problems that may accelerate the negative effects of diabetes. These include smoking, elevated cholesterol levels, obesity, high blood pressure, and lack of regular exercise [65].Specialized footwear is widely used to reduce risk of ulceration, or re-ulceration, in at-risk diabetic feet. Evidence for the efficacy of this remains equivocal, however [66].

8.1.Education and change in lifestyle:

People with diabetes can benefit from education about the disease and treatment, good nutrition to achieve a normal body weight and exercise, with the goal of keeping both short term and long term blood glucose levels within acceptable bounds. In addition, given the associated high risks of cardiovascular disease, lifestyle modification are recommended [67].In Germany, an insurance- based health service, diagnosis of type 1 diabetes triggers instant education according to a standard curriculum as an inpatient, until essential self-management skills have been demonstrated. This intervention and subsequent annual educational refresher course are valued and paid for by the insurance company [68].There is no single dietary pattern that is best for all people with diabetes. For overweight people type 2 diabetes, any diet that a person will adhere to and achieve weight loss on is effective [69].

8.2.Medication and surgical intervention:

Metformin is generally recommended as a first line treatment for type 2 diabetes, as there is good evidence that it decreases mortality[33].It works by decreasing the liver's production of glucose[70].Several other groups of drugs, mostly given by mouth, may also decrease blood sugar in type II DM.These include agents that increase insulin release, agents that decrease absorption of sugar from the intestines, and agents that make the body more sensitive to insulin[70].When insulin is used in type 2 diabetes, a long acting formulation is usually added initially, while continuing oral medication[70].Doses of insulin are then increased to effect[70].Since cardiovascular disease is a serious complication associated with diabetes, some have recommended blood pressure levels below 130/80mmHg[71].However, evidence supports less than or equal to somewhere between 140/90 mmHg to 160/100 mmHg; the only additional benefit found for blood pressure targets beneath this range was an isolated decrease in stroke risk, and this was accompanied by an increased risk of other serious adverse events[72].A 2016 review found potential harm to treating lower than 140mmHg[73].
A pancreatic transplant is occasionally considered for people with type 1 diabetes who have severe complications of their disease, including end stage kidney disease requiring kidney transplantation [74].Weight loss surgery in those with obesity and type two diabetes is often an effective measure[75].Many are able to maintain normal blood sugar levels with little or no medication following surgery[76].

8.3 Prevention

There is no known preventive measure for type 1 diabetes[11].Type 2 diabetes-which accounts for 85-90% of all cases-can often be prevented or delayed by maintaining a normal body weight, engaging in physical activity, and consuming a healthful diet[11].Higher levels of physical activity(more than 90 minutes per day) reduce the risk of diabetes by 28%[77].Dietary changes known to be effective in helping to prevent diabetes include maintaining a diet rich in who grains and fiber, choosing good fats, such as the polyunsaturated found in nuts,vegetable oils and fish[78].Limiting sugary beverages and eating less red meet and other sources of saturated fat also help prevent diabetes[78].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[79].

XI. Conclusions

Diabetes mellitus (DM) is one of the metabolic disorders, with high mortality worldwide. Patient education, treatment compliance and regular exercise has better outcome.

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*Murtaza Mustafa. "Diabetes Mellitus: Management Challenges, and Prevention." IOSR Journal of Dental and Medical Sciences (IOSR-JDMS) 16.12 (2017): 08-15