The Facts about Diabetes Mellitus- A Review

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ABSTRACT

Diabetes mellitus is a growing health problem in the world that causes severe morbidity and mortality. The prevalence of diabetes was rising day by day. The facts about the diabetes mellitus, its prevalence, morbidity, and mortality were published in many statistical reports. It is unfortunate that there is the unavailability of a recent compilation of the diabetes-related evidence in one article. The main aim of the present review is to compile the reports related to diabetes and their prevalence in India as well as in the world. This review includes the contents which briefly explain the facts related to the development of diabetes, history of diabetes, burden of diabetes in the world as well as in India, complications of diabetes, its treatment and the alternative remedies. The relevant pieces of evidence were obtained from many currently available articles and statistical reports. This review will be useful for new researchers in the field of diabetes.

Key words: Diabetes mellitus, mortality, morbidity.

INTRODUCTION

HISTORY OF THE DIABETES

Diabetes mellitus (DM) is one of the very oldest diseases and was mentioned three thousand years ago in Egyptian literature.¹ Around 1500 B.C the physicians in India noticed the sweetness of urine of the diabetic people and called it as “Madhumeha”. Ebers papyrus, the oldest literature was written around the same time by Egyptians and it was also the first document that describes a condition of frequent emptying of urine.²³ Around 5th and 6th century the ancient Indian physician Susruta and Sharuka described first time about the extreme thirst, foul breath and polyuric state associated with sweet taste substance in the urine. They were the first identified the difference between the type I and type II DM.⁴⁻⁵ Aretaeus of cappodocia a Greek physician, he was the first person coined the term diabetes by observing the clinical condition that increased frequency of urine in diabetic individuals. He was also the first to distinguish diabetes mellitus and diabetes insipidus. Later on, Thomas Willis in 1670 was added the term mellitus (honey sweet) after rediscovering the sweetness of urine in the patient was due to the high blood glucose level. In 1776, Matthew Dobson, a British physiologist first confirmed that the sweetness of urine is due to the presence of excess glucose in blood and urine.⁶ Around 30 BC- 50AD, the Aulus Cornelius Celsus has given the complete clinical description for diabetes mellitus in Latin and entitled De medicina.⁷⁻⁸ In 1857 Claude Bernard established the concept that excess glucose production and the role of the liver in Glycogenesis.⁹ In 1889, Joseph von Mering and Oskar Minkowski found that the removal of the pancreas in the dog caused the development of symptoms of diabetes which greatly attributed to the discovery of the role of the pancreas in diabetes mellitus.¹⁰ Later, their discovery influences the Banting to focus his research on diabetes. In 1921 Banding and Best-isolated insulin from the pancreas and got Nobel Prize in 1923.
GLUCOSE HOMEOSTASIS AND DIABETES MELLITUS

Glucose is a chief fuel in biology. Glucose is metabolized in the mitochondria to release the ATP which provides energy to the cell. This energy is utilized for cell movement, nerve conduction, hormone production and to nourish the genetic machinery of the cell (DNA). Glucose in the body is maintained within the narrow range by two main hormones- Insulin and Glucagon- which acting antagonistically to increase or decrease blood glucose level in the blood. Both these hormones are released by the pancreas. High blood sugar level stimulates the release of insulin which is secreted by Beta cells of Islets of Langerhans in the pancreas that increases the uptake of glucose by cells. Moreover, in the cell, the glucose is used as energy, converted to glycogen and stored mainly in the liver and muscles or used in the synthesis of fats. In some abnormal conditions, the cell resists insulin which leads to considerable reduction in the glucose uptake, glycogen synthase activity, glycogen synthesis and storage in peripheral tissue. While there is a lack of insulin secretion or cell resists insulin, which leads to diabetes mellitus.

TYPES OF DIABETES MELLITUS

Diabetes mellitus (DM) is a globally expanding endocrine disorder, growing at a frightening rate both in developing and developed countries. There are two major types of diabetes mellitus these are type I, type II and one minor type called Gestational diabetes and maturity onset diabetes mellitus (MODY). The main cause of type I or Juvenile diabetes is due to autoimmune insulinitis, where the insulin-producing beta cells in the pancreas are destructed by the body’s defense system. As a result, the body is unable to produce sufficient insulin that needs. Hence type I diabetes requires exogenous insulin therapy to survive. The other causes of type I dm are genetic and environmental factors such as viral infection and certain chemicals.

Despite the fact that this disease usually occurs in children or young adults, it can also affect people irrespective of age. Type I diabetes is less common and accounts for only about 10% of the diabetic people. Type II diabetes is the most common type of diabetes it usually occurs in adults which accounts for about 90% of the diabetic people. In type II diabetes mellitus, the body is capable of produce insulin but this is not adequate or the body is unable to respond to its effects (insulin resistance), leading to increases in blood glucose level. In gestational diabetes, some women have developed insulin resistance that occurs around the 24th week of pregnancy. This condition arises when the hormones produced by the placenta probably block the action of insulin. Even though this type of diabetes typically disappears following delivery, 40% of the women with gestational diabetes have more chance to develop type II diabetes later in life.

Maturity-onset diabetes mellitus is very rare and accounts for 1-2% of the population. Molecular genetic studies on the MODY showed that genetic mutations cause the destruction of beta-cells.

PREDISPOSING FACTORS OF TYPE II DIABETES MELLITUS

The major predisposing factors of type II diabetes in the Indian population are advancing age, poor dietary habits, physical inactivity and rapid urbanization which are leading to lifestyle changes, genetic predisposition to diabetes, central obesity, and higher insulin resistance in Asian Indians. Some of the research studies also shown that the type of food, sex and race also main contributing factors for diabetes mellitus. The family history of diabetes mellitus is a strong predisposing factor. Few recent studies also reported that environmental factors and modified alpha cell functions also cause diabetes mellitus. Apart from this, the other aggravating factors of diabetes are poor diabetes screening and preventive services, non-adherence to diabetes management.
guidelines, long-distance travel to health services mainly in the rural sector, disparities in diabetes management between urban and rural areas.\textsuperscript{35} Furthermore, in India, the awareness of people with diabetes is low as compared with Western countries. The Chennai Urban Rural Epidemiology Study (CURES) has stated that the knowledge for risk factors associated with diabetes among Indian population was very less and only 11.9 percent of study subjects acknowledged that obesity and physical inactivity were the predisposing factors.\textsuperscript{36}

**GLOBAL BURDEN OF DIABETES**

There is a steady rise in the health burden of diabetes were observed throughout the world. The increasing population, aging, lifestyle changes, urbanization and decreased physical activity are the main factors that cause a global increase in the prevalence of diabetes. The primary determinants of the epidemic of diabetes are decreased physical activity associated with increased calorie intake. The global burden varies from country to country which depends upon the economic status of the countries. The proportion of the rate of diabetic prevalence is inverse to the current economic status of the country. The highest rise was seen in fewer income countries (92%), followed by lower-middle income countries (57%), upper-middle-income countries (46%) and finally high-income countries (25%).\textsuperscript{37} The diabetic report published by IDF showed that 4 out of 5 people live in low and middle-income countries. In the western countries, the elderly people are usually affected by diabetes but in contrast, the young and middle-aged adults are mainly affected in Asian countries.\textsuperscript{38,39} Since the last few decades, diabetes status has increased from mild disorder to one of the foremost reason for morbidity and mortality among the population. Huge reports published by the international diabetic federation and world health organization given the data that express the number of people affected by diabetes at present and in the future.

The estimation of diabetes prevalence is given by IDF and WHO showed a tremendous increase in the Global burden of diabetes. According to IDF diabetes atlas the global prevalence of diabetes in adults between the age of 24 to 79 years was 151 million in 2000, \textsuperscript{40} 194 million in 2003, \textsuperscript{41} 246 million in 2006, \textsuperscript{42} 285 million in 2010, \textsuperscript{43} 366 million in 2011, 382 million in 2013, \textsuperscript{18} 413 million in 2015, \textsuperscript{44} and 425 million in 2017.\textsuperscript{45} This level will have been increased to 642 million in 2040.\textsuperscript{44} At the same time reports also implied that 1 in 11 adults has diabetes in 2015; this will rise to 1 in 10 adults in 2040. The current IDF diabetes atlas highlighted that the prevalence of diabetes in the adult is 10 million more in 2017 than in 2015. Recent statistics of diabetic people in the individual continent showed that, 37 million in 2013, 44.3 million people in 2015 and 46 million in 2017 have diabetes mellitus in North America; 56 million in 2013 and 59.8 million in 2015 in Europe; 20 million in 2013 and 24.2 million in 2015 in Africa; and 138 million in 2013 and 153.2 million people in 2015 in western Pacific. This showed that the number of diabetic people is greater than their earlier estimation. The estimation of diabetic mortality shows that every 6 seconds 1 person dies from diabetes.\textsuperscript{18,44} According to WHO 2016 reports, 3.7 million people have died of diabetes in 2012, this was rise to 5.0 million in 2015. The estimation given in IDF 2013, among top 10 countries with more diabetic people between the age of 20-79 years, China was in first place (98.4 million) followed by India (65 million), USA (24.4 million), Brazil (11.9 million), Russian Federation (10.9 million), Mexico (8.7 million), Indonesia (8.5 million), Germany (7.5 million) and Japan (7.2 million). Globally there was the considerable amount spent for diabetes in 2013 the global expenditure was 548 billion us dollar that raised to 627 billion us dollar in 2015, which consist of 12% of the global health expenditure. The majority of the people affected by type II diabetes. This used to
affect adults but now it is seen in children too.

**DIABETES BURDEN IN INDIA**

In India, the potential epidemic status of Diabetes seems to be high in level. According to world health organization reports, there were 32 million people affected by diabetes in the year 2000,[47] 37.76% million in 2004,[48] 50.8% in 2010. Now it has increased to more than 62 million in 2016 in India this number was predicted to rise to 109 million by 2035.[49,50] The Indian Council of Medical Research (ICMR) was conducted a study that showed that higher proportions of the people were affected in Maharashtra followed by Tamilnadu.[51] The report of national urban diabetes survey conducted in the metropolitan cities in India also confirmed that the prevalence of type II diabetes was 16.6% in Hyderabad, 13.5% in Chennai, 12.4% in Bangalore, 11.7% in Kolkata, 11.6% in New Delhi, 9.3% in Mumbai and 6.1% in Kashmir valley.[52]

The Urban-rural differences in the prevalence of diabetes have been consistently reported from India. The national study conducted on the prevalence of type 2 diabetes in India was by the Indian Council Medical Research (ICMR) showed that the prevalence in the urban population was 2.1 per cent, 1.5 percent in rural areas at the age above 14 years, and 5% in the urban population and 2.8% in the rural areas in those above 40 years.[53] A later study showed that the prevalence was three times higher among the urban (8.2%) compared to the rural population (2.4%).[54] According to the study conducted by Ramachandran A (2007) [55] the estimated cost needed to treat Type 2 dm would be USD 2.2 billion in India. This was raised to USD 61 billion in 2012 (WHO, 2012).[56] in the year 2005 the cost expenditure for treating type 2 dm was INR6212.4 in Delhi of which more than half were spent for the diabetic drug.[57] Similarly, another study on type I and II DM in India reported that in 2005, a total direct expenditure of INR 4,966 for six months; 62% comprises of drug costs (INR 3,076). Further, the expenditure on diabetic complications constitutes indirect cost. The total INR 2,087 was indirectly spent for dm over a six-month period in 2005 and 61% of the total income accounted for indirect expenditure.[58] A study conducted in North India reported as the treatment costs were found to be considerably higher in individuals who have well educated (INR 2,810.20) than those who have less educated (INR 398.66).[59] Another study conducted in Chennai found that total expenditure for dm without any complications in 2008 and 2009 was INR 4,493 compared to INR 14,691.75 (USD 301.32) for patients with complications.[60]

**COMPLICATIONS OF DIABETES**

The increased blood glucose in diabetes mellitus leads to many complications such as metabolic changes, increased oxidative stress, cardiovascular and renal diseases.[61,62] The complications of diabetes are increasing in the poor urban slum dwellers, the middle-class people and even in the rural areas. This is due to increased physical inactivity and dietary changes and increased stress among the people of the society. Unfortunately increased risk of complications in the underprivileged diabetic subjects might be due to delay treatment.[63] A research study mentioned that people with less physical activity are more prone to metabolic syndrome and hypertension.[64] The same study also indicated that the chances of development of coronary artery disease were higher light grade physical activity people compared to the heavy grade physical activity group. Among the diabetic subjects, the major cause of morbidity and mortality are both macrovascular and microvascular complications. The studies in India such as The Chennai Urban Population Study and Chennai Urban Rural Epidemiology Study (CURES) given important data on the complications related to diabetes. According to that study, the prevalence of coronary artery disease
among diabetic subjects was greater compared to the subjects with normal glucose tolerance.\textsuperscript{[65]} It was also noted that subclinical atherosclerosis measured by intimal medial thickness was high in diabetic subjects at every age. The prevalence of diabetic retinopathy was studied by CURES Eye study is the largest population-based data in India showed that the overall prevalence was 17.6 percent.\textsuperscript{[66]} A population-based study in Indians was reported that the prevalence of nephropathy was 2.2 percent and microalbuminuria was 26.9 percent.\textsuperscript{[67]} Overall, cardiovascular complications seem to appear greater in Asian Indians. A recent Chennai urban population study showed that the overall mortality rates are 18.9 per 1000 persons in a year which was nearly three-fold greater in people with diabetes compared to nondiabetic subjects (5.3 per 1000 person-year).\textsuperscript{[68]} Thus the hazard ratio of all-cause mortality for diabetes was found to be higher compared to nondiabetic subjects. The study also showed that mortality in diabetic subjects due to cardiovascular (52.9\%) and renal disease (23.5\%) was greater than the mortality due to cardiovascular (24.2\%) and renal disease (6.1\%) in the nondiabetic subject. A study showed that migration from the village to the city in India led to obesity, glucose intolerance, and dyslipidemia.\textsuperscript{[69]}

**MANAGEMENT OF DIABETES**

The most important goal in the management of type II diabetes is to control high blood sugar levels and their complications. Type II DM is typically controlled with precise medical therapy and a stepwise approach, which includes initial lifestyle modifications, treatment with Oral Antidiabetic Drugs (OADs) and the addition of insulin. In spite of the possible lifestyle modifications and early intervention to prevent disease progression, the majority of patients presently have poor glycemic control and high glycosylated hemoglobin (HbA1c) level.\textsuperscript{[18,70]} When the diabetes is initially diagnosed, the preliminary therapy modality includes lifestyle modifications such as the low-calorie diet intake with appropriate weight reduction exercise associated with patient education and self-management are advised to reduce the blood glucose level. The meal plans and diet modifications are generally individualized by a registered dietitian to meet patient’s needs and lifestyle. A typical healthy diet composed of 60-65\% carbohydrate, 25-35\% fat and 10-20\% protein with limited or no alcohol consumption.\textsuperscript{[71]} Regular physical activity and low dietary fat consumption with less calorie intake is a successful way to achieve weight loss.\textsuperscript{[72]} Exercising more than five times per week enhances weight loss. The study conducted by Kartono et al proved that repeated physical exercise prevents diabetes mellitus.\textsuperscript{[73]} The appropriate exercise selection depends on patient interest, physical status, capacity, and motivation. Exercise should start at a low level and gradually increase to avoid adverse effects such as injury, hypoglycemia or cardiac problems.\textsuperscript{[74]} The increased glucose utilization by the cell and decreased hepatic glucose production occur during moderate exercise in type 2 diabetic patients.\textsuperscript{[75]} Even though exercises given many benefits, there is some risk of exercise is seen in the diabetic patient suffering from complications like the diabetic foot, diabetic neuropathy, and loss of perception, all these can lead to injuries in a patient while performing exercise or walking. The self-management skills, including self-glucose monitoring, compliance with diabetic treatment, maintenance of proper diet to control blood sugar and reduction in complications can be achieved by patient education.\textsuperscript{[76]} When the diet and exercise are unable to achieve the required glycemic control, oral glucose-lowering drugs and insulin injections are initiated. Oral antidiabetic drugs (OADs) are usually introduced when lifestyle modifications fail to satisfactorily control hyperglycemia. These oral antidiabetic drugs are commonly given to the diabetic patients which act on the organs such as pancreas, liver and
skeletal muscle. They are very useful for managing high blood glucose especially in the early stages of the disease, achieving typical HbA1c reductions of 0.5% to 2%. The commonly used OADs are Sulphonylureas (SU) eg. Glibenclamide, Biguanides eg. Metformin, α glucosidase inhibitors eg. Acarbose and the Thiazolidinediones (TZD) eg. Pioglitazone, Rosiglitazone. The sulfonylureas and the biguanides are the major groups of oral hypoglycemic agents widely used in the treatment of diabetes, the other OADs are insulin sensitizer (Troglitazone), dipeptidyl peptidase- 4 inhibitors (Sitagliptin, Saxagliptin, and Vildagliptin), incretin mimetics (glucagon-like peptide (GLP-1), Thiazolidinedione, Alpha-glucosidase inhibitors (Acarbose). normally OAD s are initiated when the fasting blood glucose level is more than 140mg/dl, postprandial blood glucose is level is 160mg/dl or above and the Glycosylated hemoglobin level exceeds 8.0%. [77]

Despite the fact that the OADs are rapidly acting and exhibit high therapeutic effects, they have several limitations that prevent from reaching their potential. The major limitation is their mechanisms of action which often reduces the symptoms of diabetes rather than its underlying pathophysiology. OADs may also have undesirable side effects. The main side effect of Sulphonylureas is hypoglycemia in patients who are elderly or have renal insufficiency. The use of TZDs causes lowering bone density and increased fracture risk in women with type II DM. Nissen et al., (2007)[78] showed that the increased risk of myocardial infarction was significant in the Rosiglitazone treatment. The other medications such as GLP-1 mimics causes nausea which lost for a long time. When the blood glucose level is very high and OAD's are not enough to control blood glucose level and Insulin is typically prescribed. Human insulin has a slower onset of action and a prolonged effect compared with endogenous insulin when it is injected subcutaneously at meal time but must be injected 30 to 60 minutes before the meal in order to avoid postprandial hyperglycemia and between meal hypoglycemia. Weight gain and hypoglycemia and needle stick injury are the common side effect of insulin therapy.[79,80] These side effects can have a negative impact on patient adherence to the treatment resulting in higher HbA1c levels and increased risk for all-cause hospitalization and all-cause mortality.[81]

**ALTERNATIVE THERAPIES TO DIABETES MELLITUS**

Many effective alternative therapies have been developed for treating diabetes mellitus, particularly in India. These therapies posses high efficacy without any troublesome side effects. Nowadays these alternate therapies becoming popular which includes yoga, acupuncture hydrotherapy, and medicinal plants.

**Yoga:**

The word Yoga is derived from the Sanskrit word ‘Yuj’ meaning the union of the body, breath, and mind. Stretching of the abdomen during yoga exercise causes regeneration of cells of the pancreas and increasing the utilization and metabolism of glucose in peripheral tissues, liver, and adipose tissues through the enzymatic process.[82-85] During the yoga, there is an improved blood supply to the muscles and muscular relaxation which leads to increased glucose uptake and thus reducing blood glucose level.[86] The yoga practice increases the activity of hepatic lipase and lipoprotein lipase at the cellular level, which affects the lipid metabolism and also increases the storage of triglycerides in the adipose tissue and decreases blood triglyceride level.[87] In the different Yoga postures, the sensitivity of the pancreatic β-Cells to glucose has improved and causes subsequent insulin secretion.[86] In interventional research on yoga demonstrated that fasting blood sugar (FBS), serum total cholesterol, low-density lipoproteins (LDL), very low-density lipoproteins (VLDL), and total triglycerides
were significantly reduced, and HDL-C was significantly increased after performing the yoga.\[^{[88]}\]

**Acupuncture:**

Acupuncture is best known as an alternative therapy for chronic pain. However, during the past few years, it has been used in diabetes treatment and its associated complications. Acupuncture stimulates the pancreas to increase insulin synthesis, enhance the number of receptors on target cells, and hasten the utilization of glucose, which lead to lowering of blood glucose.\[^{[89]}\] Although acupuncture shows some effectiveness in diabetes treatment, its mode of action is still unknown.

**Hydrotherapy:**

Some type II diabetes mellitus patients are unable to do exercise due to diabetic complications, hot tub therapy is recommended to increase blood flow to skeletal muscles. A study reported that 30 minutes of hot tub therapy in diabetic patients decreased body weight, mean plasma glucose level, and mean glycosylated hemoglobin level. Necessary care should be taken while prescribing hot tub therapy for diabetic patients to ensure proper water sanitation and appropriate temperature.\[^{[90]}\]

**Medicinal plants:**

According to Ayurveda, there are several medicinal plants has been identified to possess antidiabetic potential. Most of the herbal preparations from these medicinal plants are reported to have minimal or no side effects.\[^{[91]}\] Since the ancient period, herbal plants are being used to treat diabetes mellitus. Some of the very common and beneficial antidiabetic herbal plants of Indian origin are Acacia arabica (Babul), Aegle marmelos (Bael), Agrimonia eupatoria (Church steeples), Allium cepa (Onion), Allium sativum (Garlic), Ghrita kumara (Aloe vera), Azadirachta indica (Neem), Benincasa hispida (Ash Gourd), Caesalpinia bonducella (Fever Nut), Citrullus colocynthis (Bitter Apple), Coccinia indica (Ivy Gourd), Ficus benghalensis (Banyan Tree), Gymnema sylvestre (Gurmar), Hibiscus rosa-sinensis (Gurhal), Jatropha curcas (Purging Nut), Mangifera indica (Mango), Momordica charantia (karela), Morus alba (Mulberry), Mucuna pruriens (Kiwach), Ocimum sanctum (Tulsi), Pterocarpus marsupium (bisasar), Punica granatum (Anar), Syzygium cumini (Jamun), Tinospora cordifolia (Giloy), and Trigonella foenum-graecum (Methi).\[^{[92-98]}\] Shreds of evidence showed that the modern allopathic medicines which use currently to treat diabetes mellitus are also developed from the active chemicals of the medicinal plants. For instance, Metformin the first line conventional drug was developed from a medicinal plant called Galega officinalis which is rich in guanidine.\[^{[99]}\] In developing countries, low cost and less or no side effect of herbal medicine, 70-95% of the population have considered herbal medicines for primary health care. The report of World Health Organization (WHO, 2013)\[^{[100]}\] estimation on herbal medicine also supports the fact that 80% of the global population still uses herbs and other conventional medicines for satisfying their major health care needs. In India, many of the diabetic people dependent on herbal drugs. Due to the lack of regulatory standards and implementation protocol, the number of standardized herbal drugs is very less regardless of such wide acceptability. Though more than 1000 plants were used in antidiabetic herbal formulations only about 100 plants have been scientifically approved and no single official herbal drug is present till date for large-scale usage.\[^{[101]}\] It is basically due to lack of standardization protocols adopted prior to the development of a drug. Apart from all the herbal medicine is considered a unique alternative therapy for diabetic people.

**CONCLUSION**

The above review has given the information about diabetes, its prevalence, complications current management and their
alternative therapies. This will be useful for current and future researchers in the field of diabetes mellitus.

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Both the authors contributed equally in the preparation of the manuscript.

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No conflict of interest

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