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Diabetes Mellitus: A Review and Update

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ABSTRACT

Diabetes mellitus is a group of metabolic diseases which are typified by the development of hyperglycaemia which do emanate from defects in insulin secretion, insulin action, or both. The chronic hyperglycaemia of diabetes is associated with long-term damage, dysfunction, and failure of various organs, especially the eyes, kidneys, nerves, heart, and blood vessels. Various types of diabetes mellitus exist which have been discussed in the main part of this article. Many pathogenic processes are involved in the development of diabetes mellitus. These pathogenic processes range from autoimmune destruction of the beta-cells of the pancreas with consequent insulin deficiency to abnormalities which result in resistance to insulin action. The basis of the abnormalities in carbohydrate, fat, and protein metabolism in diabetes is deficient action of insulin on target tissues. Deficient insulin action ensues inadequate insulin secretion and / or diminished tissue responses to insulin at one or more points within the complex pathways of hormone action. Impairment of insulin secretion and defects in insulin action frequently coexist in the same patient, and it is often unclear which abnormality, if either alone, is the primary cause of the hyperglycaemia.

The manifestations of marked hyperglycaemia do include: polyuria, polydipsia, weight loss, sometimes with polyphagia, and blurred vision. Impairment of growth and susceptibility to certain infections may also ensue chronic hyperglycaemia. Acute, life-threatening consequences of diabetes mellitus include: hyperglycaemia with ketoacidosis or the nonketotic hyperosmolar syndrome. Long-term complications of diabetes mellitus do include: diabetic retinopathy with potential loss of vision; diabetic nephropathy which leads to kidney (renal) failure; peripheral neuropathy with risk of foot ulcers, amputation, and Charcot joints; as well as autonomic neuropathy which cause gastrointestinal, genitourinary, as well as cardiovascular symptoms and sexual dysfunction. Glycation of tissue proteins and other macromolecules and excess production of polyol compounds from glucose are among the mechanisms that had been postulated to produce tissue damage from chronic hyperglycaemia. Patients who have diabetes mellitus do have an increased incidence of atherosclerotic cardiovascular, peripheral vascular, and cerebrovascular disease. Hypertension, abnormalities of lipoprotein metabolism, and periodontal disease are often found in people who have diabetes mellitus. The emotional and social impact of diabetes mellitus as well as the demands of treatment of diabetes and its complications could cause significant psychosocial dysfunction in patients who have diabetes mellitus as well as their families. Even though there are many types of diabetes mellitus, the vast majority of cases of diabetes mellitus do fall into two broad etiopathogenetic categories which have been extensively discussed in the ensuing article below that has been divided into (a) Overview and (b) miscellaneous narrations. In one category of diabetes mellitus type 1 diabetes mellitus, the cause is an absolute deficiency of insulin secretion. Individuals at increased risk of developing this type of diabetes could often be identified by serological evidence of an autoimmune pathological process that occur within the pancreatic islets and by genetic markers. In the other type of diabetes mellitus, which is the much more prevalent category that is referred to as type 2 diabetes mellitus, the cause of the disease is a combination of resistance to insulin action and an inadequate compensatory insulin secretory response. In the latter category, a degree of hyperglycaemia sufficient to cause pathological and functional changes in various target tissues, but without clinical symptoms, could be present for a long period of time before diabetes mellitus is diagnosed. During this asymptomatic period, it is possible to demonstrate an abnormality in carbohydrate metabolism by measurement of plasma glucose in the fasting state or after a challenge with an oral glucose load. Considering that diabetes mellitus is common as well as the symptoms of diabetes mellitus are non-specific symptoms that may simulate diabetes mellitus, a number of individuals who are afflicted by diabetes mellitus do not know they have diabetes mellitus, there is need for a global educational program on the manifestations and approach that is needed for early diagnosis of the disease so that all clinicians and the entire global population would have a high index of suspicion of the disease. There also a global life style education including regular exercise that would delay onset of or reduce the severity of type 2 diabetes and to improve the quality of life of patients who have diabetes mellitus. It is important to dedicate time to read the article carefully which contains documentations related to the World Health Organization's global effort to reduce the incidence and severity of diabetes mellitus and all individuals globally should follow carefully recommendations of the World Health organization as well as recommendations of other organizations in the world that have devoted their time to health education on diabetes mellitus. and a number of people.

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Introduction

It has been documented that the number of people with diabetes

mellitus had nearly quadrupled since 1980 and that the prevalence of diabetes mellitus is increasing globally, especially within low- and middle-income countries [1]. The ensuing summating iterations related to diabetes mellitus had been made: [1]

- The causes of diabetes mellitus are complex, however, the rise in cases of diabetes mellitus, is due in part to increases in the number of people who are overweight, including an increase in obesity, and in a widespread lack of physical activity.
- Diabetes mellitus of all types could emanate in the development of complications in many parts of the body and increase the risk of dying prematurely.
- In 2012 diabetes mellitus was reported to be the direct cause of 1.5 million deaths within the world.
- A large proportion of cases of diabetes mellitus and its complications can be prevented by a healthy diet, regular physical activity, maintaining a normal body weight and avoiding tobacco use.
- In April 2016, WHO had published the Global report on diabetes mellitus, which had called for action to reduce exposure to the known risk factors for the development of type 2 diabetes mellitus and to improve upon access to and quality of care for people who have all forms of diabetes mellitus.

Cases of diabetes mellitus are diagnosed in all villages, towns, cities, regions, and countries through out the world and considering that there are many complications associated with diabetes mellitus in all age groups, it is important for all clinicians all over the world as well as all individuals all over the world to be educated and updated about the manifestations of diabetes mellitus to enable early diagnosis and appropriate and effective treatment of diabetes mellitus. Every clinician globally irrespective of his or her specialty would continue to encounter patients who have diabetes mellitus in association other diseases that are not directly linked with diabetes mellitus and as part of the general management of each patient who presents to a clinician with a non-diabetes related condition, each clinician does need to carefully attend to the management of the diabetes mellitus as part of the general management in the process of the management of the case the patient manifests with. The ensuing article on diabetes mellitus is divided into two parts: (A) Overview which has discussed various relevant aspects of diabetes mellitus and (B) Miscellaneous Narrations and Discussions from Few Case Reports, Case Studies and Other General overview facts and summating iterations.

Aims

To provide a general review and relevant brief update of the literature on diabetes mellitus in human beings.

Methods

Internet data bases were searched including: Google; Google Scholar; Yahoo; and PUBMED. The search words that were used included: diabetes Mellitus; Type 1 Diabetes; Type 2 Diabetes mellitus; and other types of diabetes mellitus. One hundred and seventy-eight (178) references were identified which were used to write that article which has been divided into two parts: (A) Overview which has discussed various relevant aspects of diabetes mellitus and (B) Miscellaneous Narrations and Discussions from Few Case Reports, Case Studies and Other General overview facts and summating iterations related diabetes mellitus.

Results:

[A]

General Overview

- Chronic disorder of carbohydrate, fat and protein metabolism due to defective or deficient insulin secretory response [2,3].

Epidemiology

- 3% of world population, 26 million in U.S. but only 75% are clinically diagnosed
- Diabetes Mellitus was the 7th leading cause of death in 2007 and underlying cause on 71,382 death certificates, and in 2019, Diabetes was the seventh leading cause of death in the United States in 2019 based on the 87,647 death certificates in which diabetes was listed as the underlying cause of death. In 2019, diabetes was mentioned as a cause of death in a total of 282,801 certificates [4].
- Lifetime risk of diabetes: type 1 - 0.5%, type 2 - 5%
- Numerous variations of diabetes mellitus exist, all with hyperglycaemia

Aetiology General Comment

- Diabetes mellitus does tend to be caused by the destruction of islets due to drugs (steroids, thiazides, pentamidine), hemochromatosis ("bronze diabetes" due to hemosiderin deposition in pancreas), hereditary ceruloplasmin deficiency, infections (congenital rubella, CMV, coxsackievirus. [6-7].

Type 1 Diabetes Mellitus

- Type 1 Diabetes Mellitus is a chronic disease of carbohydrate, fat and protein metabolism due to reduction in beta cell mass causing severe, absolute lack of insulin [2].
- Type 1 diabetes mellitus accounts for 10% of all cases of diabetes mellitus [2].
- Without insulin, patients Develop Diabetic Ketoacidosis (DKA), coma and death [2].

Aetiology

- Type 1 diabetes mellitus is presumed to have an autoimmune cause for islet cell destruction but precise aetiology unclear [9].
- Usually Type 1 Diabetes Mellitus tends to be common in individuals of Northern European descent
- In cases of type 1 Diabetes Mellitus there tends to be 70% concordance in identical twins, HLA-D linked
- Genetic predisposition may affect immune responsiveness to a beta cell autoantigen or method of presentation to T cells

Viruses and Iddm

- It has been documented that in cases of type 1 Diabetes Mellitus, viruses may damage beta cells, exposing antigens which trigger an autoimmune response
- It has been iterated that Diabetes Mellitus may be due to molecular mimicry (immune response develops against shared amino acid sequences): GAD and Coxsackie B4 virus share a six amino acid sequence
- It has been documented that in a case of Diabetes Mellitus, retrovirus may serve as a superantigen

Autoimmune Aspects

- It has been pointed out that in cases of type 1 Diabetes Mellitus, Islet cell autoantibodies present in 70%; also, CD8+ T cell infiltrate tends to be seen in islets
- It has been iterated that in type 1 Diabetes Mellitus, the Antigens are glutamic acid decarboxylase (GAD), islet autoantigen 2, insulin associated antibody, gangliosides
- It has been iterated that in type 1 Diabetes Mellitus, GAD antibodies precede clinical symptoms, present in most newly diagnosed patients and 80% of first-degree relatives

- It has been pointed out that in Diabetes Mellitus, GAD antibody also causes stiff man syndrome, whose patients often have a history of IDDM
- It has been iterated that in cases of Diabetes Mellitus, many IDDM patients also have antithyroid peroxidase, anti-parietal cell and anti-adrenocortical antibodies
- It has also been documented that some NIDDM patients have autoantibodies but no other features of IDDM
- It has been pointed out that type 1 Diabetes Mellitus usually tends to be a chronic disease which lasts for many years.
- It has been iterated that Type 1 Diabetes Mellitus becomes a clinical disease when 90% of islet cells are destroyed

Clinical Features of Type 1 Diabetes Mellitus

- It has been pointed out that the onset of type 1 Diabetes Mellitus tends to be at an age which is less than (< 20) years, and the patient tends to be of normal weight unlike in most cases of Non-Insulin Dependent Diabetes Mellitus (NIDDM)
- Type 1 Diabetes Mellitus is typified by PPP (polyuria, polydipsia, polyphagia) and ketoacidosis (DKA)
- It has been pointed out that polyphagia which is combined with weight loss is specific for IDDM; type 2 patients rarely have either
- It has been iterated that severe fasting hypoglycaemia is due to cessation of glycogen storage within fat and muscle
- It has been explained that glycosemia in type 1 Diabetes Mellitus causes glycosuria with depletion of water and electrolytes
- It has also been pointed out that: low / absent plasma insulin, high plasma glucagon, unstable glucose tolerance (very sensitive to changes in insulin, diet, exercise, infection, stress), presence of free fatty acids (due to breakdown of adipose stores), which produces ketone bodies (acetoacetic acid and beta hydroxybutyric acid'
- It has been explained that a patient who has type 1 Diabetes Mellitus may get hyperosmotic nonketotic coma - dehydration due to hyperglycaemic diuresis with failure to drink enough fluids to compensate, often in an elderly person with diabetes and stroke / infection
- It has been explained that there is in type 1 Diabetes Mellitus a condition which is called "Dead in bed syndrome": which is a condition in which there is a sudden death in young people with type 1 diabetes, cause and the cause is unknown [10].

Type 2 Diabetes Mellitus Also Referred to As Non-Insulin Dependent Diabetes Mellitus (Niddm)

- It has been pointed out that Type 2 Diabetes Mellitus is also called adult-onset diabetes mellitus, non-insulin dependent diabetes mellitus / NIDDM, type 2
- It has been explained that there is a documentation to the fact that 80% to- 90% of cases of diabetes of diabetes mellitus constitute type 2 Diabetes Mellitus. [11]
- It has been iterated that type 2 Diabetes Mellitus does usually manifest in individuals who are older than (>) 30 years old, and the patients tend to be obese in 80% of cases, as well as in type 2 Diabetes Mellitus abdominal obesity is more important than subcutaneous obesity, and in cases of type 2 Diabetes Mellitus there tends to be normal or increased blood insulin, and rare diabetic cases of diabetic ketoacidosis, and no anti-islet antibodies.

Pathophysiology of Type 2 Diabetes Mellitus

Early Type 2 Diabetes Mellitus

- It has been iterated that in early type 2 Diabetes Mellitus there tends to be normal insulin secretion and plasma levels but there tends to be loss of pulsatile, oscillating pattern of secretion
- It has also been documented that in type 2 early onset Type 2 Diabetes Mellitus, there tends to be loss of rapid first phase of insulin secretion triggered by glucose
- It has been stipulated that in early onset type 2 Diabetes Mellitus NO insulinitis is present

Later Type 2 Diabetes Mellitus

- It has been pointed out that in Later Type 2 Diabetes Mellitus, there tends to be mild / moderate insulin deficiency, and this may be due to beta cell damage
- Beta cells may be "exhausted" due to chronic hyperglycaemia and persistent beta cell stimulation

Amylin

- It has been iterated that in type 2 Diabetes Mellitus, 37 amino acid-peptide, is normally produced by beta cells, packaged and co-secreted with insulin
- It has been documented that in NIDDM patients, Amylin tends to accumulate outside beta cells and resembles amyloid

Clinical Features of Type 2 Diabetes Mellitus

- It has been documented that in type 2 diabetes mellitus, there tends to be 90%+ concordance in twins, apparently due to multiple genetic polymorphisms (no HLA association)
- It has been explained that type 2 diabetes mellitus is due to insulin resistance (associated with obesity and pregnancy) or derangement in beta cell secretion of insulin
- It has been documented that type 2 diabetes mellitus is associated with amyloid deposits within islets (amyloid associated with basement membrane heparan sulfate proteoglycan [12,13].

Maturity Onset Diabetes Mellitus of The Young

- It has been documented that Maturity onset diabetes of the young constitutes 1% to 2% of all cases of diabetes mellitus.
- It has been pointed out that maturity onset diabetes of the young is also called monogenic diabetes
- It has been explained that maturity-onset diabetes mellitus of the young is Type 2 diabetes-like condition which occurs in 2+ generations, with autosomal dominant inheritance [15,16].
- It has been iterated that maturity onset diabetes of the young is an autosomal dominant but not a single entity - mutations in 9 genes identified to date (see Diagrams / Tables below)
- It has been pointed out that Common genes are affected in maturity-onset diabetes of the young are hepatic nuclear factor 1 or 4 alpha, glucokinase
- It has been iterated that maturity-onset diabetes mellitus of the young tends to associated with an onset before age 25 years, normal weight, mild hypoglycaemia
- It has been iterated that in maturity-onset diabetes of the young no GAD antibodies, no insulin resistance is noted, and no beta cell loss is identified but there tends to be impaired beta cell function

Summations related to clinical complications associated with diabetes mellitus

General complications

- The main general complications that tend to ensue diabetes mellitus include: microangiopathy, retinopathy, nephropathy, neuropathy - all due to hyperglycaemia
- It has been pointed out that kidneys that are transplanted into

diabetic patients do develop nephropathy within 3 years to 5 years but kidneys from diabetic patients transplanted into normal patients have remission of nephropathy
- It has been stated that strict control of diabetes mellitus does delay the progression of microvascular complications
- Complications in diabetes are due to nonenzymatic glycosylation and disturbances within polyol pathways

Nonenzymatic Glycosylation

The process of non-enzymatic glycosylation is summarized as follows:
- Glucose + protein => Schiff base (protein - NH = CH (CHOH)4-CH2OH) => Amadori product
- (Protein - NH-CH2-C = 0-(CHOH)3-CH2OH) => protein - protein cross linking via N-C-N bonding
- Early reactions are reversible and related to HbA1c level
- Advanced glycosylation end products (AGE) are not reversible
- AGE traps LDL in blood vessels, enhances cholesterol deposition, accelerating atherosclerosis
- AGE inhibition antagonizes diabetic complications in experimental models

Vascular Complications Associated with Diabetes Mellitus
- The relative risk for the development of vascular complications in diabetes mellitus has been iterated to be 100:1
- Vascular complications associated with diabetes mellitus does include an accelerated atherosclerosis within the aorta and large / medium sized vessels
- Myocardial infarction: It has been pointed out that myocardial infarction does occur in patients who have diabetes mellitus and it is the most common cause of death, and there is no gender preference for the development of diabetes mellitus
- Vascular complications in cases of diabetes mellitus do lead to the development of gangrene of lower extremities
- Summations related to the microscopy pathology examination features / description of vessels and other structures in diabetes mellitus include:
  - Hyaline arteriolosclerosis, associated with hypertension, more common / severe in diabetes but not specific
  - Amorphous hyaline thickening in arteriolar wall
  - Related to severity of disease and hypertension
  - Microangiopathy: diffuse basement membrane thickening with protein leakage in capillaries of skin, skeletal muscle, retina, renal glomeruli, renal medulla, renal tubules, Bowman capsule, peripheral nerves, placenta

Diabetic Renal Disease

Diabetic renal disease / diabetic nephropathy does develop in diabetes mellitus and this would be described in detail in a subsequent publication; nevertheless, it is important to know diabetes nephropathy does develop

Ocular Complications of Diabetes Mellitus
- It has been pointed out that diabetes mellitus is the 4th cause of blindness within the United States of America (USA).
- Some of the known ocular complications associated with diabetes mellitus include: retinopathy, cataracts, and glaucoma
- It has been iterated that in diabetes ocular complications, Polyol pathways are involved as well as the pathways are important within the lens and other tissues including nerves, kidney, and blood vessels, which do not require insulin for glucose transport
  - High intracellular glucose plus aldose reductase produces sorbitol and later fructose, causing water influx and osmotic cell injury
  - In lens, causes swelling and opacity
  - Inhibition of sorbitol may reduce formation of cataracts and neuropathy

Neuropathy

It has been pointed out that in diabetes mellitus, peripheral neuropathy does develop and the neuropathy tends to be symmetric neuropathy of lower extremity most common, and that sensory neuropathy is more common than motor neuropathy.

Diagnosis of Diabetes Mellitus General Comments

General statements that had been made with regard to the diagnosis of diabetes mellitus include the fact that in diabetes mellitus there tends to be high fasting glucose or impaired glucose tolerance and also without diabetes mellitus, oral glucose loads cause only slight rise in blood glucose due to brisk insulin response; with diabetes mellitus, blood glucose rises markedly for a sustained period.

Treatment of Type 1 Diabetes Mellitus and Type 2 Diabetes Mellitus

The ensuing general statements had been made regarding the treatment of diabetes mellitus type 1 and type 2 apart from insulin for Type 1 Diabetes Mellitus and oral anti-diabetes medicaments for type 2 diabetes mellitus:
- Type 1 diabetes mellitus: immunosuppressive therapy is effective in children with new onset disease
- Type 2 diabetes mellitus: diet, exercise and education
  - Lifestyle intervention and metformin delay onset of diabetes

Microscopy Histopathology Examination Description / Features of The Pancreas in Type 1 And Type 2 Diabetes Mellitus

The microscopy examination features of the pancreas in cases of type 1 and type 2 diabetes mellitus had been summarized as follows: [2]
- Type 1 diabetes mellitus: inconsistent reduction in number and size of islets, uneven insulinitis (T lymphocytes)
- Type 1 diabetes mellitus: early insulinitis with marked islet atrophy and fibrosis and severe beta cell depletion [17-19].
- Type 2 diabetes mellitus: subtle reduction in islet cell mass, amyloid replacement of islets due to amylin fibrils (also seen in aging nondiabetics); associated with marked fatty replacement
- Type 2 diabetes mellitus: amyloid in the islets of Langerhans is the uniform pathologic feature
- Gestational diabetes mellitus: lower total insulin+ area due to smaller islets.
- Infants of diabetic mellitus mothers: islet cell hypertrophy / hyperplasia

Statistics of Diabetes Mellitus

The american diabetes association [4] made the ensuing summations related to the statistics of diabetes mellitus: in 2019, overall numbers of diabetes mellitus were summarized as follows:
- Prevalence: In 2019, 37.3 million Americans, or 11.3% of the population, had diabetes mellitus.
  - Nearly 1.9 million Americans had type 1 diabetes, including about 244,000 children and adolescents
- Diagnosed and undiagnosed: Out of the 37.3 million adults with diabetes mellitus, 28.7 million were diagnosed, and 8.5 million were undiagnosed.
- Prevalence in seniors: The percentage of Americans age 65 and older than 65 years had remained high, at 29.2%, or 15.9 million seniors (diagnosed and undiagnosed).

- New cases: 1.4 million Americans tend to be diagnosed with diabetes every year.
- Prediabetes: In 2019, 96 million Americans age 18 years and older had prediabetes.

Diabetes in Youth
- About 283,000 Americans under age of 20 years were estimated to have been diagnosed as having diabetes mellitus, which amounts to approximately 0.35% of that population.
- In 2014–2015, the annual incidence of diagnosed diabetes mellitus in USA youth was estimated at 18,200 with type 1 diabetes, 5,800 with type 2 diabetes.
- Diabetes by Race/Ethnicity

The Rates of Diagnosed Diabetes in Adults by Race/Ethnic Background Within Usa Were:
- 14.5% of American Indians/Alaskan Natives
- 12.1% of non-Hispanic blacks
- 11.8% of Hispanics
- 9.5% of Asian Americans
- 7.4% of non-Hispanic whites

The Breakdown Among Asian Americans:
- 5.6% of Chinese
- 10.4% of Filipinos
- 12.6% of Asian Indians
- 9.9% of other Asian Americans

The Breakdown Among Hispanic Adults:
- 8.3% of Central and South Americans
- 6.5% of Cubans
- 14.4% of Mexican Americans
- 12.4% of Puerto Ricans

Deaths
Diabetes was the seventh leading cause of death in the United States in 2019 based upon the 87,647 death certificates in which diabetes mellitus was listed as the underlying cause of death. In 2019, diabetes mellitus was mentioned as a cause of death in a total of 282,801 certificates.

Cost of Diabetes
A summated updated cost for treating diabetes mellitus within USA in March 22, 2018 was summated as follows:
$327 billion: Total cost of diagnosed diabetes in the United States in 2017
$237 billion was for direct medical costs
$90 billion was in reduced productivity
After adjusting for population age and sex differences, average medical expenditures among people with diagnosed diabetes were 2.3 times higher than what expenditures would be in the absence of diabetes.

[B] Miscellaneous Narrations and Discussions from Some Case Reports, Case Series and Studies Related to Various Types of Diabetes Mellitus
reported an autopsy case of acute-onset insulin-dependent diabetes mellitus, type I, which had occurred in an adult [20]. The patient died 3 days pursuant to the clinical onset of diabetes. Hyperglycaemia, ketonuria, and hyperamylasaemia were observed during admission of the patient. Pathologic examination of the pancreas of the patient demonstrated a markedly decreased number of islets, and residual islets were noted to be small and shrunken. Diffuse inflammatory cell infiltrates, which were found within the islets and also within acini, were mainly T lymphocytes. Shrunken islets were demonstrated upon the examination which were composed of insulin cells, glucagon cells, somatostatin cells, and pancreatic polypeptide cells. A decreased number of zymogen granules within acini were prominent [corrected]. Kimura et al. iterated that their reported case had suggested that pan-pancreatitis, destroying whole islets and acini, could initiate insulin-dependent diabetes mellitus [21].

Lászik et al. reported a study which included nine patients with diabetes mellitus (DM) and chronic pancreatitis (CP) (group I); 11 patients without DM and with CP (group II); and a control group (group III) consisting of five autopsy cases with neither DM nor CP. Lászik et al. Evaluated these groups by routine histology stains and immunocytochemical stains for insulin, glucagon, and somatostatin [22-23]. Semiquantitative assessment of the degree of exocrine pancreatic atrophy and of two endocrine features (diffuse endocrine proliferation and ducto-endocrine proliferation) was undertaken for each pancreas. Quantitative determination of the cell composition was undertaken in three kinds of islets (parenchymal, sclerosis, and newly formed). The mean percentages of the insulin-producing B cells were found to be significantly lower in the parenchymal (44.5%) and new (34.3%) islets of diabetic patients in comparison with in the controls (67.8%) and parenchymal (59.4%) islets of nondiabetic patients. The mean percentages of glucagon-producing A cells demonstrated significant increases in the parenchymal (43.0%) and new (55.7%) islets of diabetic patients as compared with the controls (24.3%) and parenchymal (32.2%) islets of nondiabetic patients. The mean percentage of somatostatin-producing D cells was found to be significantly increased in the parenchymal islets (12.4%) of diabetic patients as compared with the parenchymal islets (8.2%) of nondiabetic patients and controls (7.5%). Lászik et al. concluded that these findings had correlated with clinical data of frequent DM in CP, but were partly in contrast with previous immunohistochemical analysis findings in CP [24].

Stated that Diabetes mellitus (DM) is the important initial symptom of hereditary ceruloplasmin deficiency (HCD) [25]. Examined the pancreas of an autopsy case of HCD and revealed a marked reduction in insulin-containing cells in the islets despite no massive iron deposition, degeneration, nor necrosis [26]. Non-insulin-containing cells in the islets had glucagon or somatostatin. They stated that their study had indicated that DM in HCD results from depletion of insulin cells and this depletion does not seem to be caused by the direct effect of iron deposition. Their observation had suggested that the defect of the ceruloplasmin gene may influence the population of islet cells.

Reported that Pancreata from five infants who had culture-proven coxsackievirus encephalomyocarditis were studied for evidence of islet cell damage [27]. Four of the five had showe islet cell change, varying from clusters of cells with pyknotic nuclei to total islet necrosis. The lesion had appeared to be characteristic of coxsackievirus and was not visualized in the pancreata of neonates with other neonatal systemic viral infections. Ujevich et al. [28] stated the following:

- This had confirmed that coxsackievirus shows tropism for insular tissue and may play a role in the genesis of some cases of juvenile diabetes mellitus. Immunostaining was used to ascertain the specificity of the lesions.
- Damage to cells other than beta cells could be clearly demonstrated.

- The finding that all islet cell types might be involved lends support to the postulate that juvenile diabetes mellitus might be a genetically determined failure to reconstitute the beta cells after viral injury.

Iterated that it had been postulated that enterovirus infections cause beta-cell damage and contribute to the development of Type 1 diabetes by replicating in the pancreatic islets [29]. Ylipaasto et al. sought evidence for this through autopsy studies and by investigating known enterovirus receptors in cultured human islets [30-31]. With regard to the methods of their study, Ylipaasto et al. et al. stated the following:

- had examined / studied autopsy pancreases from 12 newborn infants who had died of fulminant coxsackievirus infections and from 65 Type 1 diabetic patients for presence of enteroviral ribonucleic acid by in situ hybridisation.
- Forty non-diabetic control pancreases were included in the study.
- They had investigated the expression and role of receptor candidates in cultured human islets with receptor-specific antibodies using immunocytochemistry and functional assays.

Ylipaasto et al. [32] summarized the results as follows:

- Enterovirus-positive islet cells were found in some of both autopsy specimen collections, but not in control pancreases.
- No infected cells were seen within exocrine tissue.
- The cell surface molecules, poliovirus receptor and integrin alphavbeta3, which act as enterovirus receptors in established cell lines, were expressed within beta cells.
- Antibodies to poliovirus receptor, human coxsackievirus and adenovirus receptor and integrin alphavbeta3 protected islets and beta cells from adverse effects of poliovirus, coxsackie B viruses, and several of the arginine-glycine-aspartic acid motifs containing enteroviruses and human parechovirus 1 respectively.
- No evidence was found for the immunohistochemistry expression of the decay-accelerating factor which acts as a receptor for several islet-cell-replicating echoviruses in established cell lines.

Ylipaasto et al. [33] made the following conclusions:

- The results had demonstrated definite islet-cell tropism of enteroviruses in the human pancreas.
- Some enteroviruses seemed to use previously identified cell surface molecules as receptors in beta cells, whereas the identity of receptors used by other enteroviruses remained unknown.

Tu et al. [34] iterated the following:

- Dead in bed syndrome is a poorly understood cause of sudden death in young people who have type 1 diabetes mellitus.
- The underlying cause remains of this syndrome is unknown.
- One possible explanation of the cause of the syndrome may entail prolongation of the QT interval followed by a terminal malignant arrhythmia.
- Risk factors associated with QT interval prolongation include hypoglycaemia as well as cardiac autonomic neuropathy.
- Tu et al. sought to identify myocardial cellular changes and genetic influences that may contribute to the pathogenesis of dead in bed syndrome [35].
- Post-mortem reports obtained between 1994 and 2006 from the 2 largest Departments of Forensic Medicine in Australia were reviewed by Tu et al. for dead in bed syndrome cases [36].
- Post-mortem heart sections were immunohistochemically stained for collagen types I and III and connective tissue growth factor (CTGF).
- Genomic DNA was prepared from post-mortem samples, and genetic analysis was undertaken in the SCN5A, G6PC, PHOX2B, and CTGF genes.

Tu et al. [37] summarized the results as follows:

- They had identified twenty-two dead in bed syndrome cases and staining of heart sections for collagen I and III, and CTGF had shown no differences between dead in bed syndrome cases and the controls.
- Their genetic screening of SCN5A demonstrated 3 silent polymorphisms A29A, E1061E, and D1819D and 1 protein-changing variant H558R. No genetic variants were found in G6PC, PHOX2B, and CTGF, and dead in bed syndrome cases were not associated with the G-945C CTGF promoter polymorphism.

Tu et al. [38] the following conclusions:

- Their study was the first to investigate potential pathogenic mechanisms underlying the dead in bed syndrome in type 1 diabetes mellitus with the results substantially adding to knowledge of this condition.
- Understanding the causes and triggers of dead in bed syndrome would be critical in facilitating the identification of patients who have type 1 diabetes and who are at the highest risk of developing sudden death.

Young et al. [39] made the ensuing iterations:

- Amyloid in the islets of Langerhans is the uniform pathologic feature in the pancreata of patients who have type II diabetes mellitus.
- Even though the mechanisms of islet amyloid fibrillogenesis were unknown, the presence of heparan sulfate proteoglycan in many other forms of amyloid does suggest a role for this proteoglycan in amyloidogenesis in general.
- In their study, they had evaluated islet amyloid for the presence of the basement membrane heparan sulfate proteoglycan utilizing histochemical and immunohistochemical techniques.
- Staining with sodium sulfate-alcian blue had identified highly sulfated glycosaminoglycans within all islet amyloid deposits, and anti-basement membrane heparan sulfate proteoglycan antisera localized this specific proteoglycan within the islet amyloid.
- The presence of the basement membrane heparan sulfate proteoglycan links islet amyloid to other disparate forms of amyloid and further had supported the postulate that it has a role in a common pathway of amyloid fibrillogenesis.

Studied the prevalence and immunoreactivity of interstitial amyloid deposits of the pituitary glands of 109 consecutive autopsies of individuals over 84 years of age utilizing Congo red staining and antibodies directed against the major amyloid fibril proteins and pituitary hormones [40]. In addition, they evaluated the amount of interstitial amyloid formation quantitatively and compared these with all autopsy-related and clinical diagnoses available.

Röcken et al. [41] summarized the results as follows:

- Eighty-seven that amounted to 80% of the 109 cases had exhibited interstitial amyloid deposits in the anterior lobe.
- All reacted immunohistochemically with anti-amyloid lambda light chain and anti-amyloid P-component.
- Quantitative analysis in 62 cases had demonstrated a mean

volume percentage of interstitial amyloid in the anterior lobe of 0.56%.

- In statistical analysis, only two of the 25 diseases recorded were found to be associated with interstitial amyloid: chronic obstructive pulmonary disease and non-insulin-dependent diabetes mellitus.
- The prevalence of chronic obstructive pulmonary disease had correlated positively with the occurrence (chi 2; $P < .02$) as well as with the amount of amyloid (Wilcoxon; $P < .04$) in the pituitary.
- Furthermore, non-insulin-dependent diabetes mellitus was noted to be accompanied with higher amounts of interstitial amyloid than with all other disorders (Wilcoxon; $P < .03$).
- Until the publication of their article, a correlation was proposed only between non-insulin-dependent diabetes mellitus and islet amyloidosis of the pancreas.

Stated the following [42]

- Maturity onset diabetes of the young (MODY) is a heterogeneous group of disorders that result in β-cell dysfunction. It is rare, accounting for just 1% to 2% of all cases of diabetes mellitus.
- MODY is often misdiagnosed as type 1 or type 2 diabetes, as it is often difficult to distinguish MODY from these two forms. Nevertheless, diagnosis of MODY does allow appropriate individualized care, depending upon the genetic aetiology, and allows prognostication in family members [43].
- The ensuing summations had been made regarding insulinitis in human diabetes mellitus:
- The histopathology of type 1 diabetes is defined by a decreased β-cell mass in association with insulitis, a characteristic lymphocytic infiltration that is limited to the islets of Langerhans and prominent in early-stage disease in children.
- A cytotoxic T-cell mediated destruction of insulin-producing β-cells is conjectured to be initiated by an unknown (auto) antigen, leading to the destruction > 75% of β-cell mass at clinical diagnosis.
- Even though considered to be pathognomonic for recent onset disease, insulitis had only been described in about 150 cases over the past century.
- Their review had described the quest for this elusive lesion and had given its incidence in various patient subpopulations stratified for age of onset and duration of the disease.
- Their review had discussed recent new insights into the regenerative capacity of the β-cell mass in the pre-clinical stages of the disease and had related these findings to the inflammatory processes within the islet tissue.

Tancredi et al. [44] made the following summating discussions:

- Gestational Diabetes (GD) mellitus does emanate from insufficient endogenous insulin supply.
- No information had been available on features of islet cells in human GD.
- Tancredi et al. described several properties of islets from a woman with GD. Tancredi et al. reported that immunohistochemical staining and electron microscopy (EM) analyses were undertaken on pancreatic samples [45-46]. Islet isolation had been attained by enzymatic dissociation and density gradient centrifugation [47]. Tancredi et al. studied ex vivo insulin secretion in response to fuel secretagogues. Control islets were obtained from matched non-pregnant, non-diabetic women.

tancredi et al. [48] reported their results as follows:

- Total insulin positive area was lower in GD, mainly because of the presence of smaller islets.
- β-cell apoptosis and the presence of Ki67 positive islet cells were found to be similar in GD and controls, whereas the amount of insulin positive cells in or close to the ducts was decreased in GD.
- Ex vivo insulin secretion did not differ between GD and non-pregnant, non-diabetic islets.
- These findings had suggested that in their case of human GD there might mainly be a defect of β-cell amount, not due to increased apoptosis, but possibly to insufficient regeneration [49].

Detailed discussions related to diabetes mellitus had been made to enable readers to update their knowledge about diabetes mellitus as follows:

- It has been explained that diabetes, which is also known as diabetes mellitus, is a group of common endocrine diseases that are typified by sustained high levels of blood sugar [50-53].
- Diabetes is due to either the pancreas not being able to produce enough insulin, or the cells of the body are not responding properly to the insulin produced [11,24].
- If diabetes is left untreated, it does tend to lead to many health complications. [11,25] .
- Untreated or poorly treated cases of diabetes mellitus account for approximately 1.5 million deaths per year [11,26] .
- There is no widely accepted cure for most cases of diabetes mellitus.
- The commonest treatment for type 1 diabetes mellitus is replacement of insulin by insulin-replacement treatment in the form of insulin injections.
- Anti-diabetic medicaments such as metformin, and semaglutide and also life style modifications could be utilized to prevent or respond to type 2 diabetes mellitus.
- Gestational diabetes mellitus normally does tend to resolve shortly pursuant to the delivery of the baby.
- It has been iterated that as of 2019, an estimated 463 million people globally had diabetes mellitus which had amounted to 8.8% of the adult population.
- It has been documented that Type 2 diabetes mellitus does tend to account for up to about 90% of all cases of diabetes mellitus [11,27].
- It has been pointed out that the prevalence of diabetes mellitus has continued to be on the increase, and this increase most dramatically has been noted within the low- and middle-income nations of the world [11,28].
- It has been iterated that the rates of diabetes mellitus are similar in women and men, with diabetes being the 7th-leading cause of death in the world [11,29,30].
- The global pecuniary expenditure on diabetes mellitus-related healthcare is an estimated United States of America Dollars (USD) of 760 billion per one year [11,31].

Signs and symptoms of Diabetes Mellitus

The signs and symptoms of diabetes mellitus which tend to be manifested by individuals who have diabetes mellitus had been illustrated by Medscape as shown in figure 1 which has been reproduced based upon the Creative Commons Agreement License.

Overview of the most significant symptoms of diabetes
Reproduced from [11]

The symptoms of diabetes mellitus in human beings had been summated as follows:

- classical manifestations of untreated diabetes mellitus include unintended loss of body weight, polyuria (increased number of micturition) polydipsia), and polyphagia (increased hunger) [11,32].
- The symptoms of diabetes mellitus might develop rapidly within weeks or months with regard to cases of type 1 diabetes mellitus, while they usually manifest much more slowly and the symptoms could be subtle or absent in type 2 diabetes [11,33].
- Several other manifestations could the commencement of diabetes mellitus even though they tend not to be symptoms and signs that are not specific to diabetes mellitus.
- In addition to the known symptoms listed above, the possible not specific symptoms of diabetes mellitus do include (a) blurred vision, (b) headache, (c) fatigue, (d) slow-healing of cuts, (e) as well as itchy skin.
- Prolonged high blood glucose levels could cause glucose absorption within the lens of the eye, which does tend to be ensued by the development of changes in its shape, resulting in changes in vision.
- Long-term vision loss could also be an emanation sequel of diabetes retinopathy
- A number of skin rashes that could emanate in diabetes mellitus are collectively referred to diabetic dermadrome [11,34].
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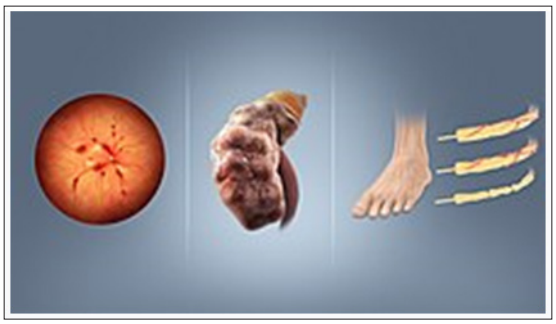
Diabetic Emergencies

- It is important to be aware of the fact that some individuals who have diabetes mellitus may manifest suddenly as emergency patients that treated by the emergency medical on call teams globally.
- People who have diabetes mellitus usually but not exclusively in type 1 diabetes, may also manifest with diabetes ketoacidosis (DKA), which is a metabolic disturbance that is typified by manifestations of (a) nausea, (b) vomiting and (c) abdominal pain, (d) the smell of acetone upon the breath, (e) deep breathing which is referred to as Kussmaul breathing, (f) as well as in severe cases a a decreased level of consciousness.
- It has been pointed out that DKA does entail emergency treatment within hospital [11,25].
- A rarer form of DKA / emergency which is a more dangerous condition is hyperosmolar hyperglycemicstate (HHS), which has tended to be more common in type 2 diabetes mellitus and which is mainly an emanation of dehydration which had been caused by caused by high blood sugars levels [11,25].
- Diabetes treatment-related low blood sugar that is referred to as hypoglycemia is common in people who have type 1 diabetes mellitus as well as type 2 diabetes mellitus depending upon the medicament that is being utilized. Majority of cases of hypoglycemia are mild and are not considered as medical emergencies.
- The effects of hypoglycemia could range from (a) feelings of unease, (b) sweating, (c) trembling, (d) and increased appetite in mild cases to more serious effects such as (e) confusion, changes in behavior such as (f) aggressiveness (g) seizures, (h) unconsciousness, and rarely permanent (i) brain damage, or (j) death in severe cases. [11] [35,36].
- Rapid breathing, sweating, and cold, pale skin had been stated to be characteristic of low blood sugar but not definitive [11,37].
- Mild to moderate cases of hypoglycemia are self-treated by eating or drinking something high in rapidly absorbed carbohydrates.
- Severe cases of hypoglycemia could emanate in unconsciousness and such cases need to be treated by means of intravenous glucose or injections with utilization of glucagon [11, 38].

Complications of Diabetes Mellitus

Figure 2 has highlighted areas of the body that tend to be afflicted by complications of diabetes mellitus as reproduced from [11].
Figure 2.



Retinopathy, nephropathy, and neuropathy are potential complications of diabetes

- has been pointed out that all forms of diabetes mellitus do increase the risk for the development of long-term complications of diabetes mellitus. These complications were stated to typically develop after many years of between 10 years and 20 years, however, the complications might be the first manifestation in those who have otherwise not been diagnosed as having diabetes mellitus before that time [11,39].
- It has been pointed out that the major long-term complications of diabetes mellitus do relate to damage to blood vessels.
- It has been iterated that diabetes mellitus does double the risk for the development of cardiovascular disease [11,40]. and about 75% of deaths in people who have diabetes mellitus are due to coronary artery disease [11,41].
- Other macrovascular diseases complicating diabetes mellitus have been stated to include stroke, as well as peripheral arterial disease [11,42].
- It has also been pointed out that these complications are also a strong risk factor for severe COVID 19 illness [11,43].
- It has been iterated that the primary complications emanating from diabetes mellitus as a sequel of damage in small blood vessels include: damage to the (a) eyes, (b) kidneys, and (c) nerves [11,44].
- has been pointed out that damage to the eyes, which is referred to as diabetic retinopathy, is caused by damage to the blood vessels within the retina of the eye, and could be ensued by a gradual loss of vision as well as eventual blindness [11,44].
- It has also been pointed out that diabetes mellitus also does tend to increase the risk of developing glaucoma, cataracts, as well as other eye problems.
- It has been recommended that people who have diabetes mellitus should visit an optometrist or an ophthalmologist once per year [11,45].
- It has been iterated that damage to the kidneys, which is referred to as diabetes nephropathy could lead to the development of tissue scarring, protein loss within urine, as well as eventually chronic renal disease, sometimes necessitating the undertaking of dialysis or renal transplantation [11,44].
- Damage to the nerves of the body, which is referred to as diabetic neuropathy, is stated to be the most common complication of diabetes mellitus [11,44].
- The symptoms of diabetes neuropathy had been stated to include (a) numbness, (b) tingling sensation, (c) sudomotor dysfunction, (d) pain, (e) and altered pain sensation, which could lead to (f) damage to the skin.
- It has been pointed out that diabetes-related-foot problems such as diabetic foot ulcers might occur and they could poove difficult to treat, occasionally requiring the undertaking of amputation.
- In addition, it has been pointed out that proximal diabetes neuropathy does tend to cause painful muscle atrophy as well as muscle weakness.
- It has been pointed out that there is a link between cognitive deficit and diabetes mellitus. It has been iterated that in comparison with individuals without diabetes mellitus, individuals who have diabetes mellitus disease have a 1.2 to 1.5-fold greater rate of decline in their cognitive function [11,46].
- It has also been iterated that having diabetes mellitus, especially when receiving insulin, increases the risk of falls in older people [11,47].

Figure 3 [Also Table 1] Comparison of type 1 diabetes mellitus and type 2 diabetes mellitus causes

Figure 3 has illustrated a comparison between the manifestations of type 1 diabetes mellitus and type 2 diabetes mellitus reproduced from with adaptation / change of reference numbers in the table to correspond with the references of the article[11].

Feature	Type 1 diabetes	Type 2 diabetes
Onset	Sudden	Gradual
Age at onset	Mostly in children	Mostly in adults
Body size	Thin or normal [49]	Often obese
Ketoacidosis	Common	Rare
Autoantibodies	Usually- present	Absent
Endogenous insulin	Low or absent	Normal, decreased or increased
Heritability	0.69 to 0.88 [50] [51] [52]	0.47 to 0.77 [53]
Prevalence (Age standardized)	<2 per 1,000 [54]	~6% (men), ~5% (women) [55]

Comparison of type 1 diabetes mellitus and type 2 diabetes mellitus causes

- It has been iterated that diabetes mellitus is classified into six categories: (a) type 1 diabetes mellitus, (b) type 2 diabetes mellitus, (c) hybrid forms of diabetes mellitus, (d) hyperglycemia first detected during pregnancy, (e) "unclassified diabetes", (f) and "other specific types" [11,56].
- "Hybrid forms of diabetes" include slowly evolving, immune-mediated diabetes of adults and ketosis-prone type 2 diabetes.
- Hyperglycemia first detected during pregnancy" does include gestational diabetes mellitus as well as diabetes mellitus in pregnancy (type 1 or type 2 diabetes first diagnosed during pregnancy).
- The "other specific types" of diabetes mellitus are a collection of a few dozen individual causes.
- Diabetes mellitus is a more variable disease than was previously thought and people may have combinations of forms of diabetes mellitus [11,57].

Type 1 diabetes mellitus

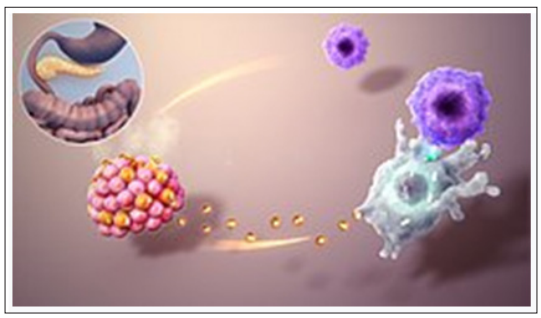
Summations that had been made related to diabetes mellitus include the following:

- 1 diabetes is typified by loss of the insulin-producing beta cells of the pancreatic islets. leading to insulin deficiency.
- This type of diabetes mellitus could be further sub-classified as immune-mediated type 1 diabetes mellitus and idiopathic type 1 diabetes.
- The majority of type 1 diabetes is of an immune-mediated nature, in which a T cell-mediated attack does lead to the loss of beta cells and thus insulin [11,58]. It has been pointed out

that this type of type 1 diabetes mellitus causes approximately 10% of diabetes mellitus cases in North America and Europe. It has been iterated that most affected people are otherwise healthy and of a healthy weight when onset of the diabetes occurs. Sensitivity and responsiveness to insulin are usually normal, especially in the early stages. It has also been pointed out that even though type 1 diabetes mellitus has been called "juvenile diabetes" due to the frequent onset in children, the majority of individuals living with type 1 diabetes are now adults [11,59].

- It has been iterated that "Brittle" diabetes, which is also referred to as unstable diabetes or labile diabetes, is a term that was traditionally utilized to describe the dramatic and recurrent swings in glucose levels, often occurring for no apparent reason in insulin-dependent diabetes. This terminology; nevertheless, is stated to have no biological basis and should not be used [11,60].
- It has also been stated that still, type 1 diabetes could be accompanied by irregular and unpredictable high blood sugar levels, and the potential for the development of diabetes ketoacidosis, or serious low blood sugar levels.
- Other documented complications of diabetes mellitus type 1 include an impaired counterregulatory response to low blood sugar, infection, gastroparesis which does lead to erratic absorption of dietary carbohydrates, as well as endocrinopathies for example Addison's disease [60]. These phenomena are conjectured to occur no more frequently than in 1% to 2% of persons who have type 1 diabetes mellitus [11,61].

Figure 4: Autoimmune attack in type 1 diabetes mellitus Reproduced from: [11]

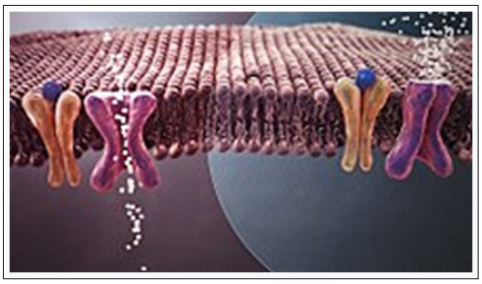


Autoimmune attack in type 1 diabetes

- It has been pointed out that Type 1 diabetes mellitus is partly inherited, with multiple genes, including certain HLA genotypes that are known to influence the risk of diabetes.
- It has been iterated that in genetically susceptible people, the commencement of diabetes mellitus could be triggered by one or more environmental factors, [11,62]. such as a viral infection or diet.
- It has been documented that several viruses had been implicated, but to date there is no stringent evidence to support this hypothesis in humans [11,62,63].
- It has been pointed out that Type 1 diabetes mellitus could occur at any age, and a significant proportion of Type 1 diabetes mellitus is diagnosed during adulthood.
- It has been iterated that "Latent diabetes mellitus of adults" (LADA) is the diagnostic terminology which tends to be used when type 1 diabetes mellitus develops in adults; it has a slower onset than the same condition in children. Given this difference, some use the unofficial term "type 1.5 diabetes" for this condition. It has also been stated that adults who have LADA are frequently initially misdiagnosed as having type 2 diabetes, based upon their age rather than a cause [11,64].

Type 2 Diabetes Mellitus

Figure 5 Type 2 Diabetes Mellitus. Reproduced from: [11]



Reduced insulin secretion or weaker effect of insulin on its receptor leads to high glucose content in the blood.

- It has been iterated that Type 2 diabetes mellitus is typified by insulin resistance, which could be combined with relatively reduced insulin secretion [11,24].
- It has been stated that it is believed that the defective responsiveness of body tissues to insulin involves the insulin receptor. Nevertheless, the specific defects are not known.
- It has been pointed out that diabetes mellitus cases that are due to a known defect are classified separately.
- Type 2 diabetes is stated to be the most common type of diabetes mellitus which accounts for 95% of diabetes mellitus [11,65].
- It has been documented that many people who have type 2 diabetes mellitus have evidence of prediabetes with impaired fasting blood glucose and/or impaired glucose tolerance before meeting the criteria for type 2 diabetes [11,66].
- It had been explained that the progression of prediabetes to overt type 2 diabetes could be slowed or reversed by lifestyle changes or medicaments that improve insulin sensitivity or reduce the liver's glucose production [11,67].
- It has been iterated that type 2 diabetes mellitus is primarily due to lifestyle factors and genetics [11,68].
- It has been pointed out that a number of lifestyle factors have been known to be important for the development of type 2 diabetes mellitus, including (1) obesity which is defined by a body mass index of greater than 30, (2) lack of physical activity, (3) poor diet, (4) stress, and (5) urbanization [11,48].
- It has been iterated that excess body fat is associated with 30% of cases in people of Chinese and Japanese descent, 60–80% of cases in those of European and African descent, and 100% of Pima Indians and Pacific Islanders [11,24].
- It has furthermore been stated that in patients who have type 2 diabetes mellitus, even those who are not obese may have a high waist-hip ratio [11,24].
- It has been pointed out that dietary factors such as sugar-sweetened drinks tend to be associated with an increased risk for the development of type 2 diabetes mellitus [11,69,70].
- It has also been pointed out that the type of fats within the diet is also important for the development of type 2 diabetes mellitus, with saturated fat and trans fats increasing the risk for the development of type 2 diabetes mellitus and poly-unsaturated and monosaturated fat decreasing the risk for the development of type 2 diabetes mellitus [11,68].
- It has been documented that eating white rice excessively might increase the risk for the development of diabetes, especially in Chinese and Japanese people [11,71].

- It has been documented that lack of physical activity might increase the risk for the development of Type 2 diabetes mellitus in some people [11,72].

Adverse Childhood Experiences

- It has been pointed out that adverse childhood experiences with the inclusion of (1) abuse, (2) neglect, and (3) household difficulties, do increase the likelihood for the development of type 2 diabetes mellitus later on in life by 32%, with childhood neglect having the strongest effect [11,73].

Antipsychotic Medication Side Effects:

- It has been pointed out that antipsychotic medicament side effects, specifically metabolic abnormalities, dyslipidemia and weight gain, as well as unhealthy lifestyles, including poor diet and decreased physical activity represent potential risk factors for the development of type 2 diabetes mellitus [11,74].

Gestational Diabetes

- It has been iterated that gestational diabetes mellitus simulates type 2 diabetes mellitus in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness [11].
- It has been pointed out that gestational diabetes mellitus does occur in about 2% to 10% of all pregnancies and might improve or disappear following delivery [11,75].
- It has been iterated that it has been recommended that all pregnant women should be tested starting around 24 weeks to 28 weeks of gestation [11,76].
- It is most often diagnosed in the second or third trimester because of the increase in insulin-antagonist hormone levels that occurs at this time [11,76]. Nevertheless, it has also been pointed out that following pregnancy approximately 5% to 10% of women who develop gestational diabetes are found to have another form of diabetes mellitus, most commonly type 2 diabetes mellitus [11,75].
- It has been iterated that gestational diabetes mellitus is fully treatable, but does require careful medical supervision throughout the pregnancy [11].
- It has also been iterated that management of gestational diabetes mellitus may include dietary changes, blood glucose monitoring, and in some cases, insulin may be required [11,77].
- It has been pointed out that even though gestational diabetes mellitus may be transient, untreated gestational diabetes could damage the health of the fetus or mother [11].
- It has been documented that the risks to the baby of a mother who develops gestational diabetes mellitus do include macrosomia, (high birth weight), congenital heart abnormalities and central nervous system abnormalities, and skeletal muscle malformations [11].
- It has been pointed out that increased levels of insulin in a fetus's blood might inhibit fetal surfactant production and cause infant respiratory distress syndrome [11].
- It has also been pointed out that a high blood bilirubin level might result from red blood cell destruction [11].
- it has been iterated that in severe cases of gestational abnormality, perinatal death might occur, most commonly as a result of poor placental perfusion due to vascular impairment [11].
- It has been pointed out that labor induction might be indicated in the scenario of decreased placental function in cases of gestational diabetes mellitus [11].
- It has been iterated that a caesarean section might be undertaken in some cases of marked fetal distress in some cases of gestational diabetes mellitus [11,78]. or an increased risk of injury associated with macrosomia, such as shoulder dystocia [11,79].

Other Types of Diabetes Mellitus

- Maturity Onset Diabetes of the Young (MODY) is stated to be a rare autosomal dominant inherited form of diabetes, which is due to one of several single-gene mutations causing defects in insulin production [11,80].
- MODY was stated to be significantly less common than the three main types, constituting 1% to 2% of all cases [11].
- It has been pointed out that the name of this disease refers to early postulates as to its nature. Being due to a defective gene, MODY varies in age at manifestation and in severity according to the specific gene defect; thus, there are at least 13 subtypes of MODY. It had also been iterated that people who have MODY often can control it without using insulin [11,81].
- It has been iterated that some cases of diabetes are caused by the body's tissue receptors not responding to insulin, even when the insulin levels are normal within ranges, which is what separates it from type 2 diabetes); this form is very uncommon [11].
- It has been pointed out that genetic mutations which be either autosomal mutation or mitochondrial mutation could lead to defects in beta cell function [11].
- It has also been explained that abnormal insulin action might also have been genetically determined in some cases [11].
- It has furthermore been stated that any disease which causes extensive damage to the pancreas might lead to the development of diabetes mellitus for example, chronic pancreatitis and cystic fibrosis [11].
- It has been pointed out that diseases that are associated with excessive secretion of insulin-antagonist hormones could cause diabetes mellitus which is typically resolved once the hormone excess is removed [11].
- It has been pointed out that many medicaments do impair insulin secretion and some toxins damage pancreatic beta cells, whereas others increase insulin resistance especially glucocorticoids which can provoke "steroid diabetes" [11].
- It had been pointed out that the ICD-10 (1992) diagnostic entity, malnutrition-related diabetes mellitus (ICD-10 code E12), was deprecated by the World Health Organization (WHO) when the current taxonomy was introduced in 1999 [11,82]. Yet another form of diabetes mellitus which people might develop is double diabetes. This is when a type 1 diabetic becomes insulin resistant, which is the hallmark for type 2 diabetes or a diabetic has a family history for type 2 diabetes [11,83]. It was first discovered in 1990 or 1991.

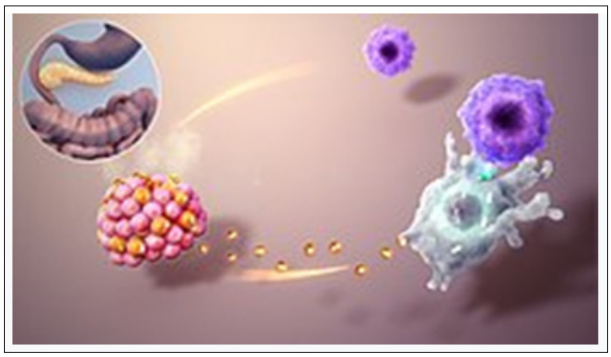
The following is a list of disorders that may increase the risk of diabetes: [11,84].

- Genetic defects of β-cell function
  - Maturity Onset Diabetes of the Young
  - Mitochondrial DNA mutations
- Genetic defects in insulin processing or insulin action
  - Defects in proinsulin conversion
  - Insulin gene mutations
  - Insulin receptor mutations
- Exocrine pancreatic defects (see Type 3c diabetes, for example pancreatogenic diabetes)
  - Chronic pancreatitis
  - Pancreatectomy

- o Pancreatic neoplasia
- o Cystic fibrosis
- o Hemochromatosis
- o Fibrocalculus pancreatopathopathy
- • Endocrinopathies
- o Growth hormone excess (acromegaly)
- o Cushing syndrome
- o Hyperthyroidism
- o Hypothyroidism
- o Pheochromocytoma
- o Glucagonoma
- • Infections
- o Cytomegalovirus infection.
- o Coxsackievirus B
- • Drugs
- o Glucocorticoids
- o Thyroid hormone
- o Beta-adrenergic agonists
- o Statins [11,85].

Pathophysiology

Figure 6: Reproduced from [11]. with adaptation / change of reference numbers in the table to correspond with the references of the article



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- It has been pointed out that Type 1 diabetes mellitus could occur at any age, and a significant proportion of Type 1 diabetes mellitus is diagnosed during adulthood.
- It has been iterated that "Latent diabetes mellitus of adults" (LADA) is the diagnostic terminology which tends to be used when type 1 diabetes mellitus develops in adults; it has a slower onset than the same condition in children. Given this difference, some use the unofficial term "type 1.5 diabetes" for this condition. It has also been stated that adults who have LADA are frequently initially misdiagnosed as having type 2 diabetes, based upon their age rather than a cause. [11] [64]

Type 2 Diabetes Mellitus

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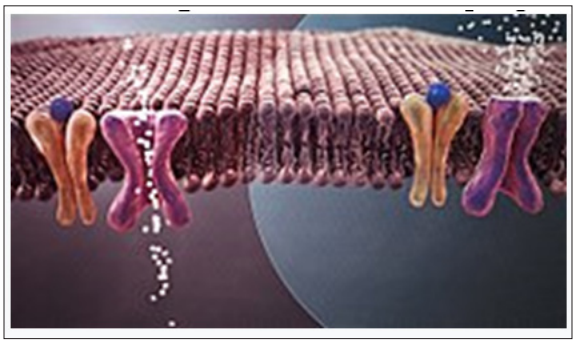

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- It has been iterated that gestational diabetes mellitus simulates type 2 diabetes mellitus in several respects, involving a combination of relatively inadequate insulin secretion and responsiveness [11].
- It has been pointed out that gestational diabetes mellitus does occur in about 2% to 10% of all pregnancies and might improve or disappear following delivery [11,75].
- It has been iterated that it has been recommended that all pregnant women should be tested starting around 24 weeks to 28 weeks of gestation [11,76].
- It is most often diagnosed in the second or third trimester because of the increase in insulin-antagonist hormone levels that occurs at this time [11,76]. Nevertheless, it has also been pointed out that following pregnancy approximately 5% to 10% of women who develop gestational diabetes are found to have another form of diabetes mellitus, most commonly type 2 diabetes mellitus [11,75].
- It has been iterated that gestational diabetes mellitus is fully treatable, but does require careful medical supervision throughout the pregnancy [11].
- It has also been iterated that management of gestational diabetes mellitus may include dietary changes, blood glucose monitoring, and in some cases, insulin may be required [11,77].
- It has been pointed out that even though gestational diabetes mellitus may be transient, untreated gestational diabetes could damage the health of the fetus or mother [11].
- It has been documented that the risks to the baby of a mother who develops gestational diabetes mellitus do include macrosomia, (high birth weight), congenital heart abnormalities and central nervous system abnormalities, and skeletal muscle malformations [11].
- It has been pointed out that increased levels of insulin in a fetus's blood might inhibit fetal surfactant production and cause infant respiratory distress syndrome [11].
- It has also been pointed out that a high blood bilirubin level might result from red blood cell destruction [11].
- it has been iterated that in severe cases of gestational abnormality, perinatal death might occur, most commonly as a result of poor placental perfusion due to vascular impairment [11].
- It has been pointed out that labor induction might be indicated in the scenario of decreased placental function in cases of gestational diabetes mellitus [11].
- It has been iterated that a caesarean section might be undertaken in some cases of marked fetal distress in some cases of gestational diabetes mellitus [11,78]. or an increased risk of injury associated with macrosomia, such as shoulder dystocia [11,79].

Other Types of Diabetes Mellitus

- Onset Diabetes of the Young (MODY) is stated to be a rare autosomal dominant inherited form of diabetes, which is due to one of several single-gene mutations causing defects in insulin production [11,80].
- MODY was stated to be significantly less common than the three main types, constituting 1% to 2% of all cases [11].
- It has been pointed out that the name of this disease refers to early postulates as to its nature. Being due to a defective gene, MODY varies in age at manifestation and in severity according to the specific gene defect; thus, there are at least 13 subtypes of MODY. It had also been iterated that people who have MODY often can control it without using insulin [11,81].
- It has been iterated that some cases of diabetes are caused by the body's tissue receptors not responding to insulin, even when the insulin levels are normal within ranges, which is what separates it from type 2 diabetes); this form is very uncommon [11].
- It has been pointed out that genetic mutations which be either autosomal mutation or mitochondrial mutation could lead to defects in beta cell function [11].
- It has also been explained that abnormal insulin action might also have been genetically determined in some cases [11].
- It has furthermore been stated that any disease which causes extensive damage to the pancreas might lead to the development of diabetes mellitus for example, chronic pancreatitis and cystic fibrosis [11].
- It has been pointed out that diseases that are associated with excessive secretion of insulin-antagonist hormones could cause diabetes mellitus which is typically resolved once the hormone excess is removed [11].
- It has been pointed out that many medicaments do impair insulin secretion and some toxins damage pancreatic beta cells, whereas others increase insulin resistance especially glucocorticoids which can provoke "steroid diabetes" [11].
- It had been pointed out that the ICD-10 (1992) diagnostic entity, malnutrition-related diabetes mellitus (ICD-10 code E12), was deprecated by the World Health Organization (WHO) when the current taxonomy was introduced in 1999 [11,82]. Yet another form of diabetes mellitus which people might develop is double diabetes. This is when a type 1 diabetic becomes insulin resistant, which is the hallmark for type 2 diabetes or a diabetic has a family history for type 2 diabetes [11,83]. It was first discovered in 1990 or 1991.

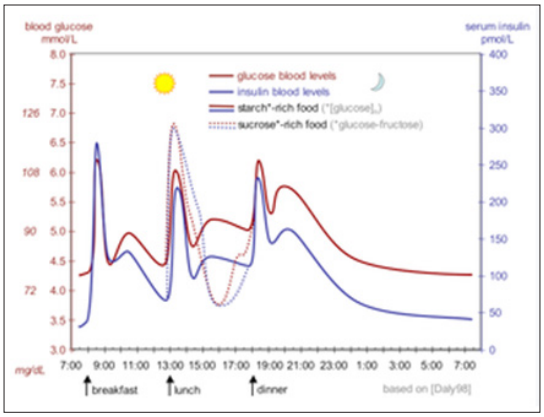
The following is a list of disorders that may increase the risk of diabetes: [11,84].

- Genetic defects of β-cell function
  - Maturity Onset Diabetes of the Young
  - Mitochondrial DNA mutations
- Genetic defects in insulin processing or insulin action
  - Defects in proinsulin conversion
  - Insulin gene mutations
  - Insulin receptor mutations
- Exocrine pancreatic defects (see Type 3c diabetes, for example pancreatogenic diabetes)
  - Chronic pancreatitis
  - Pancreatectomy

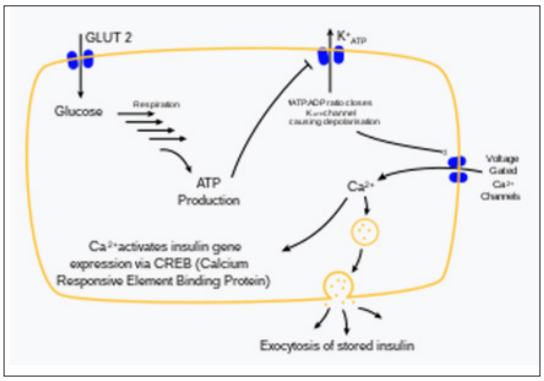
- o Pancreatic neoplasia
- o Cystic fibrosis
- o Hemochromatosis
- o Fibrocalculus pancreatopathopathy
- • Endocrinopathies
- o Growth hormone excess (acromegaly)
- o Cushing syndrome
- o Hyperthyroidism
- o Hypothyroidism
- o Pheochromocytoma
- o Glucagonoma
- • Infections
- o Cytomegalovirus infection.
- o Coxsackievirus B
- • Drugs
- o Glucocorticoids
- o Thyroid hormone
- o Beta-adrenergic agonists
- o Statins [11,85].

Pathophysiology

Figure 6: Reproduced from [11]. with adaptation / change of reference numbers in the table to correspond with the references of the article



The fluctuation of blood sugar (red) and the sugar-lowering hormone insulin (blue) in humans during the course of a day with three meals. One of the effects of a sugar-rich vs a starch -rich meal is highlighted.



Mechanism of insulin release in normal pancreatic beta cells. Insulin production is more or less constant within the beta cells. Its release is triggered by food, chiefly food containing absorbable glucose.

Figure 7 Reproduced from [11].

- has been iterated that insulin is the principal hormone which regulates the uptake of glucose from the blood into most cells of the body, especially liver, adipose tissue and muscle, except smooth muscle, in which insulin acts via the IGF-1. Therefore, deficiency of insulin or the insensitivity of its receptors play a central role in all forms of diabetes mellitus [11,86].
- It has been iterated that the body obtains glucose from three main sources including: the intestinal absorption of food; the breakdown of glycogen (glycogenolysis), the storage form of glucose that is found within the liver; and gluconeogenesis, the generation of glucose from non-carbohydrate substrates in the body [11,87]. Insulin plays a critical role in regulating glucose levels in the body. Insulin can inhibit the breakdown of glycogen or the process of gluconeogenesis, it can stimulate the transport of glucose into fat and muscle cells, and it can stimulate the storage of glucose in the form of glycogen [11,87].
- It has been pointed out that insulin is released into the blood by beta cells (β-cells), that are found within the islets of Langerhans within the pancreas, in response to rising levels of blood glucose, typically after eating [11].
- It has been iterated that insulin is utilized by about two-thirds of the body's cells to absorb glucose from the blood for use as fuel, for conversion to other needed molecules, or for storage [11].
- It has furthermore been pointed out that lower glucose levels do result in decreased insulin release from the beta cells and in the breakdown of glycogen to glucose. This process is stated to be mainly controlled by the hormone glucagon, which does act in the opposite manner to insulin [11,88].
- It has been pointed out that if the amount of insulin that is available is insufficient, or if cells respond poorly to the effects of insulin which is referred to as insulin resistance, or if the insulin itself is defective, then glucose is not absorbed properly by the body cells that require it, and is not stored appropriately in the liver and muscles. The net effect is persistently high levels of blood glucose, poor protein synthesis, and other metabolic derangements, such as metabolic acidosis in cases of complete insulin deficiency [11,87].
- It has been iterated that when glucose concentration in the blood remains high over time, the kidneys reach a threshold of reabsorption, and the body excretes glucose in the urine (glycosuria) [11,89]. This is said to increase the osmotic pressure of the urine and inhibits reabsorption of water by the kidney, resulting in increased urine production called polyuria and increased fluid loss. Lost blood volume is said to be replaced osmotically from water in body cells and other body compartments, causing dehydration and increased thirst polydipsia [11,87]. Furthermore, it has been pointed out that intracellular glucose deficiency stimulates appetite leading to excessive food intake (polyphagia) [11,90].

Diagnosis of diabetes mellitus

It has been pointed out that Diabetes mellitus is diagnosed with a test for the glucose content in the blood, and is diagnosed by demonstrating any one of the following: [11,82].

- Fasting plasma glucose level that is ≥ 7.0 mmol/L (126 mg/dL). For this test, blood is taken after a period of fasting, for example. in the morning before breakfast, after the patient had sufficient time to fast overnight.
- Plasma glucose level ≥ 11.1 mmol/L (200 mg/dL) two hours after a 75-gram oral glucose load as in a glucose tolerance test (OGTT)
- Symptoms of high blood sugar and plasma glucose ≥ 11.1 mmol/L (200 mg/dL) either while fasting or not fasting
- Glycated hemoglobin (HbA1C) ≥ 48 mmol/mol (≥ 6.5 DCCT%) [11,91].

Figure 8 (Table 2) Reproduced from [11] with adaptation / change of reference numbers in the table to correspond with the references of the article

WHO diabetes diagnostic criteria [92] [93]						
Condition	**2-hour glucose**		**Fasting glucose**		**HbA1c**	
Unit	mmol/L	mg/dL	mmol/L	mg/dL	mmol/mol	DCCT %
Normal	< 7.8	< 140	< 6.1	< 110	< 42	< 6.0
Impaired fasting glycaemia.	< 7.8	< 140	6.1–7.0	110–125	42–46	6.0–6.4
Impaired glucose tolerance	≥ 7.8	≥ 140	< 7.0	< 126	42–46	6.0–6.4
Diabetes mellitus	≥ 11.1	≥ 200	≥ 7.0	≥ 126	≥ 48	≥ 6.5

- has been iterated that a positive result, in the absence of unequivocal high blood sugar, should be confirmed by a repeat of any of the above methods on a different day.
- It has also been stated that it is preferable to measure a fasting glucose level because of the ease of measurement and the considerable time commitment of formal glucose tolerance testing, which takes two hours to complete and offers no prognostic advantage over the fasting test [11,94]. According to the current definition, two fasting glucose measurements at or above 7.0 mmol/L (126 mg/dL) is considered diagnostic for diabetes mellitus.
- It has been iterated that Per the WHO, people who have fasting glucose levels from 6.1 to 6.9 mmol/L (110 to 125 mg/dL) are considered to have impaired fasting glucose [11, 95].
- It has been pointed out that people who have plasma glucose level at or above 7.8 mmol/L (140 mg/dL), but not over 11.1 mmol/L (200 mg/dL), two hours after a 75-gram oral glucose load are considered to have impaired glucose tolerance. It has also been pointed out that out 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 [11,96].
- It has been iterated that the American Diabetes Association (ADA) since 2003 has been utilizing a slightly different range for impaired fasting glucose of 5.6 to 6.9 mmol/L (100 to 125 mg/dL) [11,97].
- It has been pointed out that Glycated Hemoglobin is better than fasting glucose for determining risks for the development of cardiovascular disease and death from any cause [11,98].

Prevention of diabetes mellitus

- It has been pointed out that there is no known preventive measure for the prevention of type 1 diabetes. Mellitus [11,65].
- Type 2 diabetes mellitus which accounts for 85–90% of all cases worldwide could often be prevented or delayed [11,99]. by maintaining a normal body weight, engaging in physical activity, and eating a healthy diet [11,65].
- It has been pointed out that higher levels of physical activity of more than 90 minutes per day reduces the risk of diabetes by 28% [11,100].
- Dietary changes that are known to be effective in helping for the prevention of diabetes mellitus include maintaining a diet rich in whole grains and fiber, and choosing good fats, such as the poly-unsaturated fats found in nuts, vegetable oils, and fish [11,101].
- It has been stated that limiting sugary beverages and eating less red meat and other sources of saturated fat could also help in the prevention of diabetes mellitus [11,101].
- It has been pointed out that tobacco smoking is also associated with an increased risk for the development of diabetes mellitus and its complications, so smoking cessation could be an important preventive measure as well [11,102].
- It has been iterated that the relationship between type 2 diabetes mellitus and the main modifiable risk factors related to the development of diabetes mellitus including excess weight, unhealthy diet, physical inactivity and utilization of tobacco is similar in all regions of the world. It has also been pointed out that there is growing evidence that the underlying determinants of diabetes mellitus are a reflection of the major forces driving social, economic and cultural change: including globalization, or urbanization, population aging, and the general health policy environment [11,103].

Management of diabetes mellitus

- It has been iterated that diabetes mellitus management concentrates on keeping blood sugar levels close to normal, without causing low blood sugar [11,104].
- It has been iterated that management of diabetes mellitus can usually be accomplished with dietary changes, [11,105]. exercise, weight loss, and use of appropriate medications (insulin, oral medications) [11,104].
- It has been pointed out that learning about the disease and actively participating in the treatment of diabetes is important, since complications are far less common and less severe in people who have well-managed their blood sugar levels [11,104,106].
- It has been iterated that the goal of treatment is attainment of an A1C level below 5.7% [11,107,108]. and that attention is also paid to other health problems which may accelerate the negative effects of diabetes mellitus including: smoking, high blood pressure, metabolic syndrome, obesity, as well as and lack of regular exercise [11,104,109].
- It has also been pointed out that specialized footwear tends to be widely utilized in order to reduce the risk for the development of diabetic foot ulcers by relieving the pressure on the foot [11,110,111,112].
- It has been iterated that foot examination for patients who live with diabetes mellitus should be undertaken annually which should include sensation testing, foot biomechanics, vascular integrity and foot structure [11,113].
- It has been iterated that with regard to those individuals who have severe mental illness, the efficacy of type 2 diabetes mellitus self-management interventions had still been poorly explored, with insufficient scientific evidence to illustrate whether these interventions have similar results to those observed within the general population [11,114].

Lifestyle Modifications in The Management of Diabetes Mellitus

- It has been pointed out that people who have diabetes mellitus can benefit from education related to the disease and treatment, dietary changes, as well as exercise, with the

goal of keeping both short-term and long-term blood glucose levels within acceptable limits. [11].

- It has also been iterated that given the associated higher risks of cardiovascular disease, lifestyle modifications had been recommended to control blood pressure [11,115, 116].
- It has been pointed out that weight loss could prevent progression from prediabetes to type 2 diabetes mellitus, decrease the risk of cardiovascular disease, or result in a partial remission of diabetes mellitus in people who have diabetes mellitus [11,117,118].
- It has been documented that no single dietary pattern is best for all people who have diabetes mellitus [11,119].
- It has been iterated that: healthy dietary patterns, including the Mediterranean diet, low-carbohydrate diet, or DASH diet, had often been recommended, even though evidence has not supported one over the others [11,117,118].
- It has been pointed out that based upon the ADA, "reducing overall carbohydrate intake for individuals who have diabetes mellitus had revealed the most evidence for improving glycemia, and for individuals who have type 2 diabetes mellitus who cannot meet the glycemic targets or where reducing anti-glycemic medicaments is a priority, low or very-low carbohydrate diets are a viable approach to the control of diabetes mellitus [11,118].
- It has also been pointed out that with regard to overweight people who have type 2 diabetes mellitus, any diet which achieves weight loss is regarded as effective [11,119,120].
- It has been iterated that a 2020 Cochrane systematic review had compared several non-nutritive sweeteners to sugar, placebo and a nutritive low-calorie sweetener tagatose, however, the results were unclear for effects on HbA1c, body weight and adverse events [11 ,121]. It was also pointed out that the studies that were included were mainly of very low-certainty and did not report upon health-related quality of life, diabetes complications, all-cause mortality or socioeconomic effects [11,121].

Diabetes Medications in Glucose Control

- It has been iterated that majority of medicaments that are utilized for the treatment of diabetes mellitus act by lowering blood sugar levels via different mechanisms [11].
- It has been stated that there is broad consensus that when people who have diabetes mellitus maintain tight glucose control by keeping the glucose levels in their blood within normal ranges, they do experience fewer complications, such as kidney problems or eye problems [11,122,123].
- It has been pointed out nevertheless, that there is debate as to whether this is appropriate and cost-effective for people later on in life in whom the risk of hypoglycemia may be more significant [11,124].
- It has been pointed out that there are a number of different classes of anti-diabetic medications and that Type 1 diabetes mellitus does require treatment with insulin, ideally utilizing a "basal bolus" regimen which most closely matches normal insulin release: long-acting insulin for the basal rate and short-acting insulin with meals [11,125].
- It has been iterated that Type 2 diabetes has tended to be generally treated with medicament that is taken by mouth for example metformin even though some eventually require injectable treatment with insulin or GLP-1 agonist [11,126].
- It has been iterated that Metformin is generally recommended as a first-line treatment for type 2 diabetes mellitus, in view of the fact that there is good evidence which had shown that that it decreases mortality [11,127].
- It has been pointed out that Metformin works by decreasing the liver's production of glucose, and increasing the amount of glucose that is stored within peripheral tissue [11,128].
- It had also been iterated that many other groups of medicaments, mainly oral medication, might also decrease blood sugar in type 2 diabetes mellitus. These medicaments include (1) agents which increase insulin release for example sulfonylureas, (2) agents that decrease the absorption of sugar from the intestines for example (acarbose), (3) agents that inhibit the enzyme dipeptidyl peptidase-4 (DPP-4) that inactivates incretins such as GLP-1 and GIP for example sitagliptin, (4) agents which make the body more sensitive to insulin for example thiazolidinedione, and (5) agents which increase the excretion of glucose in the urine (SGLT2 inhibitors) [11,128].

- It has been pointed out that when insulin is utilized in the treatment of type 2 diabetes mellitus, a long-acting formulation is usually added initially, while continuing oral medicaments [11,127].
- It had also been pointed out that some severe cases of type 2 diabetes mellitus might also be treated with utilization of insulin, which is increased gradually until glucose targets are reached [11,127,129].

Blood pressure lowering and management of miscellaneous aspects of cardiovascular disease

- It is important for all patients and clinicians to be mindful of the fact that cardiovascular disease as serious complication that tends to be associated with diabetes mellitus and in view of this, many international guidelines had recommended blood pressure treatment targets that are lower than 140/90 mmHg for people who diabetes mellitus [11,130].
- Nevertheless, it has been iterated that there is only limited evidence regarding what the lower blood targets should be [11].
- A 2016 systematic review of the literature had found potential harm to treating to targets lower than 140 mmHg, [11,131]. and a subsequent systematic review in 2019 had found no evidence of additional benefit from blood pressure lowering to between 130 – 140mmHg, even though there was an increased risk of adverse events [11,132].
- It has been pointed out that the 2015 American Diabetes Association recommendations are that people who have diabetes mellitus and albuminuria should receive an inhibitor of the renin-angiotensin system in order to reduce the risks of progression to end-stage renal disease, cardiovascular events, and death [11,133].
- It has also been pointed out that evidence exists evidence that angiotensin converting enzyme inhibitors (ACEIs) are superior to other inhibitors of the renin-angiotensin system such as angiotensin receptor blockers (ARBs), [11,134]. or aliskiren in the prevention of cardiovascular disease [11,135].
- It has been pointed out that even though a more recent review had found similar effects of ACEIs and ARBs on major cardiovascular and renal outcomes [136]. there has been no evidence that combining ACEIs and ARBs does provide additional benefits [11,136].

Aspirin

- It has been iterated that utilization of aspirin in order to prevent cardiovascular disease in diabetes is controversial [11,133].
- It has also been stated that Aspirin has been recommended by some clinicians in people who are at high risk for the

development of cardiovascular disease; nevertheless, routine use of aspirin had not been found to improve the outcomes in uncomplicated cases of diabetes mellitus [11,137].

- It has also been iterated that the 2015 American Diabetes Association recommendations for aspirin utilization based upon expert consensus or clinical experience, are that low-dose aspirin utilization is reasonable in adults who have diabetes mellitus who are at intermediate risk for the development of cardiovascular disease with a 10-year cardiovascular disease risk, (5% to10%) [11,133].
- It has been pointed out that National guidelines for England and Wales by the National Institute for Health and Care Excellence (NICE) had recommended against utilization of aspirin in people who have type 1 diabetes mellitus or type 2 diabetes mellitus who do not have confirmed cardiovascular disease [11,125,126].

Surgery

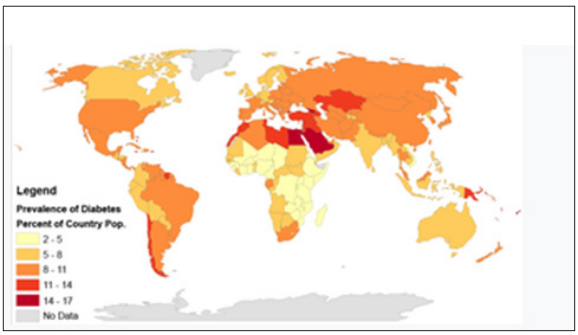
- It has been pointed out that the undertaking of weight loss surgery in patients who have type 2 diabetes mellitus in association with obesity is quite often an effective measure [11,138].
- It has been iterated that many patients had been able to maintain normal blood sugar levels with little or no medications pursuant to their undergoing surgery [11,139]. and long-term mortality had been decreased [11,140].
- It has been pointed out nevertheless, that there is a short-term mortality risk of less than 1% from the surgery [11,141].
- It has been pointed out that the body mass index cutoffs for when surgery is appropriate had not yet been clarified clear [11,140].
- It had been recommended that the option of undertaking weight loss surgery should be considered in those individuals who are unable to get both their weight and blood sugar under control [11,142].
- It has been pointed out that a pancreas transplant surgery is occasionally considered for people who have type 1 diabetes mellitus who have severe complications of their disease, including end stage renal disease that has required the undertaking of kidney transplantation [11,143].

Self-Management and Support

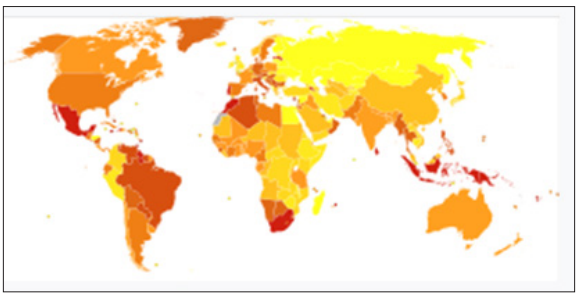
- It has been pointed out that within countries utilizing a general practitioner system, such as in the United Kingdom, care may take place mainly outside hospitals, with hospital-based specialist care used only in case of complications, difficult blood sugar control, or research projects [11].
- It has also been stated that within other circumstances, general practitioners and specialists share care in a team approach as well as home telehealth support could be an effective management technique [11,144].
- It has also been iterated that utilization of technology in order to deliver educational programs for adults who have type 2 diabetes mellitus does include computer-based self-management interventions to collect for tailored responses to facilitate self-management [11,145].
- It has been pointed out that there is no adequate evidence to support the effects on cholesterol, blood pressure, behavioral change for example physical activity levels and dietary, depression, weight, health-related quality of life, nor in other biological, cognitive, or emotional outcomes [11,145,146].

Additional Epidemiology Information on diabetes mellitus

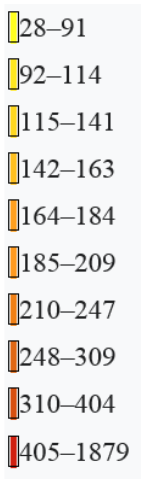
Figure 9 Reproduced from: with adaptation / change of reference numbers in the table to correspond with the references of the article[11].



Rates of diabetes worldwide in 2014. The worldwide prevalence was 9.2%.



Mortality rate of diabetes worldwide in 2012 per million inhabitants



- • It has been documented that in 2017, 425 million people had diabetes mellitus globally, [11,147]. which was up from an estimated 382 million people in 2013 [11,148]. and from 108 million in 1980 [11,143].
- • It has been iterated that accounting for the shifting age structure of the global population, the prevalence of diabetes is 8.8% among adults, which was nearly double the rate of 4.7% in 1980 [11,147,149]
- • It has been pointed out that Type 2 diabetes mellitus does constitute up to about 90% of the cases [11,29,150].
- • It has also been iterated that some data had indicated that the rates are roughly equal in women and men, [11,29]. but male excess in diabetes mellitus has been found in many populations with higher type 2 diabetes mellitus incidence, possibly 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 [11,150,151].

- It has been iterated that the WHO had estimated that diabetes mellitus resulted in 1.5 million deaths in 2012, making it the 8th leading cause of death [11,149,152]. Nevertheless, it has been pointed out that another 2.2 million deaths worldwide were recorded as attributable to high blood glucose and the increased risks of cardiovascular disease and other associated complications for example kidney failure, which often lead to premature death and are often listed as the underlying cause recorded on death certificates rather than diabetes mellitus [11,149,153].
- For example, in 2017, it was reported that the International Diabetes Federation (IDF) had estimated that diabetes mellitus had resulted in 4.0 million deaths worldwide, [11,147]. utilizing modeling to estimate the total number of deaths that could be directly or indirectly attributed to diabetes [11,147].
- It has been iterated that diabetes mellitus occurs throughout the world but diabetes mellitus is more common, especially type 2 diabetes mellitus in more developed countries [11].
- It has been pointed out that the greatest increase in diabetes mellitus rates has nevertheless, been seen within low- and middle-income countries, [11,149]. where more than 80% of diabetic deaths occur [11,154].
- It has been documented that the fastest diabetes mellitus prevalence increase is expected to occur within Asia and Africa, where most people with diabetes will probably live in 2030 [11,155].
- It has been pointed out that the increase in rates in developing countries follows the trend of urbanization and lifestyle changes, including increasingly sedentary lifestyles, less physically 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) [11,149,155].
- It has been iterated that the global number of diabetes mellitus cases might increase by 48% between 2017 and 2045 [11,147].
- It has been documented that as of 2020, 38% of all United States of America (USA) adults had prediabetes [11,156]. It had also been pointed out that prediabetes is an early stage of diabetes mellitus.

History of Diabetes Mellitus

- It has been pointed out that diabetes mellitus was one of the first diseases that had been described, [11,157]. with an Egyptian manuscript from about. 1500 BCE mentioning "too great emptying of the urine [11,158]. The Ebers papyrus included a recommendation for a drink to taken in such cases [11,159]. The first described cases of diabetes mellitus are believed to have been type 1 diabetes [11,158].
- It has been stated that Indian physicians around the same time had identified the diabetes mellitus disease and classified it as madhumeha or "honey urine", noting the urine would attract ants [11,158,159].
- It has been pointed out that the terminology "diabetes" or "to pass through" was first utilized in 230 BCE by the Greek Apollonius of Memphis [11,58]. The disease was stated to be considered rare during the time of the Roman empire, with Galen commenting that he had only seen two cases during his career [11,158]. It was explained that this was possibly because of 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 the urine" (diarrhea urinosa) [11,160].
- It has been pointed out that the earliest surviving work that contained a detailed reference to diabetes mellitus is that of Aretaeus of Cappadocia (2nd or early 3rd century CE). He was stated to have described the symptoms and the course of the disease, which he attributed to the moisture and coldness, reflecting the beliefs of the "Pneumatic School". He was stated to have postulated a correlation between diabetes mellitus and other diseases, and he was stated to have discussed the differential diagnosis from the snakebite, which also provokes excessive thirst. His work was stated to have remained unknown in the West until 1552, when the first Latin edition was published in Venice [11,160].
- It has been documented that two types of diabetes mellitus were identified as separate conditions for the first time by the Indian physicians Sushruta and Charaka in 400–500 CE with one type being associated with youth and another type with being overweight [11,158].
- It has been pointed out that effective treatment had not been developed until the early part of the 20th century when Canadians Frederick Banting and Charles Herbert Best had isolated and purified insulin in 1921 and 1922 [11,158]. This was stated to have been followed by the development of the long-acting insulin NPH in the 1940s [11,158].

Etymology of Diabetes Mellitus

- It has been iterated that the word diabetes (/ˌdaɪ.əˈbiːtiːz/ or /ˌdaɪ.əˈbiːtɪs/) comes from Latin diabētēs, which in turn comes from Ancient Greek διαβήτης (diabētēs), which literally means "a passer through; a siphon"[11] [161].
- It has been iterated that Ancient Greek physician Aretaeus of Cappadocia (fl. 1st century CE) utilized that word, with the intended meaning "excessive discharge of urine", as the name for the disease [11,162,163].
- It has also been pointed out that ultimately, the word comes from Greek διαβαίνειν (diabainein), meaning "to pass through"[11,161]. which is composed of δια- (dia-), meaning "through" and βαίνειν (bainein), meaning "to go"[11,162].
- It has also been documented that the word "diabetes" was first recorded in English, in the form diabete, in a medical text written around 1425.
- It has been iterated that the word mellitus (/məˈlaɪtəs/ or /ˈmɛlɪtəs/) comes from the classical Latin word mellītus, meaning "mellite" [11,163]. (i.e., sweetened with honey; [11,164]. honey-sweet [11,165]. And that the Latin word comes from mell-, which comes from mel, meaning "honey"; [11,164,165]. sweetness; [11,165]. pleasant thing, [11,165]. and the suffix -ītus,[164]. whose meaning is the same as that of the English suffix "-ite" [11,166].
- It had been iterated that it was Thomas Willis who in 1675 had added "mellitus" to the word "diabetes" as a designation for the disease, when he noticed the urine of a person with diabetes had a sweet taste (glycosuria). This sweet taste had been noticed in urine by the ancient Greeks, Chinese, Egyptians, Indians, as well as Persians [11].

Society and culture aspects of diabetes mellitus

- It has been pointed out that the 1989 " St Vincent Declaration" "[11,167,168]. was the result of international efforts to improve the care accorded to those patients who have diabetes mellitus. It had been explained that doing so was important not only in terms of quality of life and life expectancy but also economically – expenses due to diabetes had been shown to be a major drain on health – and productivity-related resources for healthcare systems and governments.

- It has been documented that several countries had established more and less successful national diabetes programs to improve upon treatment of the disease [11,169].
- It has been iterated that people who have diabetes mellitus and who have neuropathic symptoms such as numbness or tingling in feet or hands are twice as likely to be unemployed as those without the symptoms [11,170].
- It has been pointed out that in 2010, diabetes mellitus-related emergency room (ER) visit rates within the United States of America were higher among people from the lowest income communities (526 per 10,000 population) than from the highest income communities (236 per 10,000 population) and that approximately 9.4% of diabetes-related ER visits were for the uninsured [11,171].

Naming

- It has been pointed out that the terminology "type 1 diabetes" had replaced several former terminologies, including childhood-onset diabetes, juvenile diabetes, and insulin-dependent diabetes mellitus.
- It has also been pointed out that likewise, the terminology "type 2 diabetes" has replaced several former terms, including adult-onset diabetes, obesity-related diabetes, and noninsulin-dependent diabetes mellitus. Beyond these two types, there is no agreed-upon standard nomenclature [11,172].
- It has been explained that diabetes mellitus is also occasionally referred to as "sugar diabetes" to differentiate it from diabetes insipidus [11,173].

Other animals Diabetes Mellitus in dogs and cats

- It has been documented that diabetes mellitus can occur in mammals or reptiles [11,174,175].
- It has also been documented that birds do not develop diabetes because of their unusually high tolerance for elevated blood glucose levels [11,176].
- It has been iterated that inn animals, diabetes mellitus is most commonly encountered in dogs and cats. Middle-aged animals are most commonly affected. The following summating iterations had also been made: [11].
- Female dogs are twice as likely to be affected as males, while according to some sources, male cats are more prone than females. In both species, all breeds may be affected, but some small dog breeds are particularly likely to develop diabetes, such as Miniature Poodles [11,177].
- It has been stated that Feline diabetes is strikingly similar to human type 2 diabetes. The Burmese, Russian Blue, Abyssinian, and Norwegian Forest cat breeds are at higher risk than other breeds. Overweight cats are also at higher risk [11,178].
- It has been documented that the symptoms might relate to fluid loss and polyuria, but the course may also be insidious.
- Diabetic animals are more prone to infections.
- The long-term complications recognized in humans are stated to be much rarer in animals.
- The principles of treatment including: weight loss, oral antidiabetics, subcutaneous insulin and management of emergencies for example ketoacidosis are similar to those in human beings [11,177].

Summary and Conclusions

- Diabetes mellitus is a chronic disease which occurs either when the pancreas does not produce insulin or when the body cannot effectively utilize the insulin it produces.
- Insulin is a hormone which regulates blood glucose.
- Hyperglycaemia which is also referred to as raised blood sugar, is a common effect on uncontrolled diabetes mellitus and over a time hyperglycaemia emanates I serious damage to many of the body's systems, especially the nerves as well as blood vessels.
- The number people who had diabetes mellitus rose from 108 million in 1980 to 422 million in 2014.
- The prevalence of diabetes mellitus had been rising more rapidly within low-income as well as middle-income countries.
- Diabetes Mellitus is a major cause of blindness, renal failure, heart attacks, stroke, as well as lower limb amputation.
- Between 2000, and 2019, there was a reported increase in diabetes mellitus mortality rates by age.
- It had been documented that in 2019, diabetes mellitus and kidney disease that was due to diabetes mellitus had caused an estimated 2 million deaths.
- A healthy diet, regular physical activity, maintenance of a normal body weight as well as avoiding utilization of tobacco are ways of preventing or delaying the onset of type 2 diabetes mellitus.
- Diabetes Mellitus can be effectively treated and the consequences of diabetes mellitus can be avoided or delayed with diet modification, life style changes entailing physical activity, medicaments, as well as regular screening and treatment for complications.
- In 2014, 8.5% of adults who were aged 18 years or older than 18 years had diabetes mellitus.
- In 2019, diabetes mellitus was documented to be the direct cause of 1.5 million deaths and 48% of all deaths due to diabetes mellitus had occurred before the age of 70 years.
- Another 460,000 kidney disease deaths were caused by diabetes mellitus and raised blood glucose does cause about 20% of cardiovascular deaths.
- Between 2000 and 2019, there was a 3% increase in age-standardized mortality rates from diabetes mellitus. Within the lower-middle-income countries, the mortality rate due to diabetes mellitus increased to 13%.
- By contrast, the probability of dying from any one of the four main non-communicable diseases including cardiovascular diseases, cancer, chronic respiratory diseases or diabetes mellitus between the ages of 30 years and 70 years had decreased by 22% globally between 2000 and 2019.

Conflict of Interest– None

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