International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

An Insight on Diabetes Mellitus: A Comprehensive Review

Tiwari Pratima[1], Singh Udai Pratap[2]

[1]Research Scholar, Department of Anthropology, Faculty of Arts, University of Lucknow, India
[2]Professor, Department of Anthropology, Faculty of Arts, University of Lucknow, India

Abstract
This paper thoroughly overviews diabetes mellitus, focusing on its introduction, classification, and management strategies. Initially, the paper outlines the fundamental concepts of diabetes mellitus, including its impact on global health and its underlying pathophysiological mechanisms. It distinguishes between the two primary types of diabetes: Type 1 diabetes (T1D), an autoimmune condition leading to the destruction of insulin-producing beta cells, and Type 2 diabetes (T2D), characterized by insulin resistance and relative insulin deficiency. The paper further explores gestational diabetes and its implications for maternal and fetal health. Management strategies for diabetes are examined in detail, encompassing lifestyle modifications, pharmacotherapy, Anthropo-therapeutic Healing, and technological interventions. Key aspects include dietary management, physical activity, and blood glucose monitoring to achieve glycemic control. Additionally, advancements in diabetes care, such as novel pharmacological agents, insulin delivery systems, and continuous glucose monitoring, are discussed. The paper aims to provide a comprehensive understanding of the types of diabetes mellitus and their management, offering insights into current practices and future directions for improving patient outcomes and enhancing quality of life.

Keywords - Type 1 diabetes (T1D), Type 2 diabetes (T2D), Gestational diabetes, pharmacotherapy, Anthropo-therapeutic Healing

INTRODUCTION

Diabetes Mellitus is a carbohydrate metabolism complication and an endocrine disorder caused by damage to the body's ability to produce or respond to insulin to control blood sugar(glucose). It is a major cause of morbidity and mortality, leading toward the immediate or prolonged effects of many cardiovascular, retinal, nervous, and renal diseases (Britannica, 2024).Diabetes is a widespread disease characterized by high blood glucose levels. It is caused by the autoimmune destruction of the pancreatic islets in type 1 diabetes and is associated with genetic and environmental factors in type 2 diabetes. (Ankit. et.al.) It is a syndrome characterized by elevated glucose levels, stemming from various causes like pancreatic issues, hormonal imbalances, and metabolic dysregulation, leading to different types of the condition. (Turner and Neil,1992). Its complex etiology involves various genetic, acquired, and environmental factors having a heterogeneous group of disorders with diverse pathogenetic mechanisms and clinical presentations. (Ganda,1997). Diabetes mellitus is a significant global health concern, with increasing prevalence and

incidence rates observed worldwide. The global incidence of diabetes rose from 11.3 million in 1990 to 22.9 million in 2017, with an age-standardized incidence rate (ASIR) increasing from 234 to 285 per 100,000 persons (Liu et al. 2020). Diabetes Mellitus (DM) is characterized by hyperglycemia and impaired carbohydrate, lipid, and protein metabolism resulting from complete or partial deficiency of insulin secretion and insulin action. (Wu, Ding,2014). According to the International diabetes federation, (IDF, 2022) 537 million adults (1 in 10) were living with diabetes in 2021. This number is expected to rise to 643 million by 2030 and 783 million by 2045. The regulation of glucose is regulated by a polypeptide hormone secreted by β cells in the islets of Langerhans of the pancreas in coordination with Glucagon, another hormone. When blood sugar levels rise, glucose uptake into the cells for energy and storage is facilitated by the release of Insulin, an endocrine hormone secreted by the Pancreas. During the fasting stage (between meals), when the blood sugar levels decrease, the level of insulin drops, and Glucagon (the other hormone), is released for the breakdown of glycogen (stored glucose in the liver) into glucose by the process called Glycogenesis, which then is released into the bloodstream to regulate blood sugar level and other metabolic activities. (Abdelrahman, 2016) .thus preventing hyperglycemia (Bhavya & Sanjay 2022)(Ali et al. 2017).In diabetes, either insulin production is insufficient, or cells become resistant to its effects, leading to elevated blood glucose levels and subsequent complications(Ali et al. 2017)(Bolli et al. 2021. In India, about 77 million people under the age of 18 have diabetes (type 2) and about 25 million have pre-diabetes (higher risk of diabetes in the future). More than 50% of people do not know they have diabetes, and this condition can lead to health problems if not diagnosed and treated early. (WHO, 2022)The blood sugar levels in the human body are maintained by 2 hormones i.e. Insulin and Glycogen

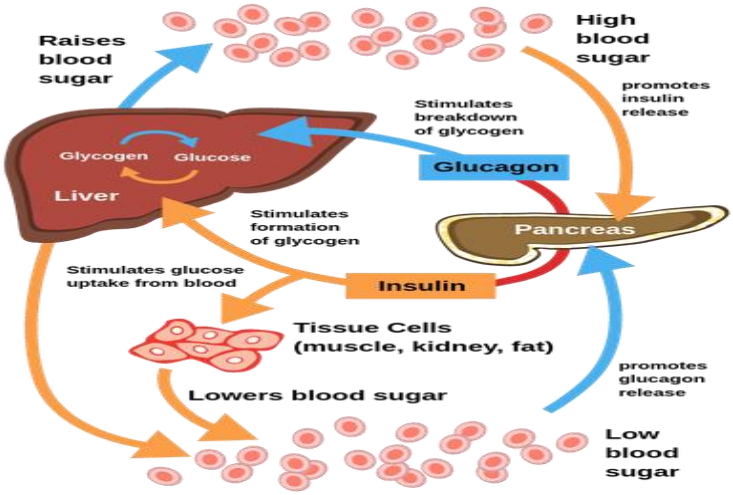

Figure 1 Mechanism of insulin and glucagon in the regulation of blood sugar levels in the hyperglycemic and hypoglycemic conditions. Source : (Steinbusch Laura, 2011)

Ancient References and Understanding, key discoveries in the 19th and 20th centuries, and modern developments The earliest known references to diabetes date back to ancient Egypt around 1500 BCE, where symptoms were documented in healing texts(Haider & Mehdi 2023). Ancient Indian and Chinese medical literature, as well as Greek and Arab writings, also describe the disease, highlighting its long-standing presence in human history(Mahajan & Mahajan 2023).In the 19th century, significant advancements included identifying the pancreas's role in diabetes by Joseph von Mering and Oskar Minkowski, who demonstrated that pancreas removal in dogs induced diabetes(Haider & Mehdi

2023)(March et al. 2022). The landmark discovery of insulin in 1921 by Frederick Banting and Charles Best revolutionized diabetes treatment, providing a critical tool for managing type 1 diabetes(Mejía-Rivera. 2023). The last century has seen rapid advancements in diabetes management, including continuous glucose monitoring and synthetic insulin development, significantly improving patient outcomes(March et al. 2022)(Kuzina et al. 2022). Despite these advancements, diabetes remains a complex challenge, with ongoing research needed to address its increasing prevalence and the intricacies of its pathophysiology.

Diabetes mellitus is influenced by a variety of risk factors that can significantly increase an individual's likelihood of developing the condition. Understanding these factors is crucial for prevention and management strategies. The following sections outline the key risk factors identified in recent research.

Key Risk Factors

- Obesity: Identified as the most significant risk factor, obesity is closely linked to the onset of diabetes. A weight loss of 5% can improve glycemic control and reduce the need for medication(Merwass et al. 2024).
- Age: Increasing age is associated with a higher risk of diabetes, particularly in women, as physiological functions decline over time(Olaleye et al. 2024).
- Family History: A genetic predisposition plays a critical role, with family history being a significant risk factor for diabetes(Muwakhidah 2023).
- Hypertension and Dyslipidemia: Conditions such as high blood pressure and abnormal cholesterol levels further elevate diabetes risk, particularly in obese individuals (Merwass et al. 2024)(Olaleye et al. 2024).
- Lifestyle Factors: Sedentary behavior and poor dietary choices contribute to obesity and, consequently, diabetes risk (Merwass et al. 2024) (Muwakhidah 2023).

While these factors highlight the multifaceted nature of diabetes risk, it is essential to consider that lifestyle modifications can mitigate these risks. However, some individuals may still develop diabetes despite healthy habits, indicating the complexity of the disease's etiology.

Diabetes mellitus (DM) presents a range of symptoms that vary by type and individual. The most common symptoms include hyperglycemia, polyuria, polydipsia, and polyphagia, which indicate the body's inability to manage blood sugar levels effectively. Understanding these symptoms is crucial for timely diagnosis and management.

Common Symptoms of Diabetes Mellitus

- Hyperglycemia: The most prevalent symptom, reported by 48.1% of patients with type 2 diabetes, often leading to increased thirst and urination(Tan & Ng 2023).
- Polyuria: Frequent urination is a classic symptom, observed in 78% of type 1 diabetes cases(Pina et al. 2024).
- Polydipsia: Increased thirst accompanies polyuria, as the body attempts to compensate for fluid loss(Chaudhari et al. 2023).
- Polyphagia: Increased hunger results from the body's inability to utilize glucose effectively(Chaudhari et al. 2023).

Neurological Symptoms

- Neurological manifestations such as irritability, mood swings, and confusion are prevalent, particularly among female patients(Masood et al. 2023). These symptoms can complicate the management of diabetes and affect quality of life.

While these symptoms are critical for diagnosis, some patients may underreport them, leading to inadequate management(Tan & Ng 2023). This underreporting highlights the need for better communication between patients and healthcare providers regarding symptom recognition and management.

CLASSIFICATION OF DIABETES MELLITUS

The classification of diabetes mellitus (DM) is crucial for effective treatment and management. The current consensus categorizes diabetes into four primary types: Type 1 DM, Type 2 DM, gestational diabetes (DMG), and other specific types. This classification is based on the underlying pathophysiology and clinical characteristics, allowing for tailored therapeutic strategies. (World Health Organisation, 2019)

Type 1 diabetes

The autoimmune destruction of the pancreatic b-cell, which produces insulin, is the hallmark of type 1 diabetes mellitus (T1DM), a condition of glucose homeostasis that gradually results in insulin insufficiency and hyperglycemia. Insulin insufficiency causes a steadily deteriorating metabolic disturbance that might result in mortality, hunger, and escalating hyperglycemia if treatment is not received. (Gregory, Moore & Simmons,2013) . The majority of cases are immune-mediated, in which a T cell-mediated autoimmune attack causes loss of beta cells and thus insulin deficiency(Rother, 2007) Type 1 diabetes is partially genetic; the risk of the disease is known to be linked to several genes, including specific HLA genotypes. Diabetic onset in people with a genetic predisposition may be accelerated by one or more extrinsic variables, such as nutrition or viral infection. Although several viruses have been linked, there is currently insufficient proof to back up this theory in human beings.(Petzold , Solimena , Knoch,2015)

Table 1 – Risk factors of Type 1 Diabetes

Genetic and Immunological Factors	• The presence of autoantibodies against pancreatic beta-cell antigens is a significant risk factor for T1D development, indicating an autoimmune response that damages insulin-producing cells("Risk Factors of Type 1 Diabetes Mellitus", 2022). • Ethnic minorities show a higher prevalence of T1D, suggesting genetic susceptibility plays a role("Risk Factors of Type 1 Diabetes Mellitus", 2022).
Environmental and Prenatal Influences	• Prenatal factors such as maternal weight gain, gestational hypertension, and neonatal jaundice have been linked to increased T1D risk in children(Dalili et al. 2023). • Environmental exposures vary by geography, affecting disease incidence and risk factor interactions("Risk Factors of Type 1 Diabetes Mellitus", 2022).

Type 2 diabetes-

Insulin resistance, a disorder in which cells do not react to insulin as they should, is the first step toward type 2 diabetes. As the illness worsens, an insulin shortage could also occur. This type was once known as "non-insulin-dependent.", "adult-onset diabetes" or "diabetes mellitus" (NIDDM). The main reason is

overweight and insufficient exercise. (Shouip,2018). Roughly 90% of all instances of diabetes are type 2 diabetes mellitus (T2DM). Insulin resistance is the term used to refer to the reduced response to insulin in type 2 diabetes. Insulin is ineffective and is initially countered by increased insulin production to keep glucose homeostasis during this condition. However, over time, insulin production diminishes, leading to type 2 diabetes. Adults over 45 are most typically diagnosed with type 2 diabetes. However, as obesity, physical inactivity, and energy-dense diets increase, it is becoming more common in kids, teens, and young adults.(Goyal, Singhal, Jialal ,2015). The primary causes of morbidity and mortality from this medical condition are the semi-permanent issues with the kidneys, eyes, nerves, blood vessels, and kidneys that occur in each variant.

GESTATIONAL DIABETES

Gestational diabetes mellitus (GDM) is a form of carbohydrate intolerance that arises during pregnancy, affecting approximately 5-7% of pregnancies globally (Shaunak 2016) (Boyd & Conway 2023). It is characterized by insufficient insulin production to counteract insulin resistance, which is exacerbated by hormones from the placenta (Buchanan et al. 2007) (Cowie 2022). GDM poses significant health risks for both mothers and infants, including complications such as fetal macrosomia, preeclampsia, and increased perinatal mortality (Boyd & Conway 2023) (Cowie 2022).

Table 2 .1 Risk factors associated with gestational diabetes (Demographic factors)

Age	Women over 25 years old are at increased risk for GDM(Liu & Liu 2009).
Ethnicity	Non-Caucasian women have a higher prevalence of GDM(Liu & Liu 2009).
Family history	A strong family history of diabetes, particularly type-2 diabetes, significantly raises the risk(Ouyang et al. 2002)(Saeed et al. 2016).

Table 2.2 Lifestyle Factors Associated with Gestational Diabetes

Obesity	A pre-pregnancy BMI over 25 kg/m² is a well-established risk factor(Liu & Liu 2009)(Alhinti et al. 2023).
Physical inactivity	Lack of exercise is associated with higher GDM risk(Saeed et al. 2016).
Stress	Pregnancy-related stress has been linked to increased GDM incidence(Saeed et al. 2016).

Table 2.1 Other Contributing Factors associated with Gestational Diabetes

Polycystic Ovary Syndrome (PCOS)	This condition is increasingly recognized as a risk factor(Liu & Liu 2009).
Hypertension	High blood pressure during pregnancy is also correlated with GDM(Saeed et al. 2016).
Low Birth Weight History	Maternal history of low birth weight can contribute to GDM risk(Dode & Santos 2009).

Other specific types

"Maturity-onset diabetes of the young" (MODY) refers to a broad category of monogenic illnesses characterized by dysfunctional β cells. In 1-2% of patients with diabetes, it is thought to be the underlying cause of the condition; nevertheless, prevalence estimates won't be reliable until extensive population screening studies are carried out. (Thanabalasingham G, Owen KR,2011).

This form of diabetes is sporadic; it is caused when the body's tissue receptors do not respond to insulin, even when insulin levels are normal. Defects in beta cell function may result from autosomal or mitochondrial genetic mutations. In a few instances, abnormal insulin action can have been inherited. Diabetes can result from any condition that severely damages the pancreas (such as cystic fibrosis and chronic pancreatitis). Diabetes is a condition brought on by diseases linked to the overproduction of insulin-antagonistic hormones; once the excess hormone is eliminated, the condition usually resolves. While some poisons and many medications harm pancreatic beta cells and reduce insulin release, other substances—particularly glucocorticoids, which can cause "steroid diabetes"—increase insulin resistance. Urakami T,2018 in a study done on MODY identifies at least 14 genes to be mutated, including six that encode proteins that correspond to MODY subtypes 1–6 in turn: glucokinase (GCK), pancreatic and duodenal homeobox 1 (PDX1), neurogenic differentiation 1 (NEUROD1), hepatocyte nuclear factor (HNF) 4α (HNF4α), and HNF1α (HNF1α).

Few medical cases have revealed that any damage to the Pancreas after a major disease such as Cystic fibrosis and chronic Pancreatitis may lead to diabetes in some form.

COMPLICATIONS IN DIABETES –

Diabetes mellitus is associated with a range of complications that can significantly impact health and quality of life. Understanding these complications is crucial for effective management and prevention as it is associated with both microvascular and macrovascular diseases affecting several organs, including muscle, skin, heart, brain, and kidneys.

Table 3.1 Microvascular Complications -These complications involve small blood vessels such as capillaries

Retinopathy	Damage to the retina can lead to vision loss, often requiring early detection and management (Saienko et al. 2024)(Wagh et al. 2022).
Nephropathy	Kidney damage can progress to renal failure, necessitating dialysis or transplantation (Wilson 2023) (Pradeepa & Mohan 2024).
Neuropathy	Nerve damage can result in pain, loss of sensation, and complications like diabetic foot syndrome (Przyborowska et al. 2024)(Wagh et al. 2022).

Table 3.2 Macrovascular Complications- These complications involve large vessels, such as arteries and veins

Cardiovascular Disease	Increased risk of myocardial infarction and stroke due to vascular damage(Saienko et al. 2024)(Pradeepa & Mohan 2024).
Peripheral Vascular Disease	Reduced blood flow to limbs can lead to severe complications, including amputations(Wilson 2023)(Wagh et al. 2022).

Diagnostic criteria for Diabetes:

1.HbA1C test

In this method, blood glucose over the previous two to three months is determined. This method of diagnosis has the benefit of not requiring us to fast or consume any liquids. The average blood glucose control you had during the preceding three months is determined by an A1c test, also known as a glycosylated hemoglobin test. The A1c test is advised by the American Diabetes Association for the diagnosis of diabetes and pre-diabetes. A1c readings above 6.5% are thought to be indicative of diabetes, values between 5.7 and 6.4% are indicative of pre-diabetes, and test results below 5.6% are considered normal, according to the American Diabetes Association. Glycosylated hemoglobin, or hemoglobin A1c, is another name for the hemoglobin A1c test.

2. Random (also called Casual) Plasma Glucose Test

A test for plasma glucose detects the amount of sugar or glucose that is circulating in the bloodstream. Simply stated, having blood obtained at a laboratory at any time qualifies as "random" or "casual." The test will not be impacted by recent eating or fasting. A person may have diabetes if the plasma glucose test result is 200 mg/dl or above. An oral glucose tolerance test, a fasting plasma glucose test, or another random test on a different day will be needed to validate the test findings just to be sure.

3. Oral Glucose Tolerance Test (OGTT)

If one meets this criterion, the subject will be required to fast for eight hours without eating or drinking anything other than water, after which he or she will be required to consume a liquid that contains a known quantity of glucose—typically 75 grams. Two hours before consuming the glucose mixture, the blood is tested. The subject will be requested to stop eating until the exam ends. The term for this type of test is the Oral Glucose Tolerance Test (OGTT). Normally, the plasma glucose level after fasting is less than 100 mg/dl. Levels between 100 mg/dl and 126 mg/dl are indicative of pre-diabetes. Diabetes can be diagnosed by measuring fasting plasma glucose levels that are 126 mg/dl or higher. Plasma glucose should generally be less than 140 mg/dl two hours after the glucose drink. If the values fall between 140 and 199 mg/dl, the person is diabetic. The plasma glucose readings of 200 mg/dl or higher indicates diabetes.

4. Fasting Plasma Glucose (FPG)

This blood test is done after the examiner has gone at least 8 hours without food and drink. A measure between 60 and 99 mg/dl is considered to be normal whereas a condition between 100mg/dl to 126 mg/dl and 126 mg/dl or greater is considered to be pre-diabetic and diabetic respectively.

Table 4. Risk factors associated with gestational diabetes

Type	Normal range	Pre-Diabetes	Diabetes
HbA1C Test	<5.7%	5.7-6.4%	6.5% or greater
Random)Plasma Glucose Test			200 mg/dl or greater
Oral Glucose Tolerance Test (OGTT)	< 140 mg/dl	100mg/dl to 126 mg/dl	Above 126 mg/dl
. Fasting Plasma Glucose (FPG)	60 and 99 mg/dl	100-125 mg/dl	126 mg/dl or greater

PREVENTION AND MANAGEMENT -

The prevention of diabetes is a multifaceted challenge that requires a combination of lifestyle interventions, pharmacological approaches, and innovative strategies. Research indicates that effective

prevention can significantly reduce the incidence of diabetes, particularly in at-risk populations.

Lifestyle Intervention

The Diabetes Prevention Program demonstrated that lifestyle changes, including diet and exercise, reduced diabetes incidence by 58% over 2.8 years (Heneghan et al. 2006). However, replicating these interventions in broader healthcare settings remains challenging due to their labor-intensive nature(Heneghan et al. 2006).

Pharmacological Approaches

Medications like metformin have shown a 31% reduction in diabetes incidence, while rosiglitazone demonstrated a 60% reduction in a controlled trial (Heneghan et al. 2006). Despite these benefits, concerns about side effects, such as heart failure associated with rosiglitazone, highlight the need for careful consideration of drug use in prevention strategies(Heneghan et al. 2006).

Anthropo-therapeutic Healing:

This holistic approach, integrating allopathic, ayurvedic, and homeopathic treatments, showed better overall wellness in diabetic patients than single-line treatments. (Singh,2024)

Innovative Strategies Research suggests that vaccines, such as a combination of insulin fragments and traditional vaccines, may offer a preventive approach for at-risk populations(Elliott 1995). Community-based prevention programs are essential to effectively test and implement primary prevention measures (Tuomilehto & Wolf 1987). While significant progress has been made in diabetes prevention, the complexity of the disease necessity ates ongoing research and the development of pragmatic, scalable interventions

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