A review on Diabetes Mellitus

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***Abstract*—Diabetes Mellitus (DM) is a metabolic disorder marked by chronic hyperglycemia, affecting an estimated 366 million people in 2011, with projections of nearly 552 million by 2030, and diagnosis can be approached via either fasting plasma glucose or oral glucose tolerance tests, making consistent follow-up with healthcare providers crucial to prevent long-term complications. The various classes of diabetes mellitus, including type 1, type 2, and gestational diabetes, are examined regarding their diagnostic criteria, causes, and genetic factors, alongside a review of recent extensive research into the molecular genetics and mutations affecting glucose metabolism and pancreatic cell functions. Despite the wealth of molecular and cellular data, the processes behind diabetes development and complications remain unclear, highlighting the necessity for further research to enhance diagnostics, treatments, and reduce chronic complications. Diabetes mellitus, commonly referred to as diabetes, is a group of metabolic disorders characterized by prolonged high blood sugar levels, leading to symptoms like frequent urination, increased thirst, and hunger, and if untreated, it can lead to serious complications, including diabetic ketoacidosis and nonketotic hyperosmolar coma, with three main types identified. Type 1 diabetes, formerly known as insulin-dependent diabetes or juvenile diabetes, arises from insufficient insulin production, while Type 2 diabetes, once referred to as non-insulin-dependent or adult-onset diabetes, begins with insulin resistance and may also involve reduced insulin production as it advances.**

***Keywords*— Diabetes mellitus, diagnosis, cause and treatment.**

I. INTRODUCTION

Diabetes mellitus is a metabolic disorder that affects the body's ability to regulate blood sugar levels due to issues with its endocrine response.[1] The pancreas regulates blood sugar by moving glucose into cells for storage or energy, but with diabetes, insufficient insulin production or usage can lead to nerve, eye, kidney, and organ damage due to untreated high blood sugar.[2] A malady may occur when the pancreas fails to produce insulin or the body becomes resistant to its effects, hindering glucose from entering cells for energy.[3] If your body produces little to no insulin or is resistant to it, excess sugar stays in your bloodstream, resulting in higher than normal glucose levels for those with diabetes.[4] The duct gland produces hormones, but their effectiveness is diminished in a condition called endocrine resistance; to better understand diabetes, it's essential to know how the body metabolizes food into simple sugars like glucose, which provides the energy needed for daily activities.[5] Diabetes Mellitus (DM) is an ancient metabolic disorder marked by chronic high blood sugar and disrupted metabolism of carbohydrates, fats, and proteins, with references dating back to around 3000 years ago in Egyptian texts.[6] Diabetes mellitus (DM) has diverse origins and causes, always involving defects in insulin secretion or response, with the most common form being type 2 diabetes, characterized by hyperglycemia, insulin resistance, and relative insulin deficiency.[7] Diabetes mellitus encompasses a range of metabolic disorders marked by persistent high blood sugar levels due to issues with insulin secretion or action, leading to imbalances in carbohydrates, lipids, and proteins because of insulin's crucial role as an anabolic hormone. Insufficient insulin levels and/or insulin resistance in key tissues, primarily skeletal muscles and adipose tissue, along with some impact on the liver, contribute to these metabolic issues. The severity of diabetes symptoms varies based on the type and duration of the condition, with some patients remaining asymptomatic, particularly in the early stages of type 2 diabetes, while others, especially children with severe insulin deficiency, may experience serious symptoms like excessive thirst, frequent urination, significant weight loss, and blurred vision, with uncontrolled cases risking stupor, coma, or death from ketoacidosis or rare nonketotic hyperosmolar syndrome if untreated.[8.9.10] The female hormone 17-β estradiol, through its receptor ER-α, is crucial for maintaining pancreatic β cell function, as evidenced by the destruction of these cells in ER-α knockout mice subjected to oxidative stress, while ER-α activity also protects islets from glucolipotoxicity and helps prevent β-cell dysfunction.[11] Diabetes

mellitus (DM) is the most prevalent endocrine disorder, affecting over 100 million individuals globally (6% of the population), resulting from insufficient or ineffective insulin production by the pancreas, which leads to abnormal blood glucose levels and can cause damage to various body systems, including blood vessels, eyes, kidneys, heart, and nerves.[12] Medications primarily aim to save lives and alleviate symptoms, while also preventing long-term complications and promoting longevity; insulin replacement therapy is essential for type 1 diabetes, whereas dietary and lifestyle changes are fundamental for managing type 2 diabetes[13]

II. EPIDEMIOLOGY

It is estimated that 366 million people had DM in 2011; by 2030 this would have risen to 552 million. The number of cases of type 2 DM increases in all the countries around with 80 percent of persons diagnosed with DM found in Low- and middle-income countries. It accounted for 4.6 million deaths in 2011[14] By 2030, it is estimated that 439 million people will have type 2 Diabetes. Because of lifestyle and environmental risk factors, type 2 Diabetes has a substantial variation across geographical regions[15] It seems like you're sharing some information about the projected increase in the prevalence of type 2 diabetes (DM), particularly in adults aged 45 to 64 years, with a focus on developing countries. This is indeed a significant concern, as type 2 diabetes is linked to factors like obesity, sedentary lifestyles, and poor dietary habits, all of which are becoming more common in developing regions.[16]

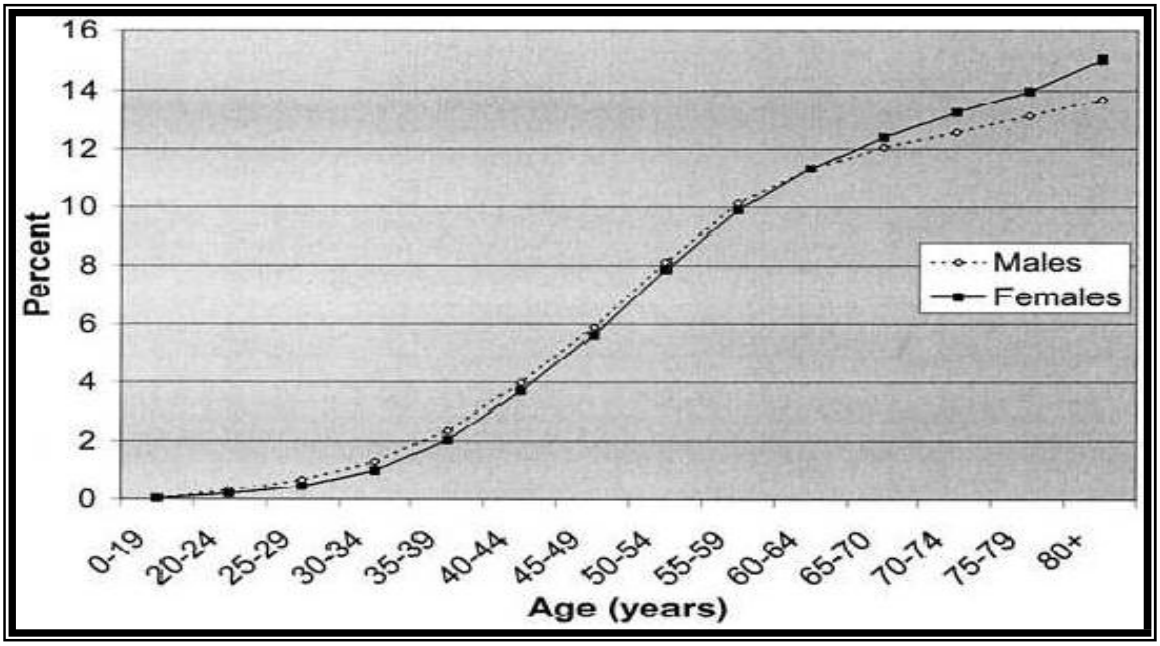

Fig. 1: Epidemiology of diabetes: A global view

Diabetes in India: These statistics highlight a very concerning global trend in the rise of diabetes, especially in India, which is projected to continue experiencing a sharp increase in cases. The “diabetes capital of the world” title reflects the challenges India faces due to a combination of genetic, lifestyle, and environmental factors. The "Asian Indian Phenotype" that you mentioned is particularly interesting—it points to specific biological markers in the Indian population that make them more prone to developing type 2 diabetes, such as increased insulin resistance and abdominal adiposity despite lower body mass index (BMI).This unique combination of factors makes early diagnosis, prevention, and intervention critical in managing the spread of diabetes in the region. Additionally, changing dietary habits (such as increased consumption of processed foods and sugars) and reduced physical activity due to urbanization are accelerating the trend.The rise in diabetes also poses serious health and economic risks for developing countries. If the estimated increase in cases continues, it will likely strain healthcare systems, particularly as more people experience diabetes-related complications such as cardiovascular disease, kidney issues, and vision problems.[17]

III. CLASSIFICATION SYSTEMS FOR DIABETES

3.1Purpose of a classification system for diabetes: Hyperglycaemia is the defining common feature of all types of diabetes, but aetiology, underlyingpathogenic mechanisms, natural history, and treatment of the various forms of diabetes are different. Ideally,All types of diabetes will be defined on the basis of specific and exclusive defining features that are characteristic of that type.of diabetes.[18] However, some forms of diabetes are too indefinite to classify.

Classification systems can broadly be used for three primary aims:

»» Guide clinical care decisions

»» Stimulate research into aetio-pathology

»» Provide a basis for epidemiological studies

Any classification system should be able to help with all three of these key activities, but at present there are so many gaps in understanding the causes of diabetes that the current classification cannot fulfil this triple role.

3.1.1 Clinical care decisions: Subtyping diabetes is essential in clinical care for diagnosis, to guide treatment choices, and whendecision to treat a patient whose glycaemic control is unsatisfactory. IncorrectSuch a treatment decision may risk a person developing diabetic ketoacidosis or lead to unnecessaryInsulin therapy in the case of some forms of monogenic diabetes. Both T1DM phenotypesOverweight or obese and T2DM (younger, normal weight) have evolved over time and contributesto clinicians' increasing difficulty classifying types of diabetes.

3.1.2 Aetio-pathology; The aetiology and pathogenesis of diabetes can be described simply enough as defects with insulin sensitivity and insulin secretion but the underlying specific defects are quite complex and little understood. As some specific defects have been determined (such as genetic abnormalities which lead to the problems with secretory activity), defining mechanisms responsible for common types of diabetes are challenging as more and more often they have turned out to represent a very intricate interplay between genetic, epigenetic,proteomic and metabolomic processes. The identification of these abnormalities will better our understanding ofthe mechanisms underlying diabetes and its treatment, although currently, our knowledge on these complexabnormalities is only superficial, which in turn limits the appropriate and clinically useful classification systemfor diabetes.[19]

3.1.3 Epidemiological studies: Most epidemiological studies report overall prevalence of diabetes without distinguishing betweensubtypes, despite the value of subtyping for such studies. Subtyping T1DM and T2DM in populationThis, too, is feasible using frequently available clinical information . Some studies have reportedOther forms of diabetes: Population prevalence, for example, of monogenic diabetes and diabetesDue to pancreatic disease, (19) Type of diabetes is classified specially for incidence.studies and studies on diabetes-related complications.

3.2 Previous WHO classifications of diabetes: Diabetes has been understood for thousands of years. It was first identified by the physician Aretaeus in the 5th century as the disease "a siphon" meaning to describe the situation of "melt down flesh and limbs to urine". Madhu meha, meaning the sweet, honey-like taste, described by 5th BC Indian physicians. In polyuric patients with this condition that attracted ants, among other insects.but the word "mellitus" (Latin for "honey") was added in the 17th century. As early as the 5th centuryAD descriptions of diabetes mentioned two forms, one in older, fatter people and the other in thinnerpeople with short survival [20] WHO published the first classification for diabetes in the year 1965, in four age categories of diagnosis :Infantile or childhood (with age of onset between 0–14); young (with age of onset between the agesof 15–24 years); adult, with onset at ages 25–64 years; and the elderly, where the onset falls at theage of 65 years or older). In addition to classifying diabetes by age, WHO recognized other forms ofdiabetes: juvenile-type; brittle; insulin-resistant; gestational; pancreatic; endocrine and iatrogenic [21]

3.3 Recent calls to update the WHO classification of diabetes*:* There have been recent calls to review and updatetheclassification system for diabetes. This isbecause many people with diabetes do not fit into any single category; there have been recent advancesin knowledge of pathophysiological pathways and emerging technologies to examine pathology andtreatments that act on specific pathways; and there is a trend towards individualized treatment.There is well-established acceptance of the

overlap of diabetes subtypes, especially in relation toT1DM, T2DM and so-called latent autoimmune diabetes of adults (LADA) (3). Laboratory tests couldin some instances improve disease classification and potentially improve the efficacy of treatmentfor diabetes, but many of these tests are beyond the reach or affordability of most clinical settingsthroughout the world.A recent proposal suggested a classification system centred on the β-cell (10). Proponents for thisnote that all forms of diabetes have abnormal pancreatic β–cell function and that individually or in concert, 11 distinct pathways contribute to β–cell stress, dysfunction, or loss. In this way treatments could be targeted to specific mediating pathways of hyperglycaemia in a given patient. This proposal expands on an earlier model which described eight core defects of diabetes[22]

4.4 Types of diabetes:

4.4.1. Hormone Dependent diabetes (Type1 IDDM)
4.4.2. Non-Insulin Dependent polygenic disorder Mellitus(Type2 Niddm)

4.4.1. Hormone Dependent diabetes (Type1 IDDM)
This type of diabetes, also known as reaction diabetes and previously called juvenile-onset or ketosis-prone, may occur alongside other autoimmune disorders such as Graves' disease, Hashimoto's thyroiditis, and Addison's disease.[23] Type 1 diabetes is often marked by the presence of antibodies to anti-glutamic acid decarboxylase, island cells, or hormones, which trigger processes leading to beta-cell destruction.[24] Markers of immune destruction and various auto-antibodies are found in 85-90% of individuals with type 1 diabetes when fasting diabetic hyperglycemia is first identified.[25] Type 1 diabetes, commonly known as insulin-dependent diabetes (IDDM), primarily affects youth and young adults, with a sudden onset that can be life-threatening. The precise cause of diabetes remains unclear, but there is substantial evidence suggesting an autoimmune response that attacks the beta cells.[26] Research on the interplay between stress, autonomic arousal, and diabetes-related glucose control reveals that in studies by Lee et al. only about half of the rats with chemically induced diabetes reacted similarly to stress, showing significantly different levels of plasma EPI following footshock compared to nonreactive and control groups. The three groups exhibited similar NE responses to stress, with both reactive and nonreactive animals showing high baseline blood glucose levels compared to controls, and all groups demonstrating increased glucose levels under stress, indicating that reactive animals likely have heightened EPI secretion from the adrenal medulla rather than slower EPI removal from the bloodstream.[27]

4.4.2. Non-Insulin Dependent polygenic disorder Mellitus(Type2 Niddm)
Type 2 diabetes is also known as ketosis-resistant diabetes mellitus and is characterized by a progressive defect in insulin secretion alongside insulin resistance.[28] The contributing factors include obesity, a sedentary lifestyle, aging (particularly affecting middle-aged and older individuals), and genetic predispositions, which increase the risk of severe macrovascular and microvascular complications in these patients (Ross and Wilson 2010). Complications affecting blood vessels, kidneys, eyes, and nerves are prevalent in all types and are primary contributors to illness and mortality from diabetes.[29.30] While type 1 diabetes is now understood to result from autoimmune destruction of pancreatic p-cells, the underlying mechanisms of type 2 diabetes remain unclear, with traditional theories proposing a primary defect in p-cell responsiveness to glucose or severe insulin resistance leading to p-cell exhaustion.[31] The desert-dwelling rodent that the sand rat is,lives in the North African part of its natural habitat,exclusively feeds on low calorie, succulent plants.Maintaining sand rats on a diet low incalories, carbohydrates, leads to no signs of diabetes,whereas providing these rodents with lab chowand feeding them ad libitum till obese resultsin an increased percentage of these animalsexpressing an analogue of type II diabetes[32] This study suggests that stress factors, such as the physical stress of intubation, can lead to glucose intolerance, even in animals that are genetically predisposed to diabetes (like sand rats). The researchers were investigating how diet, stress, and obesity could affect hyperglycemia, and they specifically looked at glucose tolerance in sand rats and Sprague-Dawley rats.Interestingly, the sand rats maintained on a low-calorie, low-carb diet remained euglycemic (normal blood glucose levels), but when they were stressed by intubation, they exhibited abnormal glucose tolerance, similar to that seen in diabetes. In contrast, Sprague-Dawley rats didn’t show the same response to intubation.The key takeaway is that the stress induced by intubation can

precipitate glucose intolerance in certain animals, even in those that are not obese or typically at risk for diabetes, highlighting how stress can be a significant factor in the development of metabolic disorders.[33]

5.Etiology of DM: The study of the causes or origins of diseases. In the context of diabetes, understanding its etiology involves looking at several possible factors—genetic, autoimmune, viral, and metabolic—that might contribute to the development of the condition.[[34]

1. Juvenile-onset (insulin-dependent) type 1 diabetes is believed to have an autoimmune origin. In this case, the body's immune system mistakenly attacks and destroys the insulin-producing beta cells in the pancreas, leading to a lack of insulin production.
2. Viruses may play a role in the etiology of diabetes, particularly type 1. Certain viruses, such as Coxsackievirus B, have been shown to potentially trigger an autoimmune response that affects the pancreas. Epidemic parotitis (mumps) and German measles (rubella) viruses have also been implicated in causing structural damage to pancreatic islet cells.
3. The genetic role in the etiology of diabetes is still a topic of debate. There is evidence that genetic predisposition plays a part, but it is not fully understood. Certain genes may make an individual’s pancreas more vulnerable to viral infections that could eventually lead to the onset of diabetes.
4. The cause of diabetes could also involve disturbances in the glucose receptor on beta cells in the pancreas. This leads to poor insulin secretion in response to high blood sugar levels or a relative deficiency in beta cells, both of which impair insulin production and can progress to beta-cell failure.
5. From a vascular perspective, diabetes can lead to small vessel disease, which affects the nerves and can contribute to complications. Hyperglycemia, or high blood sugar, can directly impact vegetative cell metabolism and the functioning of nerves, contributing to the progression of diabetic complications.

6.Some Common Sign and Symptoms:

In Diabetes Mellitus (DM), the inability of cells to metabolize glucose (aldohexose) properly leads to a state where the cells are essentially "starved," even though there may be an abundance of glucose in the bloodstream. This metabolic dysfunction occurs because the body either doesn't produce enough insulin (in the case of Type 1 diabetes) or the cells become resistant to the insulin produced (in Type 2 diabetes). As a result, glucose cannot efficiently enter cells to be used for energy, leading to a variety of complications over time.The long-term effects of diabetes are wide-ranging and often involve complications due to high blood sugar levels (hyperglycemia) causing damage to various tissues and organs. Some of the most significant complications include:[35.36]

1. Retinopathy: The damage to the blood vessels in the retina can lead to progressive vision problems and even blindness if not managed. Diabetic retinopathy is one of the leading causes of vision impairment among individuals with diabetes.
2. Renal Disease: The kidneys are also vulnerable to damage in diabetes, especially through a condition called diabetic nephropathy. This can lead to kidney failure if not treated or controlled. Diabetic nephropathy can progress to the point where dialysis or a kidney transplant may be necessary.
3. Neuropathy: Diabetic neuropathy refers to nerve damage caused by prolonged high blood sugar levels. It often affects the feet and hands, leading to pain, numbness, and tingling. In severe cases, it can cause foot ulcers and the loss of sensation, which increases the risk of infections and complications requiring amputation.
4. Joint and Musculoskeletal Issues: People with diabetes are also at higher risk for joint problems, such as stiffness, pain, and conditions like frozen shoulder or charcot joint disease. This is due to the effects of prolonged hyperglycemia on tissues and blood vessels.
5. Autonomic Dysfunction: Diabetes can affect the autonomic nervous system, which controls involuntary functions like heart rate, digestion, and blood pressure. This can result in conditions like gastroparesis (delayed stomach emptying), heart arrhythmias, and other serious problems.
6. Sexual Dysfunction: Diabetes can also lead to sexual dysfunction, including erectile dysfunction in men and reduced sexual desire in women, as a result of nerve damage and blood vessel problems.

7.Diagnosis of DM:

If a diagnosis of Diabetes Mellitus is being considered, it is crucial for the practitioner to ensure

that the diagnosis is well-established. A single abnormal blood sugar reading is not sufficient, as diabetes can present with fluctuating blood glucose levels. The consequences of an incorrect or missed diagnosis can be severe and involve ongoing health problems, including complications like those mentioned earlier (retinopathy, neuropathy, nephropathy, etc.).Some of the diagnostic tests and methods used to confirm Diabetes Mellitus include:[37]

1. Excretory Product Sugar: This test measures the amount of glucose present in urine. Normally, glucose is not present in the urine unless the blood glucose level exceeds the kidney's threshold for glucose reabsorption.
2. Blood Glucose Tests: Measuring blood glucose levels at specific times (e.g., fasting, postprandial, etc.) is essential in diagnosing diabetes. Fasting blood glucose and random blood glucose tests are commonly used.
3. Glucose Tolerance Test (GTT): The oral glucose tolerance test (OGTT) is a standard test used to diagnose diabetes or prediabetes. It involves measuring blood sugar levels after fasting and then at intervals after ingesting a sugary drink.
4. Urinary Organ Threshold of Glucose: The kidneys have a specific threshold beyond which they cannot reabsorb glucose. When blood glucose levels exceed this threshold, glucose will spill into the urine, which can be used as a diagnostic indicator.
5. Diminished Glucose Tolerance: This refers to a condition where an individual's blood glucose levels are higher than normal after a glucose challenge, but not high enough to be classified as diabetes. This can be an early indicator of potential diabetes and may be referred to as prediabetes.
6. Exaggerated Glucose Tolerance: In some cases, the body may take longer to process glucose or have abnormal glucose clearance. This could also point to diabetes or an increased risk for developing it.
7. Renal Symptoms: Kidney dysfunction (diabetic nephropathy) can be detected through tests that measure how well the kidneys are filtering waste products, and this can be a sign of diabetes or kidney complications caused by it.
8. Cortisone-Stressed Glucose Tolerance Test: This test involves administering a stress hormone (cortisone) to see how the body's glucose tolerance responds to stress. It can be used to assess the body's ability to handle glucose under conditions of stress, which can reveal prediabetes or diabetes.
9. Endovenous Glucose Tolerance Test: This method involves injecting glucose directly into the bloodstream to evaluate how well the body handles the sugar. It's more invasive and typically used in specialized clinical settings

8.Treatment of DM:

The treatment of Diabetes Mellitus (DM) focuses on addressing the underlying causes of the disease while managing blood sugar levels to restore normal metabolic function. Effective treatment helps to achieve control over blood glucose levels, and for some forms of diabetes, such as Type 2 Diabetes (T2DM), it may involve targeting the root causes of insulin resistance, inflammation, and metabolic dysfunction.

A.The main goals of managing Diabetes Mellitus (DM) include:

1. Restoring Normal Metabolism: The primary aim is to bring the diabetic patient's metabolism as close to normal as possible, balancing comfort and safety. This often involves a combination of lifestyle changes (such as diet and exercise) and medications to regulate blood sugar levels effectively.
2. Preventing or Delaying Complications: Both short-term (e.g., hyperglycemia, hypoglycemia) and long-term complications (e.g., diabetic retinopathy, neuropathy, nephropathy) should be prevented or delayed. This involves managing blood glucose levels carefully, regular monitoring, and addressing other risk factors like blood pressure and cholesterol.
3. Empowering the Patient: It's essential to provide the patient with the knowledge, motivation, and resources they need to manage their diabetes effectively. This includes educating them on healthy eating, exercise, blood sugar monitoring, and how to deal with potential complications.

B.Types of Therapy Involved in Diabetes Management:

1. Cellular Therapy:
   - In Type 2 Diabetes (T2DM), researchers have identified that monocytes/macrophages (types of white

blood cells involved in inflammation) may play a major role in contributing to chronic inflammation and insulin resistance. This inflammation can impair the body's ability to use insulin properly, making it harder for cells to take in glucose.
   - Understanding the role of immune cells like monocytes/macrophages has led to the exploration of therapies that target these inflammatory pathways, aiming to reduce insulin resistance and help the body use glucose more effectively.

2. Medication:
   - The use of hypoglycemic agents (medications that lower blood sugar) is common in the treatment of diabetes. These may include oral medications (such as metformin or sulfonylureas) or insulin injections for those with Type 1 Diabetes or more severe cases of Type 2 Diabetes.
   - For Type 1 Diabetes, insulin therapy is essential as the body no longer produces insulin. In Type 2 Diabetes, medications can help improve insulin sensitivity, reduce glucose production by the liver, or stimulate the pancreas to produce more insulin.
3. Lifestyle Changes:
   - Dietary modifications and physical activity play a key role in managing diabetes. A balanced diet, regular exercise, and maintaining a healthy weight can improve insulin sensitivity and help regulate blood glucose levels.
   - Weight management is particularly important in Type 2 diabetes, as obesity is a major contributing factor to insulin resistance.
4. Advanced Therapies:
   - For patients with severe complications or poorly controlled diabetes, more advanced therapies might be required, including insulin pumps, continuous glucose monitors (CGMs), and in some cases, pancreatic transplants or islet cell transplants.

CONCLUSION

Diabetes mellitus encompasses various metabolic disorders characterized by high blood sugar levels, with type 1 arising from the loss of insulin production due to autoimmune destruction of pancreatic beta cells, while type 2 is linked to autoimmune attacks and/or insulin resistance, potentially coupled with normal or excessive insulin production. The primary aim of diabetes management is to normalize carbohydrate metabolism, achieved through insulin replacement for those with an insulin deficiency and lifestyle changes for those with insulin resistance, while also preventing complications to allow individuals to manage their diabetes and enjoy life fully. Diabetes mellitus is a pressing global health crisis that necessitates early and effective diagnostic methods, as this comprehensive review examines the various types of diabetes, their diagnostic criteria, and highlights the importance of identifying genetic factors for enhanced personalized treatment. For over 300 years, it has been observed that significant life stress often precedes the onset of diabetes, and while this connection may be attributed to the rarity of both events, there is some evidence indicating that stress can trigger the disease or worsen glycemic control, leading to further complications. A century ago, William Osier recognized the potential impact of stress on type II diabetes, prompting recommendations for stress-reducing treatments, and recent animal studies indicate that stress negatively influences glycemic control in this condition, with evidence suggesting that individuals with type II diabetes may have heightened sensitivity to stress due to altered adrenergic responses. Stress's influence on type II diabetes, initially highlighted by William Osler over a century ago, has been reinforced by recent animal studies showing that it negatively impacts glycemic control and suggests that individuals with this condition may have heightened sensitivity to stress.

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