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A BRIEF REVIEW ON DIABETIC & ITS COMPLICATIONS

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ABSTRACT

Diabetes is a condition that affects how your body processes sugar, also known as glucose. It happens when your body can't make enough insulin, the hormone that helps move glucose from your blood into your cells, or when your cells don't respond properly to insulin. There are a couple of types: Type 1 diabetes is an autoimmune disease where the body mistakenly attacks the insulin-producing cells in the pancreas. Type 2 diabetes, which is more common, occurs when the body becomes resistant to insulin or doesn't produce enough of it. This type is often linked to lifestyle factors like diet, exercise, and weight. Gestational diabetes happens during pregnancy and usually goes away after the baby is born, but it increases the risk of developing Type 2 diabetes later on. Diabetes is becoming more common worldwide due to factors like unhealthy eating habits, lack of exercise, and rising obesity rates. If left uncontrolled, it can lead to serious health problems such as heart disease, kidney damage, nerve issues, and even blindness. However, with early diagnosis and good management—such as making healthier lifestyle choices, using medication, or taking insulin—people with diabetes can lead long, healthy lives. Research is also continually advancing to better understand diabetes and improve treatment options.

KEYWORD: Diabetes, Glutamic Acid Decarboxylases, Major Histocompatibility Complex, Glucagon Like Peptide, American Diabetes Association, Hyperglycemia Hyperosmolar State.

1. INTRODUCTION

Diabetes mellitus is a metabolic condition where the body's ability to use glucose, fat, and protein is disrupted due to issues with insulin secretion and/or insulin resistance, resulting in persistent hyperglycemia. Thus, comprehending the fundamental pathophysiology and the immediate and/or chronic complications of diabetes will facilitate the creation of approaches for improving the condition. People can be categorized as having pre-diabetes or diabetes depending on their fasting blood glucose and/or post-meal blood glucose. In this context, people with impaired fasting glycaemia (IFG) exhibit fasting plasma glucose levels greater than 6.1 mmol/L.[1] A hormone essential for transforming sugar, starches, and other foods into energy. A lack of insulin or decreased levels of it results in consistently elevated blood sugar and impaired glucose tolerance. It is likely one of the earliest diseases recognized by humanity. It is also known as the black death from the 14th century. The metabolic disorders linked to diabetes primarily impact tissues like adipose tissue, skeletal muscles, and the liver because of insulin resistance. The intensity of symptoms may differ based on the type and length of diabetes. People with elevated blood sugar levels, especially those with no insulin production like children, might show signs including heightened appetite, excessive thirst, urinary issues, weight reduction, increased hunger, and vision difficulties. Certain individuals with diabetes might not show any symptoms, particularly those with type 2 diabetes in the initial phases.[3]

In 2014, the WHO reported that 8.5% of adults who are 18 years old and older had diabetes. In 2019, diabetes caused 1.5 million fatalities, with 48% of these happening before the age of 70. Moreover, diabetes caused an additional 460,000 fatalities from kidney disease, and approximately 20% of deaths related to cardiovascular issues were linked to high blood glucose levels. Between 2000 and 2019, there was a 3% increase in standardized mortality rates associated with diabetes. In lower-middle-income nations, the death rate linked to diabetes rose by 13%. Conversely, the chances of falling victim to any of the four main non-communicable diseases (which comprise cardiovascular diseases, cancer, chronic respiratory diseases, or diabetes) between the ages of 30 and 70 decreased by 22% globally from 2000 to 2019.[4] These modifications result in the formation of clearly defined clinical entities, known as 'complications of diabetes.' The consequences of diabetes mellitus encompass prolonged damage, dysfunction, and failure of several organs, particularly the eyes, kidneys, heart, and blood vessels[5], as well as leading to blindness, strokes, and amputations.[6] Diabetes can manifest with typical symptoms including excessive thirst, frequent urination, blurred vision,

weight loss, and increased hunger, and its most severe forms may involve ketoacidosis or non-ketotic hyperosmolarity, which, if not treated effectively, can result in stupor, coma, and death. Symptoms are frequently mild or may even be nonexistent. Hyperglycemia, which can lead to pathological functional changes, is often present for an extended period before a diagnosis is reached.[7]

2. DIABETES

Diabetes is a long-term metabolic disorder marked by high blood glucose levels, which can result over time in significant harm to the heart, blood vessels, eyes, kidneys, and nerves. The most prevalent is type 2 diabetes, typically found in adults, which arises when the body becomes resistant to insulin or produces insufficient insulin. Over the last 30 years, the occurrence of type 2 diabetes has increased significantly in nations across all income brackets. Type 1 diabetes, previously referred to as juvenile diabetes or insulin-dependent diabetes, is a long-term condition where the pancreas generates minimal to no insulin independently. For individuals with diabetes, obtaining affordable treatment, such as insulin, is essential for their survival. A worldwide consensus aims to stop the increase in diabetes and obesity by 2025.[8]

❖ Types of Diabetes

Diabetes Mellitus is classified into four main types

A. Type 1 diabetes mellitus
B. Type 2 diabetes mellitus
C. Gestational diabetes mellitus (gdm)
D. Other specific types

A. Type 1 Diabetes Mellitus (T1 Diabetes Mellitus)

An autoimmune condition where the body's immune system mistakenly attacks and destroys the insulin producing beta cells in the pancreas, leading to insulin deficiency. This form of diabetes is most diagnosed in children, adolescents, and young adults, although it can occur at any age. Individuals with T1DM require lifelong insulin therapy to manage their condition.[9]

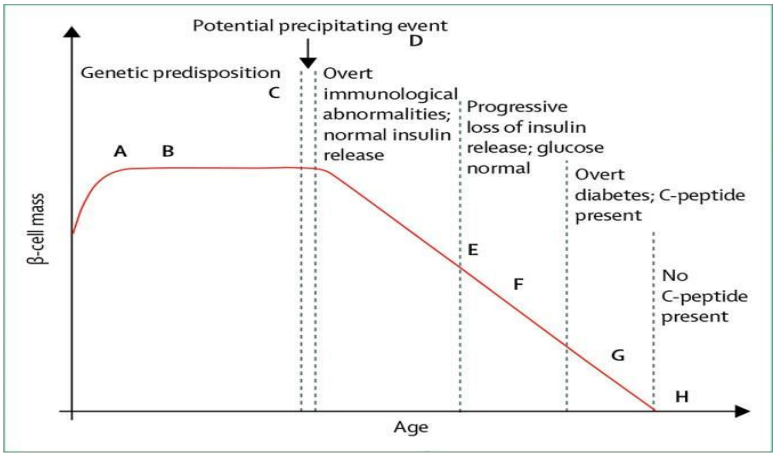

Figure 1: Challenges to the Eisen barth model of the natural history of type 1 diabetes.[10]

Key events of the Eisen barth model over the course of the disease (measured in years) are shown by dotted lines at different time points. Challenges to this model, taking into account the increasing complexity of type 1 diabetes, include the following: precipitating immune events that might occur prenatally (A); large variation in starting β-cell mass and function, defects in one or both could be developmentally programmed (B); initiation of autoimmunity is measured by autoantibodies, but other immunological abnormalities probably precede the presence of detectable pancreatic antibodies (C); the patient's environment could affect their entire disease course (D); β-cell loss could relapse or remit (E); dysglycaemia occurs before clinical diagnosis (F); decline in β-cell function might not mirror decline in β-cell mass—methods to measure β-cell mass have not been established (G); and residual C-peptide is detectable in many people who have long duration type 1 diabetes (H). Furthermore, progression through stages A–C is heterogeneous, and will be affected by immune, genetic, environment, and key demographic features (ie, age, body-mass index). Adapted from Atkinson et all.[10]

- **Pathophysiology of type 1 Diabetes Mellitus**

T1 Diabetes Mellitus is a complicated disorder that results from both genetic risk (Figure 2) and environmental triggers that alter immune pathways. T1DM arises from the cell-mediated autoimmune destruction of insulin producing pancreatic b-cells by CD4+ and CD8+ T-cells and macrophages. There are four different markers for this pancreatic b-cell destruction namely; 1) islet cell autoantibodies, 2) autoantibodies to insulin, 3) autoantibodies to glutamic acid decarboxylase (GAD65), and 4) autoantibodies to the tyrosine phosphatases IA-2 and IA-2b.[11, 12]

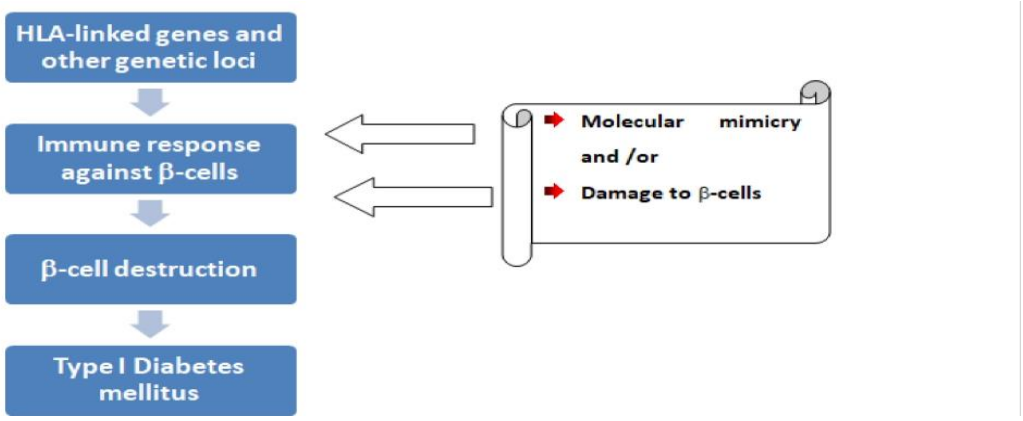

Figure 2: A diagrammatic representation of the pathogenesis of T1DM.[11,12]

1. Presence of immuno-competent and accessory cells in infiltrated pancreatic islets;
2. Association of susceptibility to disease with the class II (immune response) genes of the major histocompatibility complex (MHC; human leucocyte antigens HLA);
3. Presence of islet cell specific autoantibodies;
4. Alterations of T cell mediated immune regulation, in particular in CD4+ T cell compartment;
5. The involvement of monokines and TH1 cells producing interleukins in the disease process;
6. Response to immunotherapy and;
7. Frequent occurrence of other organ specific auto- immune diseases in affected individuals or in their family members.[13]

B. Type 2 Diabetes Mellitus (T2 Diabetes Mellitus)

The most prevalent form of diabetes, accounting for approximately 90% of all diabetes cases. T2 Diabetes Mellitus is characterized by insulin resistance, where the body's cells do not respond effectively to insulin. Over time, the pancreas may also lose its ability to produce sufficient insulin to meet the body's needs. T2DM is typically associated with aging, obesity, physical inactivity, and unhealthy lifestyle factors, such as poor dietary habits.[9] Epidemiology of T2DM is affected both by genetics and the environment.[14] People of different ethnic origins may have different specific phenotypes that increase predisposition to clusters of CVD risk factors, including hypertension, insulin resistance, and dyslipidemia.[15]

- **Pathophysiology of type 2 Diabetes Mellitus**
- In type 2 diabetes, these processes fail, leading to two primary pathological issues: reduced insulin secretion due to pancreatic β-cell dysfunction and diminished insulin

action as a result of insulin resistance.[16] In cases where insulin resistance is prevalent, the β-cell mass experiences a shift that enhances insulin production, thereby compensating for the abnormal and heightened demand. In absolute terms, the plasma insulin levels (both during fasting and after meals) are typically elevated, although "relative" to the degree of insulin resistance, these plasma insulin levels are inadequate to sustain normal glucose homeostasis. Considering the close relationship between insulin secretion and hormone action sensitivity in the complex regulation of glucose homeostasis, it is nearly impossible to distinguish the role of each in the etiology of DM2.[17]

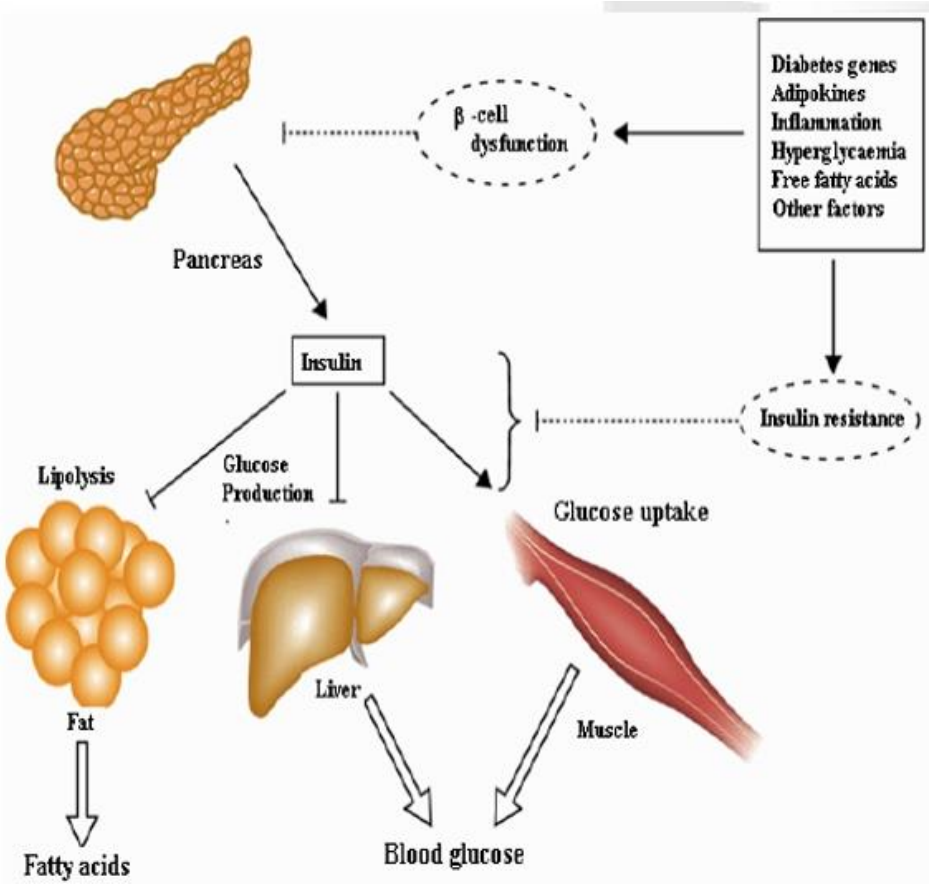

Figure 3: Pathophysiology of Hyperglycemia and increased circulating fatty acids in type 2 Diabetes.[18]

C. Gestational diabetes mellitus (gdm)

A type of diabetes that occurs during pregnancy and usually disappears following delivery. Women who have experienced gestational diabetes mellitus (GDM) are at a higher risk of developing type 2 diabetes in the future. Gdm is linked to a higher likelihood of complications for both the mother and the fetus in development.[9,19] The international

diabetes federation recently projected that worldwide, 1 in 6 live births was diagnosed with gdm.[20] In the United States, around 7% of pregnancies faced complications due to diabetes of any kind, with 86% of those cases involving pregnancies complicated by gestational diabetes mellitus (GDM).[21,22]

D. Other specific types

These consist of genetic abnormalities affecting beta-cell performance, genetic irregularities in insulin response, disorders of the exocrine pancreas (such as cystic fibrosis), and diabetes caused by drugs or chemicals (for instance, steroid-induced diabetes mellitus). These rare types of diabetes can exhibit different levels of severity and need distinct treatment approaches.[19, 23] Maturity onset diabetes of the young (MODY) is marked by reduced insulin secretion and little to no insulin resistance.[24] The evolution of MODY largely hinges on the specific genetic defect, and it usually shows mild hyperglycemia from a young age.[25]

3. PATHOPHYSIOLOGY

I. Role of pancreas in diabetes

- The pancreas produces insulin. The cells that create insulin are known as beta cells. These cells are located in a group of cells within the pancreas known as the Islets of Langerhans, named for the anatomist who found them.
- Insulin is a hormone that aids in controlling blood sugar levels by facilitating the movement of glucose from the bloodstream into adjacent cells.
- **The pancreas and type 1 diabetes**
- In type 1 diabetes, the immune system of the body assaults the beta cells that create insulin.
- When additional beta cells are destroyed, the pancreas finds it challenging to generate sufficient insulin to maintain low blood sugar levels, leading to the onset of diabetes symptoms.
- Studies indicate that although numerous beta cells perish, the body can still generate minimal amounts of insulin even after many years have elapsed.[26] These studies identified the key characteristic of the disease as a major reduction in islet beta cells, with 50–90% of islets devoid of beta cells (varying with disease duration) while other islet endocrine cells remain at normal levels. The loss of islet beta cells has been seen in organ donors who are non-diabetic and positive for islet autoantibodies.[27]

- **The pancreas and type 2 diabetes**
- In type 2 diabetes, the body develops resistance to insulin, requiring increased insulin to lower blood glucose levels. Consequently, the pancreas must generate more insulin than it typically requires.
- When the pancreas is unable to generate sufficient insulin to lower sugar levels, the signs of diabetes will start to manifest. Type 2 diabetes develops slowly, and it may take years for symptoms to manifest. The progression of type 2 diabetes can result in the loss of insulin-producing beta cells in the pancreas, potentially necessitating insulin administration. Beta cells that secrete insulin are notable for their capability to adjust to metabolic needs. Trained athletes produce up to three times less insulin for achieving euglycaemia compared to untrained individuals; on the other hand, non-diabetic obese individuals may secrete five times more insulin than control participants when faced with a glucose challenge.[28]

II. Insulin Resistance

In the transition from normal to abnormal glucose tolerance, post-meal blood glucose levels rise initially. Ultimately, fasting hyperglycemia arises when the inhibition of hepatic gluconeogenesis is unsuccessful. While insulin resistance is induced (as seen with a high-calorie diet, steroid use, or lack of exercise), elevated glucagon levels and increased glucose-dependent insulinotropic polypeptide (GIP) levels occur alongside glucose intolerance. Nonetheless, the postprandial glucagon-like peptide-1 (GLP-1) response remains unchanged.[29] Genetics is one of the primary risk factors for T2DM patients with inherited genes from parents that render their tissues insulin-resistant.[30] Additionally, stress response pathways within cells are activated, and inter-organ communication networks facilitated by specific peptide hormones and cytokines lead to insulin resistance (IR). Similarly, add to the risk of T2DM. IR is linked to issues in glucose uptake and oxidation, reduced glycogen synthesis, and a minor decrease in the ability to inhibit lipid oxidation. IR has a substantial impact on skeletal muscle, adipocytes, and liver tissue due to their elevated metabolic demands.[31,32]

III. Glucose Metabolism of Diabetes

Glucose serves as the primary source of energy and fuel for human cells. It is derived from the food eaten, metabolized in the body, and delivered from the bloodstream to specific cells. The transport of glucose through the plasma membrane is crucial.[33] Lipids, proteins, and

carbohydrates ultimately decompose to create glucose, which acts as energy for the body's metabolic functions. Glycogenesis, glycolysis, gluconeogenesis, and glycogenolysis are just some of the various processes involved in glucose metabolism. Glycolysis, a metabolic process driven by enzymes, facilitates the breakdown of glucose within cells and its transformation into pyruvate.[34] To sustain stable blood sugar and glucose concentrations while fasting, the cytosol and mitochondria of liver cells execute various metabolic processes that lead to glucose production from non-carbohydrate sources. Insulin, glucagon, and cortisol regulate it.[35] Additionally, the pancreas releases glucagon when fasting, initiating glycogenolysis. Glycogenolysis is a biological process that entails the degradation of glycogen to generate glucose and glucose-1-phosphate (Figure: 4).[36]

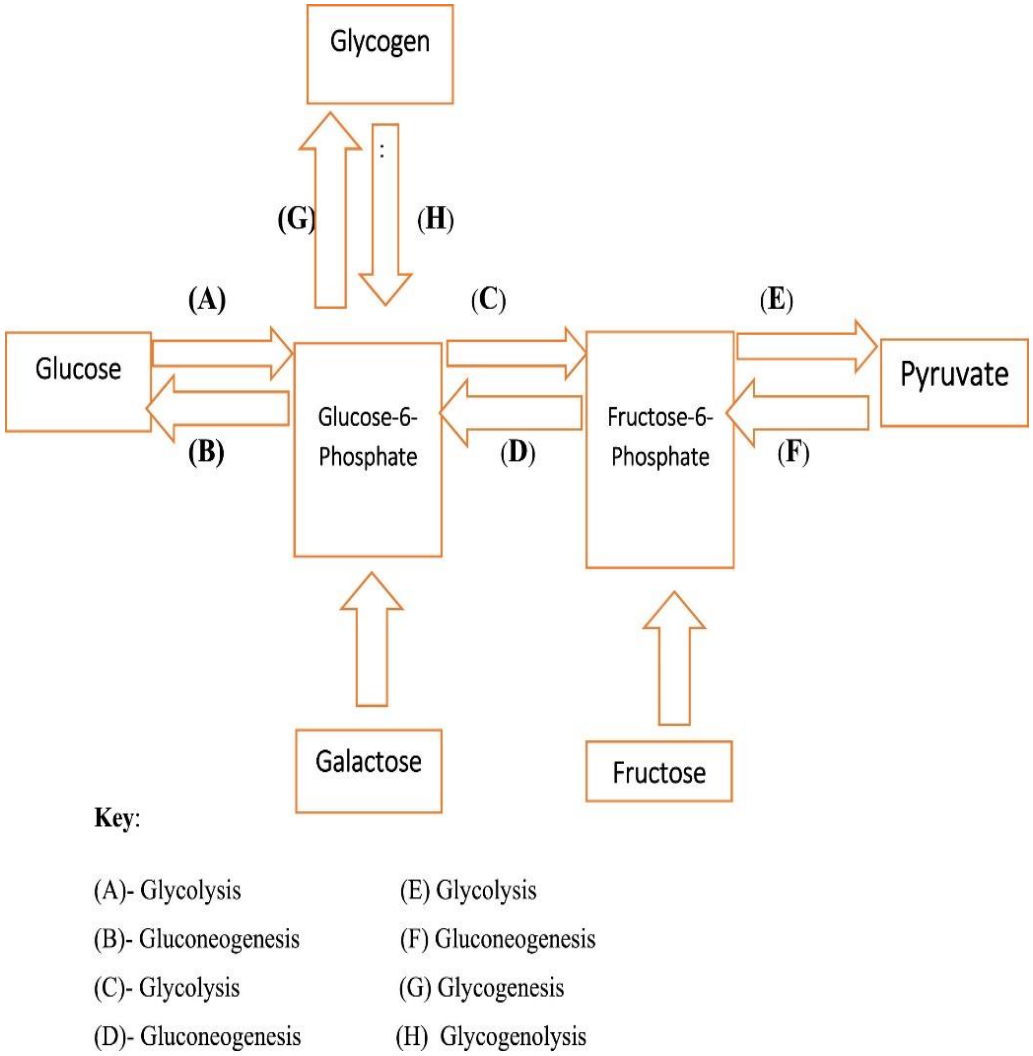

Figure 4: Chart showing the relationship between the processes of glucose metabolism.

4. CAUSES & RISK FACTORS

- **Age:** The risk of developing type 2 diabetes increases with age, particularly after 45 years.
- **Genetic Predisposition:** Having a close family member with diabetes significantly increases an individual's susceptibility to developing the disease.
- **Obesity:** Excess body fat, particularly around the abdominal region, is a major contributor to insulin resistance and the development of Type 2 diabetes.
- **Dietary Habits:** A diet high in processed foods, sugary beverages, and low in fiber is associated with a higher risk of developing diabetes.
- **Stress and Mental Health:** Chronic stress and mental health issues can affect blood sugar levels and contribute to unhealthy lifestyle choices, increasing diabetes risk.[37,38]

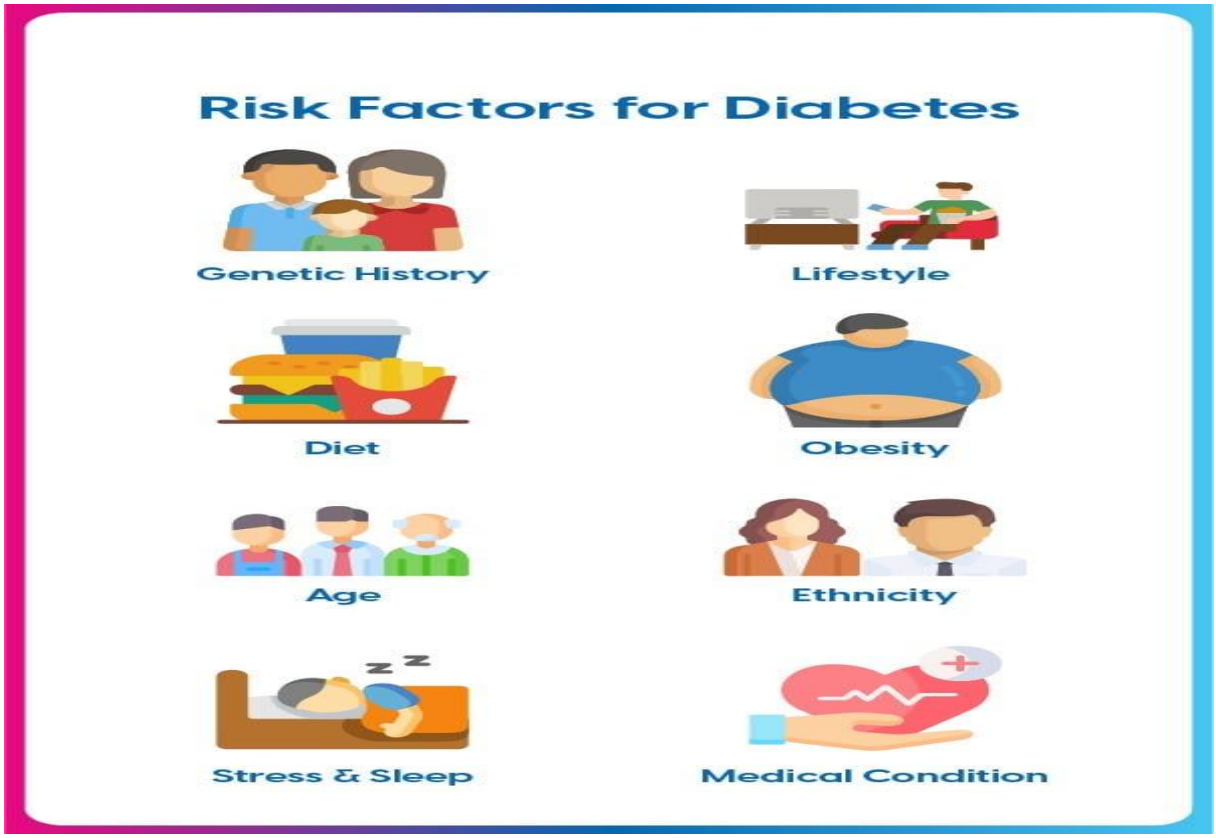

Figure 5: Causes and risk factors of diabetes mellitus.[39]

5. DIAGNOSIS OF DIABETES

The 1997 American Diabetes Association (ADA) Recommendations For Diagnosis Of Diabetes Mellitus Focus On Fasting Plasma Glucose (FPG), While WHO Focuses On The Oral Glucose Tolerance Test (OGTT)[40] Glycated Hemoglobin (Hba1c)Test.[41,42]

➢ **Fasting Plasma Glucose Test**

There Should Be Eight Hours Fasting Before Taking This Test. Blood Glucose More Than 126 Mg/Dl On Two Or More Tests Conducted On Different Days Confirms A Diabetes Diagnosis.[43]

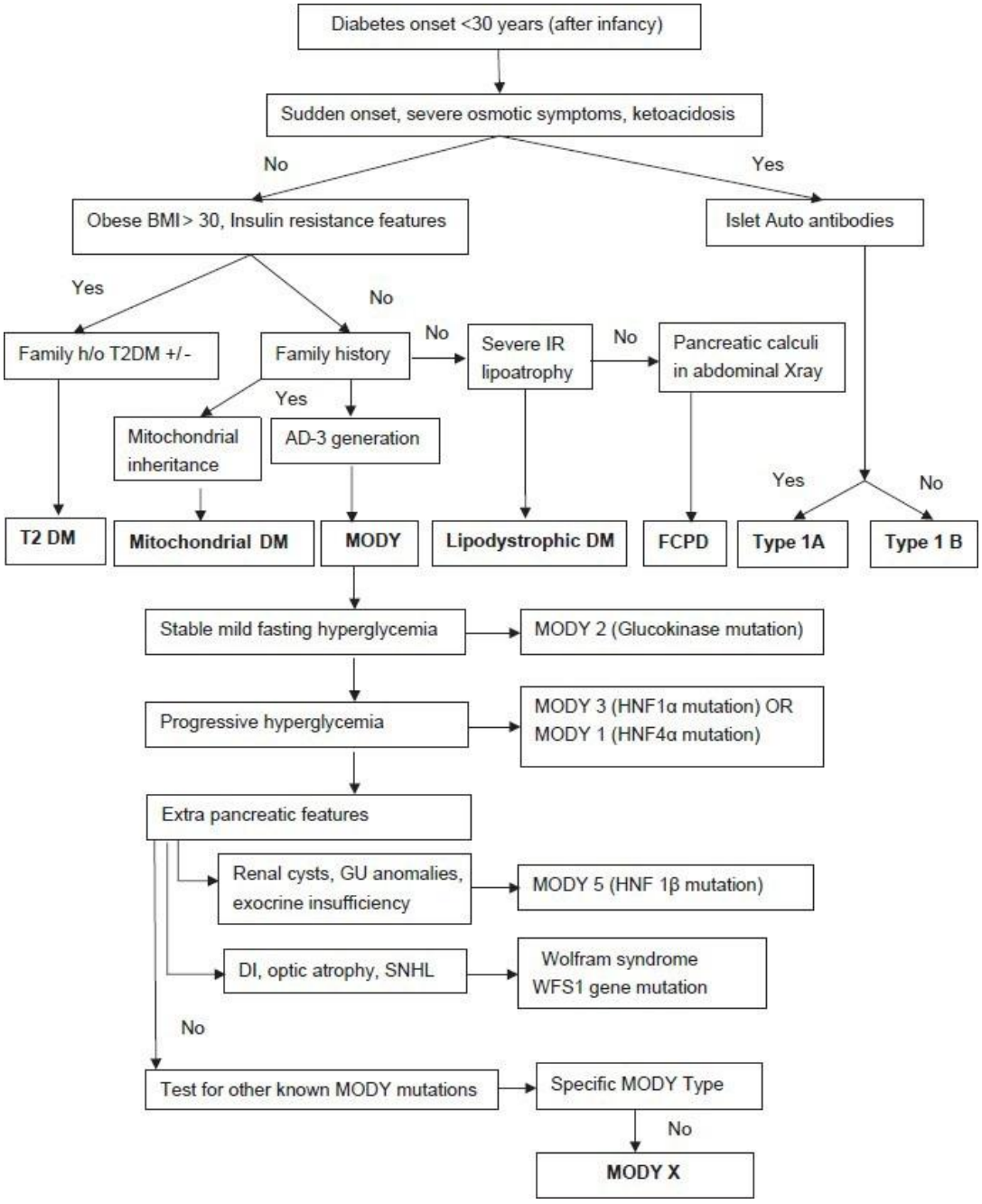

Figure 6: Suggested Approach To Screening Patients At Risk For Diabetes.[44,45]

➢ **Oral Glucose Tolerance Test**

➢ If the random plasma glucose level is between 160-200 mg/dl and the fasting plasma glucose level is between 110-125 mg/dl, then this test is performed.[46]

- This blood test assesses the body's reaction to glucose. This test demands fasting for a minimum of eight hours and a maximum of 16 hours.
- The fasting glucose level is measured, followed by the administration of 75 gm of glucose, or 100 gm for expectant mothers. The blood undergoes testing every 30 minutes to one hour for a duration of two to three hours.
- This test is considered normal if your glucose level at two hours is under 140 mg/dl. A fasting value of 126 mg/dl or higher and a two-hour glucose level of 200 mg/dl or more confirms a diabetes diagnosis.[43]

- **Hemoglobin A1c (Hba1c)**
- Represents the typical blood sugar levels from the previous 2-3 months. A result of ≥ 6.5% (48 mmol/mol) signifies diabetes.[47,48]
- It is crucial to recognize that we establish definitive blood glucose cutoff levels; however, blood glucose irregularities and the likelihood of developing T2D are ongoing processes. A meta-analysis encompassing 16 studies indicated that individuals with hba1c levels between 5.5–6% have a 5-year diabetes development risk of 9–25%, whereas those with hba1c levels between 6–6.5% face an increased 5-year risk of 25–50%.[49]

Table 1: Criteria for the diagnosis of diabetes and prediabetes.[49]

	ADA[50]	WHO[51]
Diabetes	FPG≥7mmol/L	
	2-h PG during OGTT≥11.1mmol/L	
	RPG≥11.1mmol/L	
	Hba1c≥6.5%	
Prediabetes	FPG 5.6–6.9mmol/L	FPG 6.1–6.9mmol/L
	2-h PG during OGTT 7.8 - 11.0 mmol/L	
	Hba1c 5.7–6.4%	Hba1c 6.0–6.4%

6. COMPLICATION OF DIABETES

1. Chronic Complications

- **Eye Disease**

It due to changes in fluid levels, swelling in the tissues, and damage to the blood vessels in the eyes.

- **Foot Problems**

It caused by damage to the nerves and reduced blood flow to your feet.

- **Gum Disease**

Gum disease and other dental problems, because a high amount of glucose in your saliva helps harmful bacteria grow in your mouth. The bacteria combine with food to form a soft, sticky film called plaque. Plaque also comes from eating foods that contain sugars or starches. Some types of plaque cause gum disease and bad breath. Other types cause tooth decay and cavities.

- **Heart Disease And Stroke**

It caused by damage to your blood vessels and the nerves that control your heart and blood vessels.

- **Kidney Disease**

It due to damage to the blood vessels in your kidneys. Many people with diabetes develop high blood pressure. That can also damage your kidneys.

- **Nerve Problems (Diabetic Neuropathy)**

It caused by damage to the nerves and the small blood vessels that nourish your nerves with oxygen and nutrients.

- **Sexual And Bladder Problems**

It caused by damage to the nerves and reduced blood flow in the genitals and bladder.

- **Skin Conditions,** some of which are caused by changes in the small blood vessels and reduced circulation. People with diabetes are also more likely to have infections, including skin infections.[52]

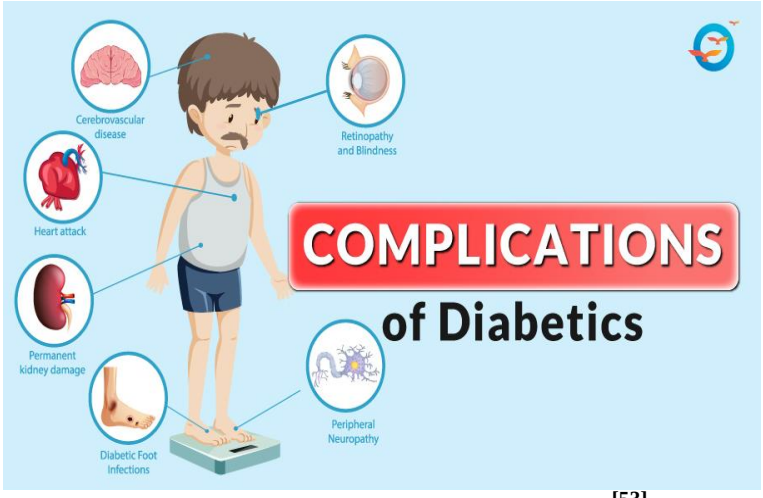

Figure 7: Complication Of Diabetes.[53]

2. Acute Complication

- **Diabetes ketoacidosis (dka)**

Diabetic ketoacidosis (DKA) is a critical and potentially fatal complication of diabetes that requires prompt response and treatment.[54] It is regarded as a medical emergency and can impact individuals with t1d (type 1 diabetes) and t2d (type 2 diabetes), though it occurs more frequently in t1d.[55] DKA arises from severely low insulin levels caused by several factors such as undiagnosed diabetes (individuals unaware of their diabetes), missed or postponed doses, inadequate insulin delivery, or experiencing physiological stress (e.g., infection, surgery, stroke, or trauma).[56,57]

- **Hypoglycemia**

Hypoglycemia, defined as excessively low blood glucose levels, is a sudden complication associated with various diabetes therapies.[58] It rarely occurs in individuals who are not diabetic or in those with diabetes. The patient might experience agitation, sweating, weakness, and various signs of sympathetic activation in the autonomic nervous system, leading to sensations similar to dread and paralyzing panic. Consciousness can change or even disappear in severe instances, resulting in coma, seizures, or potentially brain damage and death. In individuals with diabetes, this can result from multiple reasons, including excessive or poorly timed insulin, excessive or poorly timed physical activity (which lowers insulin needs), or insufficient food (particularly carbohydrates with glucose). The diverse interactions complicate cause identification in numerous cases.[59,60]

- **Hyperglycemic hyperosmolar state (HHS)**

Hyperosmolar non-ketotic state (HONK) or Hyperglycemia hyperosmolar state (HHS) is an acute complication that exhibits numerous symptoms similar to DKA, yet has a distinct origin and requires different treatment.[61] Conversely, HHS is frequently observed in individuals with T2D. Additionally, it demonstrates around ten times higher mortality rate compared to that seen in DKA.[62]

7. TREATMENT AND MANAGEMENT

- **Insulin therapy for the management of T1DM and T2DM**

For all patients with T1DM, the primary treatment is insulin. Upon initial diagnosis, individuals with T1DM typically require multiple daily injections. Usually, one or more daily injections of intermediate- or long-lasting insulin are given alongside 0 to 15 minutes of fast-acting insulin or rapid-acting insulin analogs. It is possible to utilize two or three pre-

prepared insulin injections daily. The goal for HbA1c should be < 7.5% (< 58 mmol/mol) for all children with T1DM, encompassing those in preschool age.[63]

- Insulin therapy should be initiated for T2DM patients under these circumstances: during acute illness or surgery; if pregnant; in the presence of glucose toxicity; when facing severe liver or kidney failure; are unable to meet their targets with oral antidiabetic medications, or need flexible treatment options. When HbA1c reaches 7.5% (=58 mmol/mol), insulin is viewed as a standalone treatment or alongside oral medications to assist T2DM patients in achieving their glycemic targets. When HbA1c reaches 10% (or 86 mmol/mol), insulin becomes necessary for treatment if diet, exercise, and other antihyperglycemic medications have been maximally applied.[63,64]

- **Lifestyle modification for the management of both T1DM and T2DM**

Diet and physical activity are the primary factors influencing energy balance and are fundamental to diabetes management. Individuals with T1DM need to monitor their blood sugar levels consistently. There are various methods to reduce the risk of health problems, such as developing a nutritious eating plan, engaging in regular physical activity, and working with the diabetes team to adjust insulin treatment. Clinical studies show that lifestyle changes can reduce the likelihood of developing T2DM by postponing or averting its onset.[65,66]

Herbal treatment of diabetes

Over the past few decades, environmentally friendly, bio-safe, affordable, and relatively safe plant-based remedies have transitioned from the margins to the mainstream due to heightened research in traditional medicine. Numerous literature reviews by various authors exist regarding anti-diabetic herbal agents; however, the most comprehensive is Atta-ar-Rahman's review, which has documented over 300 plant species recognized for their hypoglycaemic effects. This review categorizes the plants based on their botanical name, country of origin, utilized parts, and type of active compounds. One example of a plant is Momordica charantia (Family: Cucurbitaceae).[67] The WHO has identified 21,000 plants that are utilized for medicinal purposes globally. Among these 2500 species found in India, 150 species are utilized commercially on a significant scale. India is the top producer of medicinal plants and is referred to as the botanical garden of the globe.[68]

- **Nutrition and Exercise**

- A proper diet is the fundamental basis of nearly all diabetes management plans. Regrettably, hopes regarding diet therapy have been excessively elevated, leading to numerous misunderstandings. Currently, the American Diabetes Association asserts that a diabetic diet must be nutritious, tailored in calorie content to reach or sustain normal body weight, and scheduled suitably considering the pharmacological treatments used, like insulin. Several dietary approaches are available, including high carbohydrate, high fiber, and very low calorie strategies. Any of these diets can be justified as long as they are effective and meet the standards set by the American Diabetes Association. Regrettably, this is also a field that faces significant overexpectation and misunderstanding. Exercise as a method for managing diabetes is an area that requires additional investigation. Until additional information is provided, it is sensible to urge diabetics to participate in a daily, moderate aerobic exercise regimen.[70]

Oral Hypoglycaemic or Antidiabetic Agents

Clinically useful biguanide phenformin was produced parallel to sulfonylurea's in 1957. Newer approaches have constantly been explored and have lately yielded thiazolidinediones, meglitinide analogues, α-glucosidase inhibitors, and the latest are dipeptidyl peptidase-4(DPP-4) inhibitors.[71]

- **Monitoring**

Regular monitoring of blood glucose levels, using techniques like self-monitoring, continuous glucose monitoring, and periodic HbA1c tests, is essential for assessing the effectiveness of the treatment plan and making necessary adjustments.[72]

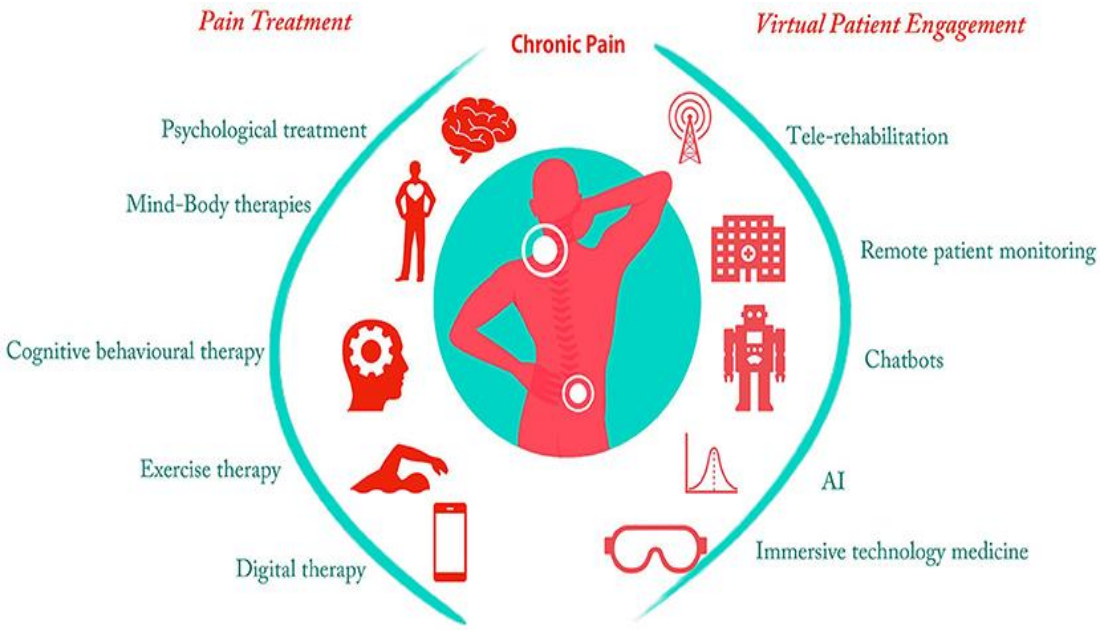

Figure 8: Chronic pain treatment and digital patient engagement methods.[73]

➢ **Diabetes and their Allopathic Medicines**

Doctors prescribed insulin and insulin analog normally with kind 1 diabetics and additionally with type2 diabetic for remedy of hyperglycemia in component due the modern lack of β-mobileular feature over time , approx 40-80% of people with kind-2 diabetes will in the long run be taken into consideration for insulin remedy which will acquire glycolic targets.

- **Treatment of Diabetes mellitus**

Table 2: Treatment of Diabetes Mellitus.[74]

Types of drug	Working	Example(s)
Biguanides	Reduce the amount of glucose your liver makes and control the blood glucose level	Metformin (Glucophage)
Alpha-glucosidase inhibitors	Slow your body's breakdown of sugars and starchy foods	Acarbose (Precose) and miglitol (Glyset)
DPP-4 inhibitors	Improve your blood sugar without making it drop too low	Linagliptin (Tradjenta), saxagliptin (Onglyza), and sitagliptin (Januvia)
Glucagon-like peptides	To help the produces sufficient amount of insulin by beta cell of pancreas	Dulaglutide (Trulicity), exenatide (Byetta), and liraglutide (Victoza)
Thiazolidinediones	Increase the amount of insulin those reduces the blood glucose at the normal range	Pioglitazone (Avandia) (Actos) and rosiglitazone
Meglitinides	Stimulate your pancreas to release more insulin which is control the blood glucose level in blood	Nateglinide (Prandin) (Starlix) and repaglinide

➢ **Simple Management of Diabetes Mellitus in Siddha**

- Take decoction of Seventhly (Tinospora) climber in empty stomach.

- Take two fresh coccidian daily.
- 15 ml of gooseberry juice, 15 ml of lemon juice mix together and take twice a day.
- Take powder of fenugreek twice a day with hot water.
- Take young leaves of Eagle marvelous.
- Take bitter gourd juice and leaves juice.
- Take 6 fresh leaves of Andrographis daily.
- Take decoction whole plant of Indian Phyllanthus.
- Take Triphala powder twice a day with hot water

➢ **Unani Medicine for Diabetes Cure**

Nateglinide (Prandin) (Starlix) and repaglinide Unani device of drugs may be a totally wealthy supply as a phytomedicine, many unmarried drugs, and compound formulations are utilized in Unani medicinal drug for the treatment of Dhayabitus (diabetes). Phytomedicine utilized in Unani medicinal drug gives an thrilling possibility for the development of recent therapeutics / formulations for DM, which include diverse photochemical corporations consisting of alkaloids, terpenes, and phenolics. Besides hypoglycemic hobby, those drugs additionally have antioxidants, bitter, and different hobby associated to a disturbance in carbohydrate metabolism. They are used within side the shape of decoctions, infusions, tablets, pills, powder, confection, etc.[74]

Table 3: Common marketed formulation of unani medicine for treatment of diabetes.[74]

S. No.	Name	Dosage	Ingredients	P/P and Ph	Manufacturing industry/ pharmacy
1.	Jamun Sirka	10–15 ml/day	Jamun fruit pulp, water	P/P	Dehlvi naturals Delhi
2.	Methi capsules	2 cap bid.	Methi dried extract, methi powder	P/P	Dehlvi naturals Delhi
3.	Kalonji sugar powder	1 tsf tid.	Kalonji powder, tukhm-e-jamun, Gudmarbooti, tuqme-katayla, tuqm-e-kasni, tuqme-methi	P/P	Mohammedia Products, Karimnagar, India
4.	Kerala Ras	10 ml bid.	Karela (bitter melon)	P/P	Dehlvi naturals Delhi
5.	Qurs-Tabasheer	5 g	Tabasheer, tukhme-khurfa, tukhme-kahu, gule-surkh, gulnar, gile-armani	Ph	Hamdard laboratories, Gurugram, India

➢ **Ayurvedic emphasised**

➢ The main and foremost principle of prevention, alongside the treatment of any illness, is the elimination of causative factors. This concept is referred to as the principle of indaba Parivarjanam in Ayurveda.

- Utilize the flesh of animals with anti-diuretic qualities (shower Muttra!), forest creatures, and forest birds, as suggested.
- Navapatala (Tricosanthus devoice), raw banana, Tanduleyaka (Amaranthus spinatus), Vistula (Bathua-Chenopodium album), Matsyakshi (Alternanthera sessilis), tangy vegetables such as Methinks (Trigonella foenum-graecum), Karavellaka (Momordica charantia); Bemba (Coccinia indica), Marcia (Piper nigrum), Sandoval vine (rock salt) should be utilized.
- Engage in regular exercise/yoga and activities that promote caloric intake (such as brisk walking, swimming, cycling, etc.).
- Steer clear of ending your meal with high amounts of simple sugars such as bananas, sapodilla, grapes, and mango, etc.

DRUG THERAPY[75]

Table 4: Single Drugs and it's drug therapy.[75]

Drugs	Dosage (per dose)	MOA/Vehicle	Duration
Alake (Phyllanthus embolic) Fruit	3-6 gm	Warm Water	90 days
Harridan (Curcumalong) Rhizoem	1-3 gm	Luke Warm Water	90 days
Maharani (Gymea Sylvester) Leaf	3-6 gm	Water	90 days
Kumara (Aloe Vera) swards-leaf Pulp	10-15 ml	Water	90 days
Mali swards	10-15ml	water	90 days

8. PREVENTION OF DIABETES

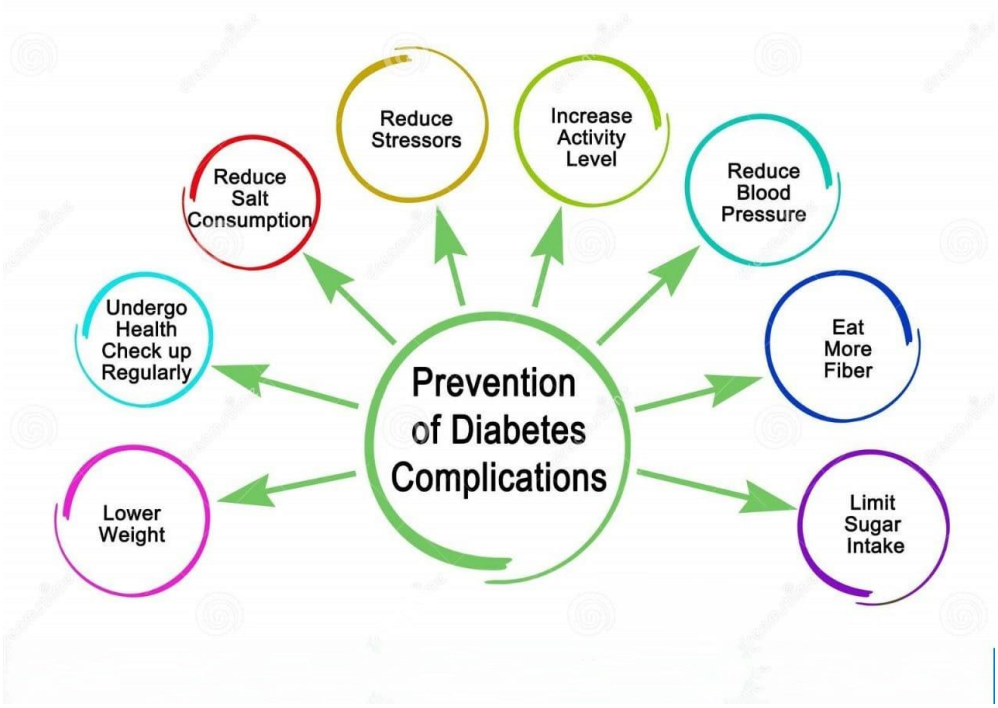

Figure 9: Prevention of Diabetes.[76]

Type 1 diabetes can't be prevented. But the healthy lifestyle choices that help treat prediabetes, type 2 diabetes and gestational diabetes can also help prevent them:

- **Eat healthy foods**

Choose foods lower in fat and calories and higher in fiber. Focus on fruits, vegetables and whole grains. Eat a variety to keep from feeling bored.

- **Get more physical activity**

Try to get about 30 minutes of moderate aerobic activity on most days of the week. Or aim to get at least 150 minutes of moderate aerobic activity a week. For example, take a brisk daily walk. If you can't fit in a long workout, break it up into smaller sessions throughout the day.

- **Lose excess pounds**
- Losing just 7% of your body weight can reduce the risk of diabetes if you're overweight. For instance, if your weight is 200 pounds (90.7 kilograms), shedding 14 pounds (6.4 kilograms) may reduce the risk of developing diabetes.
- However, do not attempt to shed pounds while pregnant. Discuss with your provider the appropriate amount of weight for you to gain during your pregnancy.
- To maintain your weight within a healthy range, focus on sustainable modifications to your diet and physical activity routines. Recall the advantages of shedding pounds, including improved heart health, increased energy, and enhanced self-esteem.
- At times, medications are a possibility. Oral medications for diabetes like metformin (Glumetza, Fortamet, among others) might reduce the likelihood of developing type 2 diabetes. However, making healthy lifestyle choices is essential. If you are diagnosed with prediabetes, ensure to have your blood sugar tested annually to confirm you haven't progressed to type 2 diabetes.[77]

- **Manage your stress**

Limit alcohol intake.

Get adequate sleep (typically 7 to 9 hours) and seek treatment for sleep disorders.

- **Quit smoking**

Take medications as directed by your healthcare provider to manage existing risk factors for heart disease.[78]

9. RECENT ADVANCES

- **Insulin infusion devices**

- Insulin delivery systems are commonly categorized into open-loop and closed-loop setups. The adjustable open-loop micro pump insulin delivery technique features a small and lightweight insulin micro pump that is easy to carry. It is linked to a cannula placed under the skin via plastic tubing that administers medication. The insulin release schedules in these devices can be programmed and triggered either via a timer or by the patient controlling their diabetes. Nevertheless, correct operation of this device requires careful monitoring of blood sugar levels. Additionally, people using this device have been reported to have a higher incidence of ketoacidosis. Moreover, there are now insertable versions of open-loop insulin infusion devices accessible. Insulin delivery systems with closed-loop chemical control function through a feedback mechanism, offering a viable alternative when successful β-cell transplantation is unfeasible. They replicate pancreatic function and are compatible with biological systems and non-harmful. Researchers are investigating a new type of insulin delivery device called the biohybrid artificial pancreas. The membrane encasing the β-cells in these devices is semi-permeable and biocompatible, permitting the flow of glucose and insulin while needing careful management to avoid immune cell infiltration and rejection.[79]

- **SGLT2 inhibitors**

Orally available, highly selective SGLT2 inhibitors such as dapagliflozin, canagliflozin, ipragliflozin, empagliflozin, and ertugliflozin have been created and/or are in clinical trial phases. Dapagliflozin and canagliflozin have received approval for clinical use in T2DM patients in the US, EU, and Australia.[80-81]

- SGLT2 inhibitors reduce blood sugar levels by promoting glucose elimination through urine. The extent of this effect relies on the level of glucose in the bloodstream and the glomerular filtration rate. As blood glucose levels drop after starting treatment with SGLT2 inhibitors, the glucose amount filtered by the kidneys decreases and additional urinary glucose excretion becomes restricted. In this manner, SGLT2 inhibitors may be regarded as possessing a self-regulating impact on blood glucose levels, evident in a low inherent tendency to induce hypoglycaemia.[82] Furthermore, glucosuria linked to SGLT2 inhibition has been correlated with calorie loss resulting in weight reduction, along with osmotic diuresis and natriuresis contributing to lower blood pressure (BP; observed in the studies on dapagliflozin and canagliflozin mentioned in this review).[83]

➢ **GLP-1 Analogs**

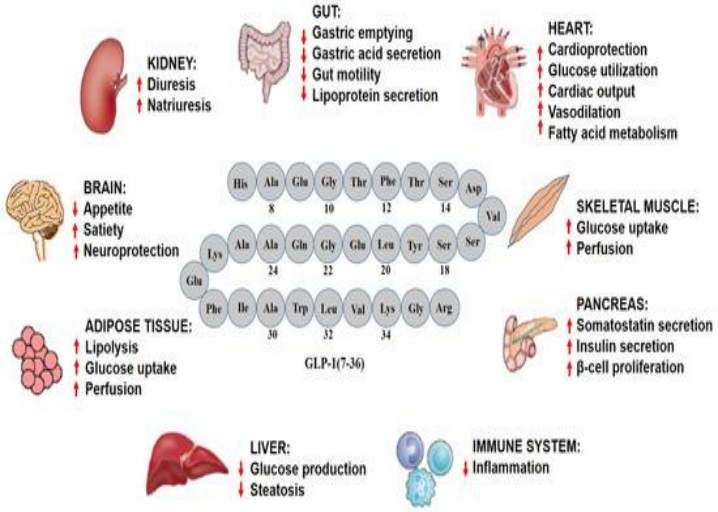

Figure 10: Systemic Effects of GLP-1 and Its Analogs.

The impacts on different tissues/organs shown in the figure are derived from findings gathered in multiple preclinical or clinical studies at physiological GLP-1 concentrations or following exposure to GLP-1R analogs. GLP-1R is widely present in the tissues and organs of both the peripheral and central nervous systems, with varying expression levels resulting in unique biological functions in each tissue or organ. GLP-1R shows high expression in the CNS and pancreas, whereas its expression is lower in the heart, lungs, gut, muscle, kidneys, liver, PNS, and other tissues. ↑, Increase; ↓, Decrease.[84]

Drug Used In Glp -1 Analogs

Drug	Dosage	Frequency and timing
Liraglutide	0.6 mg initially, up-titratable to 1.2 and 1.8 mg	Once daily, without relation to meals
Exenatide	5 µg, up-titratable to 10 µg	Twice daily, 60 min prior to meals
Exenatide LAR	2 mg	Once a week, without relation to meals

GLP-1: Glucagon-like peptide-1

Figure 11: Dosage Of Glp Analogs.[85]

10. CASE STUDIES OR SURVEY REPORT

❖ **CASE 1**

Patient id

Ms. L, 17 years and 5 months, female

Complaints

Polydipsia, polyuria

Family history

Mother with hypertension, father with heart failure.

Past medical/social history

No significant history

History of present illness

This 17-year-old girl was diagnosed with diabetes at another hospital after a 1-month history of persistent polydipsia and polyuria. She presented to konkuk university medical center for further diagnosis and treatment of her persistent symptoms.

Physical examination

On admission, her height was 173.1 cm (>97th percentile), weight was 107.2 kg (>97th percentile), and bmi was 35.8 kg/m^2 (>97th percentile) (table5). She appeared obese but did not look ill and her mental status was intact. Her vital signs were normal except for a blood pressure of 137/81 mmhg (95–99th percentile). Her skin was warm and no dry mucous membranes were observed. A chest examination was unremarkable. No enlargement of the liver or spleen was appreciated on an abdominal examination. The rest of the physical exam was unremarkable.

Table 5.

Anthropometric data and patient body composition profiles of adolescent girls with type 2 diabetes who achieved remission after stopping medications.

BMI, body mass index; FFM, fat free mass; FM, fat mass; FFMI, fat free mass index; FMI, fat mass index; FFMIZ, fat free mass index Z score; FMIZ, fat mass index Z score; PBF, percent body fat.

	Case 1		Case 2	
	Baseline	Follow up	Baseline	Follow up
Age (year)	17.5	21.5	12.1	14.9
Height(cm)	173.1	174	158.9	160.8
Weight(kg)	107.2	80.2	75.5	59.9
BMI(kg/m^2)	35.8	27.1	29.9	23.2
HeightZscore	2.38	2.13	1.01	0.43

WeightZscore	3.66	2.5	2.72	0.98
BMI Zscore	3.28	1.87	2.62	0.99
FFM (kg)	53.2	49.6	43.4	41.8
FM (kg)	54	30.6	32.1	18.1
FFMI(kg/^{2})	17.8	16.8	17.2	16.2
FMI(kg/m)	18	10.3	12.7	7
FFMIZ	2.06	1.56	2.1	1.51
FMIZ	2.87	1.47	2.51	0.32
PBF (%)	50.4	38.2	42.5	30.2

Lab finding

Labs on admission revealed a glycated hemoglobin (HbA1c) of 11.1%, fasting plasma glucose level of 102 mg/dL, insulin level of 23.12 µIU/mL, and C-peptide level of 4.13 ng/mL. Liver function tests revealed an elevated serum aspartate transaminase (AST) level of 115 IU/L and serum alanine transaminase (ALT) level of 141 IU/L. A lipid panel demonstrated a total cholesterol level of 133 mg/dL, triglycerides of 71 mg/dL, and high-density lipoprotein cholesterol (HDL-C) of 49 mg/dL (Table 6). The total protein and albumin level was 7.0 g/dL and that of albumin was 4.5 g/dL. The free fatty acid level was elevated at 1214 µEq/L.

Table 6.

Biochemical profiles of adolescent girls with type 2 diabetes who achieved remission after stopping medications.

	Case 1		**Case 1**	
	Baseline	**Follow up**	**Baseline**	**Follow up**
Age (year)	17.5	21.5	12.1	14.9
HbA1c (%)	11.1	4.9	9.9	6
C-peptide (ng/mL)	4.13	2.13	2.97	2.79
Insulin (µIU/mL)	23.12	15.69	15.85	5.62
Glucose (mg/dL)	102	84	202	97
Total cholesterol(mg/dL)	133	114	165	115
Triglyceride (mg/dL)	71	59	104	70
HDL cholesterol (mg/dL)	49	51	50	30
AST (IU/L)	115	20	47	20
ALT (IU/L)	141	12	69	34

Radiologic findings

There were no abnormal findings on a chest radiograph. An abdominal ultrasound showed severe fatty infiltration of the liver.

Treatment and progress

To manage glycemic levels, the patient was initiated on oral medications (metformin 500 mg twice daily, glimepiride 1 mg once daily) along with a diet and exercise regimen for lifestyle modification. Her nutritional and dietary understanding was assessed, and she received guidance to consume regular meals containing 70–75 g of protein daily while meeting daily nutritional needs of about 1,800 kcal. She was advised to follow a low-carb, low-fat diet, reduce high saturated fats, monitor her consumption, and go to outpatient visits every 1–2 months. She was directed to engage in aerobic and weight training exercises that enhance muscle strength for over 1 hour at least three times a week. For one year, she engaged in aerobic and anaerobic workouts for at least an hour each day. After one year, she added a daily 7 km walk and Pilates sessions over three times a week to her fitness routine. In the outpatient environment, we evaluated her compliance with treatment every 1–2 months, provided encouragement, and recommended that she slowly extend her exercise time instead of its intensity. Each year, we recorded her height and weight, utilizing InBody720, a form of bioelectrical impedance analysis (BIA), to precisely assess her obesity. Upon diagnosis, the patient had a BMI of 35.8 kg/m2 (FMI, 18.0 kg/m2; FFMI, 17.8 kg/m2), placing them above the 97th percentile, with a percent body fat (PBF) of 50.4%. Over the 2 years of outpatient follow-up, she faced no challenges in managing her blood sugar levels with the combination of oral medication and lifestyle changes. The metformin dosage was raised to 1,000 mg BID because it was challenging to keep her HbA1c under 7.0% with the earlier treatment; she was still classified as obese with a BMI of 35.1 kg/m2 (FMI, 17.2 kg/m2; FFMI, 17.9 kg/m2) and a PBF of 48.9%. Her weight and body makeup throughout the treatment, *she was still considered obese with a BMI of 35.1 kg/m^2 (FMI, 17.2 kg/m^2; FFMI, 17.9 kg/m^2) and PBF of 48.9%. Her weight and body composition during treatment are shown in Figure 12.*

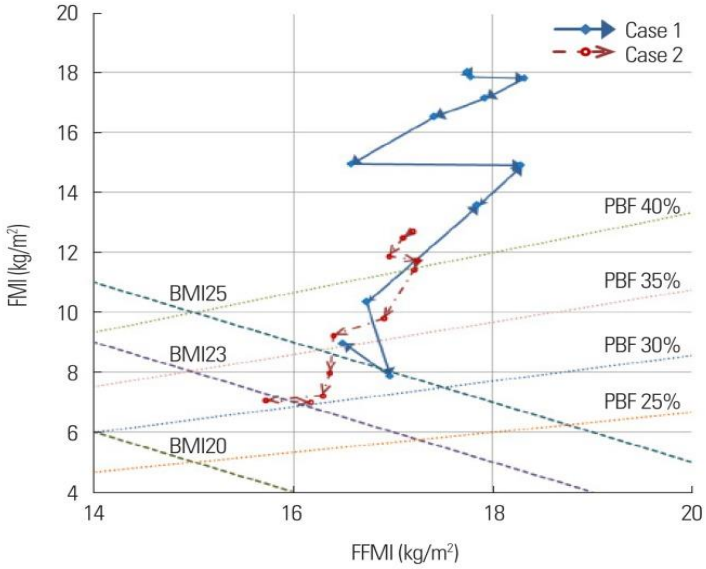

Figure 12: Treatment and Progress.

❖ Graph showcasing alterations in FFMI and FMI in two adolescent females with T2DM who attained remission. T2DM, diabetes type 2; BMI, body mass index; PBF, percentage of body fat; FFMI, fat-free mass index; FMI, fat mass index.

❖ Three years later, the patient's nutritional treatment and exercise regimen achieved an increased FFMI of 18.3 kg/m2 and a decreased FMI of 14.9 kg/m2, resulting in the cessation of glimepiride and a reduction of the metformin dosage to 500 mg BID.

❖ After four years, her HbA1c level dropped to 5.4%, prompting the discontinuation of metformin because of her effective glycemic management. At that moment, her fasting blood glucose was 97 mg/dL, insulin measured 5.62 μIU/mL, and C-peptide was 2.13 ng/mL. Her BMI measured 27.1 kg/m2 (FMI, 10.3 kg/m2; FFMI, 16.8 kg/m2) and her PBF was 38.2%, categorizing her as obese according to the World Health Organization standards for Asian adults; nevertheless, this represented a reduction of 8.7 kg/m2 from her BMI before treatment and her FMI had dropped by 7.7 kg/m2. Her FFMI decreased by 1.0 kg/m2, yet remained within the 90–95th percentile; therefore, her nutritional status was not problematic (Table 5). Liver function tests along with a lipid panel indicated AST at 20 IU/L, ALT at 12 IU/L, total cholesterol at 114 mg/dL, triglycerides at 59 mg/dL, and HDL-C at 51 mg/dL (Table 6). Her HbA1c has stayed below 5.7% for over a year without oral medications and will continue to be monitored.

❖ **Case 2**

Patient ID

Ms. A, 12 years and 10 months, female

Complaints

Hyperglycemia

Family history

Father with type 2 diabetes under treatment

Past medical/social history

No significant history

History of present illness

12-year-old female who presented to Konkuk University Medical Center with post-prandial hyperglycemia of 330 mg/dL measured by her father one day prior to admission. Menarche occurred 1 year prior and her menstrual cycles were regular.

Physical examination

On admission, the patient's height was 158.9 cm (25–50th percentile), weight was 75.5 kg (>97th percentile), and BMI was 29.9 kg/m^2 (>97th percentile) (table 5). Her vital signs were within the normal range with a blood pressure of 112/68 mmHg, pulse of 72 beats/min, respiratory rate of 20 breaths/min, and temperature of 36.6°C. She had a clear mental status, warm skin, and moist mucous membranes. A chest examination revealed no specific findings, while an abdominal examination revealed no hepatomegaly or splenomegaly. The rest of the physical examination was unremarkable.

Laboratory findings

Laboratory tests at the time of admission revealed an HbA1c level of 9.9%, fasting blood glucose level of 202 mg/dL, insulin level of 15.85 μIU/mL, and C-peptide level of 2.97 ng/mL. Liver function tests showed an elevated AST level at 47 IU/L and ALT level at 69 IU/L. A lipid panel and comprehensive metabolic panel showed a total cholesterol level of 165 mg/dL, triglyceride level of 104 mg/dL, HDL-C of 50 mg/dL, total protein of 7.6 g/dL, and albumin of 4.8 g/dL (Table 6). The free fatty acid level was elevated at 671 μEq/L.

Radiologic finding

There were no significant findings on a chest radiograph. An abdominal ultrasound showed moderate fatty liver**.**

Treatment and progress

For glycemic management, a combination of oral medication (metformin 500 mg BID) and lifestyle changes via dietary habit modifications was recommended. We assessed her understanding of diet and nutrition and subsequently advised her to have consistent meals with 70–90 g of protein daily, sustain her daily nutritional needs of around 1800 kcal, and follow a low-carbohydrate, low-fat diet. She was advised to change her usual liking for salty and spicy dishes, decrease her salt consumption, log her meals, and go to outpatient check-ups every 1–2 months.

For her exercise routine, she was advised to incorporate aerobic and strength-training exercises that enhance muscle power. She was recommended to walk for over 1 hour at least 5 days a week and attend a fitness center for at least 1 hour of strength training a minimum of 3 times a week. We recorded her height and weight bi-monthly, utilizing InBody720, a BIA tool for precise evaluation of obesity. At the time of diagnosis, the patient's BMI was 29.9 kg/m2 (FMI, 12.7 kg/m2; FFMI, 17.2 kg/m2) with a PBF of 42.5%. Two years post-diagnosis, an abdominal ultrasound revealed enhancements in her fatty liver, and her HbA1c was effectively lowered to 6.0%. The oral medication was stopped because of effective glycemic management. At that moment, her fasting blood sugar measured 97 mg/dL, insulin level stood at 5.62 μIU/mL, and C-peptide level was 2.79 ng/mL. Her BMI (FMI+FFMI) measured 23.2 kg/m2 (7.0 kg/m2+16.2 kg/m2), placing her within the overweight category (85–90th percentile), and her PBF was recorded at 30.2%. At that time, her BMI was 6.7 kg/m2 lower than before treatment, and her FMI showed a decrease of 5.7 kg/m2 (Table 5). Liver function tests and a lipid panel showed: AST, 20 IU/L; ALT, 34 IU/L; total cholesterol, 115 mg/dL; triglycerides, 70 mg/dL; and HDL-C,**,** 30 mg/dL (Table 6). The changes in the patient’s weight and body composition during treatment are shown in Figure 12. Since discontinuing the oral medication, the patient has maintained an HbA1c level <6.5%.[86]

CONCLUSION

Diabetes is a huge and growing health challenge worldwide, especially in poorer countries. It's not just about blood sugar; it messes with your whole body, affecting many organs and how they work. As we've seen in this review, diabetes isn't a single disease. There's Type 1,

Type 2, gestational diabetes (during pregnancy), and other specific kinds, each with its own unique causes, risks, and treatment needs.One of the scariest things about diabetes is the serious problems it can cause, both in the short and long run. Over time, it can lead to heart disease, kidney damage, eye problems, nerve damage, and skin infections, which really hurt your quality of life. Plus, there are urgent situations like dangerously high or low blood sugar that can be life-threatening if not treated right away. All these complications put a massive strain not just on individuals, but on our healthcare systems and society as a whole.

To really get diabetes under control, we need a well-rounded approach. Medications like insulin and various pills are crucial for keeping blood sugar in check. But just as important are lifestyle changes: eating healthy, staying active, managing stress, keeping weight in check, and avoiding smoking and too much alcohol. Even traditional practices like Ayurveda, Unani, and Siddha can offer helpful support when used wisely alongside conventional treatments. Preventing diabetes, especially Type 2, is super important. This means finding people at risk early, educating the public, encouraging healthier diets, regular check-ups, and community-based programs. The stories in this review show that it's even possible to put diabetes into remission with disciplined lifestyle changes and timely medical care. This really highlights why ongoing patient education, support, and monitoring are so vital.In a nutshell, while diabetes presents big challenges, it's a condition we can manage and often prevent. Ongoing breakthroughs in medical research, better public awareness, and care that truly puts the patient first can dramatically improve outcomes and lessen the global impact of diabetes. The real key is a team effort, involving patients, doctors, policymakers, and the entire community working together.

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