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A COMPREHENSIVE GUIDE TO THE PATHOPHYSIOLOGY OF DIABETES MELLITUS & INNOVATIONS IN THE TREATMENT

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ABSTRACT: Diabetes mellitus is a chronic metabolic disorder characterized by high levels of glucose in blood due to non-secretion of insulin or insulin insensitivity. Diabetes mellitus can cause many complications, acute complications include non ketotic hyperosmolar coma and diabetic ketoacidosis. Different types of diabetes mellitus are available – Type 1 diabetes mellitus (hormone dependent diabetes) and Type 2 diabetes mellitus (non-insulin dependent polygenic disorder mellitus) are now recognized as serious global health problem, growing rapidly worldwide and taking its place one of the main theats to human health in the 21st century. In diabetes history gestational diabetes is the major and big problem, approximately 5 to 10 percent all pregnant women in the India is diagnosed as having gestational diabetes. The main indication of diabetes mellitus is a hyperglycemia in blood which due to in appropriate pancreatic insulin secretion or low insulin directed fostering to glucose by target cells. It is silent and affects millions of people in the world. It is estimated that in 2010 there was globally 300 million people suffering from the disease. This number is estimated to 500 million in the absence of better control or cure.

INTRODUCTION: In our daily life, we need energy to perform any task and carbohydrates, especially glucose, are required for energy production in the body. Here, blood acts as a medium to deliver glucose to all the different types of cells. When glucose enters a cell, insulin acts as a lock to permeate the cell membrane. A lack of insulin means not enough glucose can enter the cells from the circulating blood, causing blood glucose (or sugar) levels to rise. If this situation continues for days, months, or even years, a complex medical condition develops, and this condition is called diabetes [1].

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The term "diabetes" was coined by Aretaeus of Cappadocia (81-138 AD). It comes from the Greek word "diabynein," which literally means "passage" or "siphon," and refers to excessive urine production, one of the main symptoms of diabetes. In 1674, Thomas Willis added "meritus" to the name of the disease, which is Latin for "honey", referring to the sweet taste of the urine due to the presence of glucose [2, 3]. In ancient Indian Vedic medical texts, the disease was identified and classified as madhumeka or honey urine. Ancient Indians tested for diabetes by observing whether ants were attracted to a person's urine and called the disease "sweet urine disease [4]."

Diabetes Mellitus: A disorder of macromolecular metabolism characterized by an impairment of the body's ability to produce or respond to the endocrine system to maintain adequate levels of sugar (glucose) in the blood [5]. The disease can be a chronic condition that occurs when the glands can

no longer produce endocrine secretions or when the body cannot control its use of the endocrine secretions it does produce. The endocrine system can be an endocrine system created by a duct gland that acts as a kind of key to allow aldohexose from the foods we tend to eat to pass from the bloodstream into the body's cells to provide energy [6]. The international diabetes Federation (IDF) is an umbrella organization of over 230 national diabetes association in 170 countries and territories.

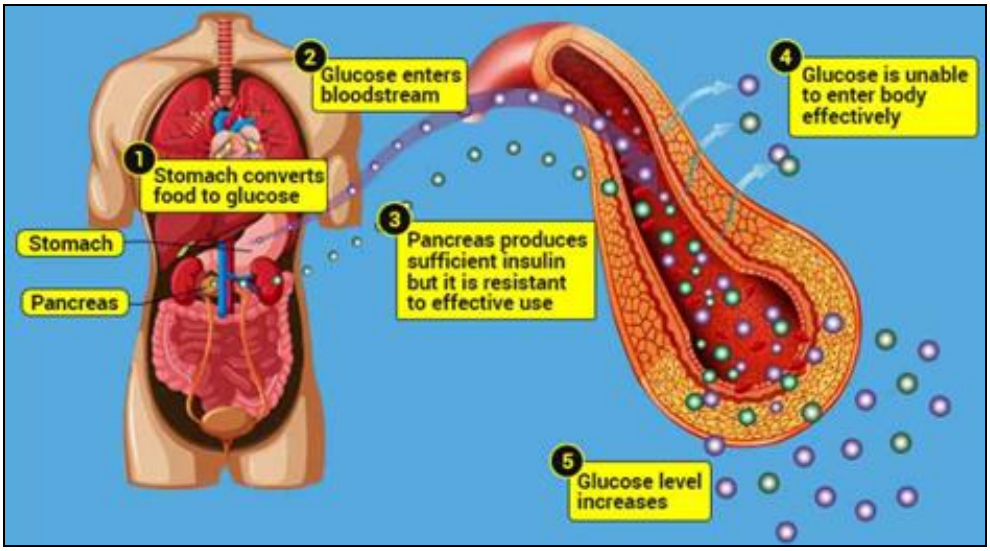

FIG. 1: DIABETES MELLITUS

The all-polymer products completely neutralize the aldo exosaux in the blood [7]. Endocrine systems use aldo exporters to enter cells. It moves sugar from the blood into cells for storage or use as energy. In polygenic disorders, the body either does not produce enough endocrine hormones or does not use the endocrine hormones it does produce effectively [8, 9]. If hyperglycemia is not treated with polygenic disorders, this can damage the nerves, eyes, kidneys and other organs. With around 200 million people with diabetes worldwide, it is one of the most common metabolic syndromes [10]. This gives rise to the desire to know the etiology of the disease and the factors that influence its development. Many infectious processes are involved in the development of diabetes. These range from reactive destruction of ductal beta cells with endocrine insufficiency to defects leading to endocrine resistance [11]. Endocrine dysfunction and symptoms of non-tissue origin reinforce the idea of abnormalities in macromolecular, lipid and supramolecular metabolism, leading to characteristic clinical variants of diabetes, mild and severe ductal complications and exaggerated risk of diabetes [12].

Disorders: Insufficient production of endocrine hormones (produced by ductal glands that lower blood glucose levels) or insufficient sensitivity of cells to the action of endocrine hormones. The ductal glands produce hormones but they don't function properly – a condition called endocrine resistance. To better understand polygenic diseases, it helps to learn more about how your body uses food to produce energy, a process known as metabolism your body is made up of billions of cells. To produce energy, cells need a very simple type of food: After you eat and drink, most of the food you eat is converted into light sugars called aldohexoses. Aldohexose provides the energy necessary to perform daily activities [13]. If the endocrine gland is almost or not at all, or if the endocrine system is resistant, excessive sugar will remain in the blood. People with polygenic disorders have higher than normal blood sugar levels. The WHO has ranked the Islamic Republic of Pakistan 7th in the list of polygenic disorder prevalence [14]. Recent prevalence studies indicate that approximately 4.5 million people suffer from the polygenic disease, whose symptoms include severe dry mouth, frequent urination, sweating, blurred vision, rapid weight loss, fatigue and slow-healing ulcers. Most patients with polygenic diseases suffer from dry mouth, polyphagia, and nephropathy [15]. Physiological conditions, that is, polygenic diseases, occur only in physiological conditions.

Changes in secretion affect the endocrine system, which leads to an ineffective endocrine product, which leads to an increase in the level of aldogesis and blood sugar that affect embryos [16, 17]. Rapid foaming was found in 38.95 % of Venezuela's sample, with a diabetic illness of 14.25 % and 40.7 % for the previous AIBET. Additionally, high blood pressure, high cholesterol, dysglycemia, and diabetes are more prevalent in women. In contrast, a WHO report estimated the prevalence of diabetes in the South American country to be 8.8%.

The International Federation of Polygenic Disorders (IFD) estimated the prevalence at 11.1% in a 2016 report. Increasing rates of obesity are likely to significantly increase the prevalence of diabetes-related complications. The growing number of people with diabetes and the complexity of their treatment may overwhelm existing healthcare systems. The need to improve management and intervention of polygenic diseases by leveraging recent discoveries at the individual and societal levels and disseminating life-saving findings into broader practice [18].

Types of Diabetes:

Type 1 Diabetes: Type 1 diabetes accounts for approximately 10% of diabetes cases and is characterized by the loss of insulin-producing beta cells from the islets of Langerhans in the pancreas, resulting in insulin deficiency. It was previously called juvenile onset diabetes mellitus (JD) or insulin-dependent diabetes mellitus (IDDM). However, a new classification based on etiology, independent of age or insulin dependence, further divides type 1 diabetes into two subtypes. It is characterized by autoimmune destruction of beta cells and usually leads to insulin deficiency, although type 1 diabetes is more common in patients under 30 years of age. But autoimmune destruction of β-cells can occur at any age, so the term JOD is obsolete. In fact, 5 to 10% of patients who develop diabetes after age 30 have type 1A diabetes. Insulin insufficiency and a propensity towards ketosis are its defining features; yet the patients' autoimmune markers are negative. Insulin replacement treatment is necessary to maintain life in people with type 1 diabetes.

Signs and Symbols of Type 1 Diabetes Mellitus:

1. Extreme hunger
2. Increased thirst
3. Unintentional weight loss
4. Frequent urination blurry
5. Vision tiredness

Pathogenesis of Type 1 Diabetes Mellitus: The pathogenesis of type 1A DM is immune mediated and has been extensively studied. While type 1B DM remains idiopathic.

Genetic Susceptibility: Type 1A diabetes involves the inheritance of several genes that determine susceptibility to the disease:

1. It has been observed in identical twins that if one twin has type 1A DM, there is about 50% chance of the second twin developing it, but not all.
2. About half the cases with genetic predisposition to type 1A DM have the susceptibility gene located in the human leukocyte antigen (HLA) region of chromosome 6 particularly HLADR3, HLADR4 and HLADQ locus. It appears that in HLA- associated susceptibility individual, β-cells acts as autoantigens and activates CD4+T lymphocytes, bringing about immune destruction of pancreatic β-cells.

Autoimmune Factors: Type 1A diabetes patients suffer from many immune disorders.

Islet cell antibodies against insulin and glutamic acid decarboxylase are present.

- The term "insulitis" refers to the presence of lymphocytic infiltration in and around the pancreatic islets.
- A healthy animal receives T lymphocytes from an ill animal, hence reinforcing the role of T cell-mediated autoimmunity.
- Destruction of the β-cell with no effect on other types of islet cells. T-cell-mediated cytotoxicity or apoptosis is the mechanism underlying this.
- Relationship between type 1A diabetes mellitus and other autoimmune disorders, including Addison's disease, Hashimoto's thyroiditis, Pernicious anemia, and Graves disease.

- Remission of type 1A diabetes mellitus brought on by immunosuppressive medication, such as cyclosporin A injections.

Environmental Factors: Environmental elements that play a role in the etiology of type 1A diabetes:

- Certain viral infections preceding the onset of disease e.g. mumps, measles, coxsackie B virus, cytomegalo virus and infectious mononucleosis.
- Type 1A diabetes mellitus is experimentally induced by particular substances, including pentamidine, streptozotocin, and alloxan.
- Seasonal and geographic variations in its occurrence point to a few shared environmental causes.
- Research is being done to determine whether early exposure to the proteins found in cow's milk can cause the autoimmune response that results in type 1A diabetes.

Type 2 Diabetes Mellitus: Previous nomenclature for type 2 diabetes included mature onset diabetes (MOD) or non-insulin dependent diabetes mellitus (NIDDM) of the obese and non-obese forms. Thus, older people are mostly affected by type 2 diabetes. But these days, it also affects fat teenage kids. Thus, it is inappropriate to use the term MOD. Not all cases of type 2 diabetes are entirely non-insulin dependent diabetic [19, 20, 21]. A significant portion of these patients additionally require insulin treatment to control their hyperglycemia. In type 2 diabetes, there is no detectable anti-β cell antibody, and blood insulin levels might be low, normal, or even high [22]. The bulk of the β-cell is either unchanged or slightly reduced.

Type 2 diabetes, which is characterized by insulin resistance and hyperglycemia, affects more than 90% of diabetic individuals. As the disease progresses, hyperglycemia is linked to long-term microvascular and macrovascular complications, including neuropathy, retinopathy, nephropathy, myocardial infarction, atherosclerosis, coronary artery disease, stroke, and lower limb amputation. Additionally, the quality of life of diabetic patients gradually decreases. These findings are supported by a number of epidemiological and clinical studies. Controlling blood glucose levels in the early stages of the illness is therefore essential [23, 24]. Moreover, a variety of additional patho-physiological disorders, including dyslipidemia, hypertension, hyperuricemia, increased plasminogen activator inhibitor type 1 (PAI-1), anomalies of the fibrinolytic system, and abdominal obesity, are all linked to this metabolic illness [25].

Signs and Symptoms of Type 2 Diabetes Mellitus:

1. Increased hunger
2. Increased thirst
3. Increased urination
4. Blurry vision
5. Tiredness
6. Sores that are slow to heal

Pathogenesis of Type 2 Diabetes Mellitus: Numerous variables have been linked to the pathophysiology of type 2 diabetes. However, there is no connection between autoimmune symptoms and HLA affiliation.

Genetic Factors: Compared to type 1 DM, type 2 DM has a stronger genetic basis. The most significant determinant in the development of type 2 diabetes is multifactorial inheritance, despite the lack of a clear and consistent gene. If one identical twin develops diabetes, the other has an 80% probability of also having the condition. A person is more likely to get diabetes if they have one parent with type 2 DM. However, if both parents have type 2 diabetes, the child's risk increases to 40%.

Constitutional Factors: Certain environmental factors such as obesity, hypertension and level of physical activity play contributory role and modulate the phenotyping of the disease.

Insulin Resistance: Insulin resistance, the reduced ability of insulin to act effectively on target tissues (especially the liver, muscle and fat), is one of the most important metabolic features of type 2 diabetes and is caused by a combination of genetic susceptibility and obesity. In obese subjects, insulin levels are usually increased to maintain normal

glucose tolerance, because 24-h basal and total insulin secretion rates are 3–4 times higher in insulin-resistant obese subjects than in lean control subjects. The hyperinsulinemia associated with insulin resistance results from a combination of increased insulin secretion and a decreased rate of insulin clearance. However, insulin resistance impairs glucose utilization by insulin-sensitive tissues and increases glucose production (or synthesis) by the liver. Both effects contribute to hyperglycemia. The exact molecular defect responsible for insulin resistance in type 2 diabetes has not yet been fully identified.

Insulin Resistance Syndrome: A collection of interrelated risk factors for cardiovascular disease (CVD) and diabetes. Thus, this cluster has been given various new names, such as metabolic syndrome, metabolic syndrome X, cardiovascular metabolic syndrome, chronic cardiovascular risk factor cluster syndrome, hypermetabolic syndrome, metabolic dysregulation syndrome, cardiometabolic syndrome, and the "deadly quartet," as well as insulin resistance syndrome. The insulin resistance syndrome is containing a number of metabolic and clinical abnormalities such as obesity, atherosclerosis, coronary artery disease, vascular endothelial dysfunction, hyperinsulinemia relative to glucose levels (at least initially in type 2 DM), hyperuricemia (raised serum uric acid concentrations), hypercoagulability (increased levels of PAI-1 and fibrinogen) hypertension (raised blood pressure) and dyslipidemia [Increased concentrations of both very low-density lipoprotein (VLDL)-triglycerides (TG) and small, dense low-density lipoprotein (LDL)-cholesterol; decreased concentrations of high-density lipoprotein (HDL)-cholesterol.

Gestational Diabetes: Pregnant women often acquire diabetes. Pregnancy produces a lot of hormones, and these hormones might reduce the body's capacity to utilize insulin, which can lead to insulin resistance. Women who develop diabetes mellitus during pregnancy as well as those who have undetected asymptomatic type 2 diabetes mellitus throughout pregnancy are both at risk for gestational diabetes mellitus. Clinically noteworthy is the fact that GDM is associated with severe fetal and maternal morbidity. In the history of diabetes, gestational diabetes is the main cause of concern. In India, 5–10% of pregnant women receive a diagnosis of gestational diabetes. Anomalies related to the fibrinolytic system and obesity in the tummy [26, 27].

Signs and Symptoms of Gestational Diabetes:

1. Extreme fatigue
2. Blurry vision
3. Increased hunger
4. Increased thirst
5. Frequent urination
6. Sores that don’t heal

Gestational Diabetes Differs for Mother: Happens when a child's or young adult's pancreas produces little or no insulin; this condition typically manifests before the age of 20. Individuals with type 1 diabetes are required to inject insulin daily [32]. Type I diabetes, often known as insulin-dependent diabetes, affects about 10% of all diabetics. Type II diabetes (previously called adult-onset diabetes or non-insulin-dependent diabetes) is also characterized by hyperglycemia, but these patients are often obese and usually lack the classic symptoms (fatigue, thirst, frequent urination, and sudden urination). Type 2 diabetes usually occurs in people over the age of 40. Many of these people can control their blood sugar levels by following a strict diet and exercise program, losing weight, or taking oral medications. 3 Some, but not all, require insulin. People with type 2 diabetes account for about 90% of all people with diabetes.

Gestational Diabetes affect Pregnancy: Gestational diabetes can have preventable and controllable complications. As soon as gestational diabetes is diagnosed, monitoring blood sugar levels closely is essential to prevention. Rest assured, there are several conditions that gestational diabetes often does not cause. Gestational diabetes, in contrast to Type I diabetes, usually does not result in birth abnormalities.

Diagnosis: It is recommended to perform a GDM risk assessment during the initial prenatal appointment. As soon as practical, women who exhibit clinical traits associated with a high risk of GDM (marked obesity, a personal history of GDM, glycosuria, or a strong family history of diabetes)

should have a glucose test (see below). At 24 to 28 weeks of gestation, they should have another screening if GDM is not discovered at that first screening. Testing should begin for women who are at average risk between weeks 24 and 28 of pregnancy. 19 No glucose test is necessary for low-risk status; nevertheless, this group is only available to women who satisfy all of the following requirements.

1. Age <25 years
2. Weight normal before pregnancy
3. Member of an ethnic group with a low prevalence of GDM
4. No known diabetes in first-degree relatives
5. No history of abnormal glucose tolerance
6. No history of poor obstetric outcome

Diabetes in India: According to recent estimates, approximately 285 million people worldwide (6.6%) in the 20–79 year age group will have diabetes in 2010 and by 2030, 438 million people (7.8%) of the adult population, is expected to have diabetes. India leads the world with largest number of diabetic subjects earning the dubious distinction of being termed the "diabetes capital of the world". According to the Diabetes Atlas 2006 published by the International Diabetes Federation, the number of people with diabetes in India currently around 40.9 million is expected to rise to 69.9 million by 2025 unless urgent preventive steps are taken.

The "Asian Indian Phenotype" refers to certain unique clinical and biochemical abnormalities in Indians which include increased insulin resistance, greater abdominal adiposity i.e., higher waist circumference despite lower body mass index, lower adiponectin and higher highly sensitive C-reactive protein levels. Higher prevalence of diabetes mellitus often results from in changes in dietary patterns and decreased physical activity in the urban population [28]. Diabetes is fast gaining the status of a potential epidemic in India with more than 62 million diabetic individuals currently diagnosed with the disease [29, 30]. In 2000, India (31.7 million) topped the world with the highest number of people with diabetes mellitus followed by China (20.8 million) with the United States (17.7 million) in second and third place respectively. According to Wild *et al.* the prevalence of diabetes is predicted to double globally from 171 million in 2000 to 366 million in 2030 with a maximum increase in India. It is predicted that by 2030 diabetes mellitus may afflict up to 79.4 million individuals in India, while China (42.3 million) and the United States (30.3 million) will also see significant increases in those affected by the disease [31].

Global Prevalence of Diabetes Mellitus: The global increase in the prevalence of DM is due to population growth, aging, urbanisation and an increase of obesity and physical inactivity. The IDF estimated that the number of people living with diabetes has soared to 366 million, representing 8.3% of the global adult population. This number is projected to increase to 552 million people by 2030, or 9.9% of adults. Literature review reported that, the top ten countries in the world, in terms of the number of peoples with diabetes, for 2010 and 2030 **Table 1.** Developing countries like India, already top of the diabetic league [32, 33]. It is estimated that every fifth person with diabetes will be an Indian. Due to these sheer numbers, the economic burden due to diabetes in India is amongst the highest in the world. The real burden of the disease is however due to its associated complications, which lead to increased morbidity and mortality [34].

TABLE 1: TOP 10 COUNTRIES FOR ESTIMATED NUMBERS OF ADULTS WITH DIABETES

Rank	Country	2010 (millions)	Country	2030 (millions)
1.	India	50.8	India	87.0
2.	China	43.2	China	62.6
3.	U.S.	26.8	U.S.	36.6
4.	Russian Federation	9.6	Pakistan	13.8
5.	Brazil	7.6	Brazil	12.7
6.	Germany	7.5	Indonesia	12.0
7.	Pakistan	7.1	Mexico	11.9
8.	Japan	7.1	Bangladesh	10.4
9.	Indonesia	7.0	Russian Federation	10.3
10.	Mexico	6.8	Egypt	8.6

Treatment:

Insulin: Insulin, discovered in 1921 by Banting and best, was purified in 1926 and its structure fully determined in 1956 by Sanger. Produced by β-cells in the islets of Langerhans, insulin is synthesized from proinsulin, a 110-amino acid precursor. Proinsulin is processed in the Golgi apparatus into insulin and C-peptide, which are stored in granules and secreted together. Insulin is a 51-amino acid polypeptide with two chains linked by disulfide bonds. Its secretion is tightly regulated by nutrients, hormones, and neurotransmitters. Insulin acts by binding to cell receptors, activating tyrosine kinase, and triggering metabolic pathways that regulate glucose transport, enzyme activity, and cell growth [35].

Effects of Insulin: Table 2 illustrates the significant impact that insulin has on glut 1–5, a group of transport molecules that help carry glucose across cell membranes. Additionally, insulin is the primary hormone regulating intermediate metabolism, affecting the muscle, fat, and liver **Table 3.**

TABLE 2: INSULIN EFFECTS ON VARIOUS GLUCOSE TRANSPORTERS

Transporter	Glucose Km* (mmol/L)	Tissues
GLUT 1	1-2	All tissues, especially red cells and brain
GLUT 2	15-20	B-cells of pancreas, liver, kidney and gut
GLUT 3	<1	Brain, kidney, placenta and tissues
GLUT 4	≈5	Muscle and adipose tissue
GLUT 5	1-2	Gut and kidney

*The Km value an indicator of the affinity of the transporter protein for glucose molecules.

TABLE 3: EFFECTS OF INSULIN ON CARBOHYDRATE, FAT AND PROTEIN METABOLISM

Metabolism	Liver cells	Fat cells	Muscle
Carbohydrate	↓ Gluconeogenesis ↓Glycogenolysis ↑Glycolysis ↑Glycogenesis	↑ Glucose uptake ↑ Glycerol synthesis	↑ Glucose uptake ↑ Glycolysis ↑ Glycogenesis
Fat	↑Lipogenesis ↓ Lipolysis	↑ Synthesis of triglycerides ↑ Fatty acid synthesis ↓ Lipolysis	-
Protein	↓ Protein breakdown	-	↑ Amino acid uptake ↑ Protein synthesis

Up (↑) arrow indicates increases and down (↓) arrow indicates decreases.

TABLE 4: DIABETES TREATMENT DRUGS AND THEIR DOSAGE FORM AND WORKING

Types of drugs	Dosage form	Uses	Working	Example
Alpha-Glucosidase	Tablet	Type 2 Diabetes mellitus	Slow your body's breakdown of sugars and starchy foods	Acarbose(precose)
Biguanides	Tablet, Fast dissolving tablet, Extended release tablets	Type 2 Diabetes mellitus	Reduce the amount of glucose your liver makes and control the blood glucose level	Metformin (Glucophage)
DPP-4 inhibitors	Tablet, Fast dissolving tablets	Type 2 Diabetes mellitus	Improve your blood sugar without making it drop too low	Linagliptin (Tradjenta), saxagliptin (Onglyza), &sitagliptin (Januvia)
Glucagon-like peptides	Tablet, Mouth dissolving tablets, Injectable	Type 2 Diabetes mellitus	To help the produces sufficient amount of insulin by beta cell of pancreas	Dulaglutide (Trulicity), exenatide (Byetta), and liraglutide (Victoza)
Sulfonylureas	Fast dissolving tablets	Type 2 Diabetes mellitus	Stimulate your pancreas to release more insulin	Glyburide (DiaBeta, Glynase), glipizide (Glucotrol), and glimepiride (Amaryl)
Thiazolidinediones	Floating tablets	Type 2 Diabetes mellitus	Increase the amount of insulin those reduces the blood glucose at the normal range	Pioglitazone (Actos) and rosiglitazone (Avandia)
Meglitinides	Dispersible tablet, Sustained release	Type 2 Diabetes mellitus	Stimulate your pancreas to release more insulin which is	Nate glinide (Starlix) & Repaglinide (Prandin)

	matrix tablets		control the blood glucose level in blood	
Sod-glucose cotransport-2 inhibitors	Film coated conventional tablet	Type 2 Diabetes mellitus	Release more glucose into the urine	Canagliflozin (Invokana) and dapagliflozin (Farxiga) [36,37]

TABLE 5: TREATMENT OF TYPE 1 & TYPE 2 DIABETES MELLITUS COMBINATION DRUGS

Active Pharmaceutical Ingredients	Drugs	Dosage Form	Uses	Working	Example
Sulfonylureas + Biguanides	Glibenclamide + Metformin	Tablet	Type 2 Diabetes	Reduce the amount of glucose your liver makes and control the blood glucose leve & Stimulate your pancreas to release more insulin	Vriglib-m
Sulfonylureas + Biguanides	Gliclazide + Metformin	Tablet	Type 1 Diabetes	Reduce the amount of glucose your liver makes and control the blood glucose level	Glykind-m
Sulfonylureas + Biguanides	Glimepiride + Metformin	Tablet	Type 2 Diabetes	improves blood glucose levels in adults	Glimet-2 [37]

Novel Approaches:

TABLE 6: NOVEL APPROACHES FOR THE TREATMENT OF TYPE I & II DIABETES

Approach/drug	Studies/development stage
Antigen-specific: Insulin (parental, oral, mucosal) Insulin β chain Proinsulin (peptide, vaccine) Glutamic acid decarboxylase 65 (Diamyd)	Efficacy studies, phase I & II Animal studies, phase I Animal studies, phase I Phase II
Antigen – nonspecific: Anti-CD20 monoclonal antibody (Rituximab) Anti-CD3 monoclonal antibody (MoAB) Anti-thymocyte globulin (ATG) DiaPep277 (HsP60 peptide)	Animal studies, phase II Phase I/II Animal studies, phase I Phase II
Non - antigen – specific: Cyclosporin Nicotinamide (± combinations) Vitamin D3/Fish oil Hydrolyzed cow's milk Dietary gluten elimination	Various Pilot, efficacy studies Pilot ongoing Phase I, ongoing Pilot
Combinations: Anti-CD3 MoAB + insulin peptide Anti-CD3 MoAB + exenatide Mycophenolate mofetil + anti-CD25 MoAB (Daclizumab) Rapamycin (Sirolimus) + interleukin-10 Rapamycin (Sirolimus) + interleukin-2	Animal studies, phase II planned Animal studies, phase II planned Open-label randomized trial, phase II ongoing Animal studies Animal studies, phase II planned
Stem cell therapy: Pilot: Autologous umbilical cord Autologous bone marrow-derived stem cells	Pilot, Pilot [38]

Prevention: Due to its autoimmune nature, type 1 diabetes cannot be prevented; instead, it must be managed with medicine (such as an oral hypoglycemic agent).

By keeping a normal body weight, engaging in physical activity, and adhering to a nutritious diet, type 2 diabetes should be avoided or postponed. Diabetes can also be prevented by consuming less red meat and other sources of saturated fat, as well as by limiting sugary drinks.

[70] Diabetes is treated with medication that lowers blood sugar levels. Diabetes mellitus is treated with oral hypoglycemic agents belonging to various classes. The first drug of choice for diabetics is metformin, which often lowers insulin resistance and hepatic glucose output [39, 40, 41].

CONCLUSION: Diabetes mellitus is the epidemic of the century, and it would only expand if early diagnosis techniques were not developed. The several forms of diabetes and the best diagnostic techniques and standards for identifying diabetes and prediabetes are the main topics of this review.

It appears that several genes play a role in the development of diabetes, making it a complex disease. Identify the genetic causes of diabetes with enough precision to perhaps offer a useful tool for better diagnosis, treatment, and results from genetic counseling. Delaying or avoiding these extremely stressful outcomes will also benefit from our increasing understanding of the link between medical genetics and the long-term consequences of diabetes.

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