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Review Article *Medical Science*

A REVIEW ON DIABETES

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ABSTRACT

Diabetes mellitus is a group of physiological dysfunctions characterized by hyperglycaemia resulting directly from insulin resistance, inadequate insulin secretion, or excessive glucagon secretion. Type 1 diabetes (T1D) is an autoimmune disorder leading to the destruction of pancreatic beta-cells. Type 2 diabetes (T2D), which is much more common, is primarily a problem of progressively impaired glucose regulation due to a combination of dysfunctional pancreatic beta cells and insulin resistance. Diabetes is also other types which are explained in this article and also pathophysiology of diabetes mellitus and their treatment.

Keywords: Diabetes, Types of Diabetes, Maturity onset diabetes in young, Genetic syndromes, risk factors, natural treatment.

INTRODUCTION

Diabetes with its ever-increasing global prevalence has emerged as one of the most important and challenging health issues confronting the human population of the present world. The increase in the prevalence of diabetes in most regions across the globe has been parallel to the rapid economic development, leading to urbanization and adoption of modern lifestyle habits. In the year 2019, the number of adult people aged 20–79 years with diabetes has been estimated to be about 463 million, which represents 9.3% of the total world adult population.

By the year 2030, this number has been estimated to increase to 578 million, representing 10.2% of the total world adult population and further increase to 700 million by the year 2045, which represents 10.9% of the total world adult population. In the year 2019, the prevalence of diabetes among men and women has been estimated to be 9.6% and 9.0%, respectively, of the total respective gender world population. Furthermore, in the year 2019, approximately 4.2 million adult people aged 20–99 years died due to diabetes, and its associated complications and health expenditure on diabetes estimated to at least 760 billion USD, which represents 10% of the total spending on adults. Diabetes during pregnancy has been estimated to have affected more than 20 million live births (1 in 6 live births) in the year 2019.

Types of Diabetes [1,3]

Diabetes is a complicated condition which is in many different forms. In addition to the more common types of diabetes - type 1, type 2 and gestational diabetes, and other types of diabetes.

About 5% of people have these other types of diabetes. These include different types of monogenic diabetes, cystic fibrosis-related diabetes, and diabetes caused by rare syndromes. Certain medications such as steroids and antipsychotics could lead to other types of diabetes, as well as surgery or hormonal imbalances, many people are misdiagnosed leading to delays in getting the right treatment.

Type 1

Type 1 diabetes is where blood glucose (sugar) level is too high because body can't make a hormone called insulin. This happens because body attacks the cells in the pancreas that make the insulin, to can't produce any at all. With type 1 diabetes, body still breaks down the carbohydrate from food and drink and turns it into glucose. But when the glucose enters the bloodstream, there's no insulin to allow it

into body's cells. More and more glucose then builds up in the bloodstream, leading to high blood sugar levels.

Type 2

With type 2 diabetes the insulin in pancreas makes can't work properly, or pancreas can't make enough insulin. This means blood glucose (sugar) levels keep rising. Around 90% of people with diabetes have type 2. It is serious condition and can be lifelong.

Having type 2 diabetes without treatment means that high sugar levels in your blood can seriously damage parts of your body, including eyes, heart and feet. These are called the complications of diabetes. But with the right treatment and care, you can live well with type 2 diabetes and reduce the risk of developing them.

Type 3c diabetes

Type 3c diabetes is a type of diabetes that develops when another disease causes damage to the pancreas. The conditions related to type 3c are pancreatic cancer, pancreatitis, cystic fibrosis or haemochromatosis. It can also develop type 3c if they have part or all of the pancreas removed because of other damage.

Gestational diabetes

Gestational diabetes is diabetes that can develop during pregnancy. It affects women who haven't been affected by diabetes before. It means patients have high blood sugar and need to take extra care. This will include eating well and keeping active. It usually goes away again after giving birth. It is usually diagnosed from a blood test 24 to 28 weeks into pregnancy. During early pregnancy, both the fasting and post-prandial blood glucose levels are usually lower than normal but the blood glucose levels increase during the third trimester of pregnancy, and in cases where this blood glucose level reaches the diabetic levels, the condition is described as GDM. More than 90% of all the cases of diabetes and its complications that occur during pregnancy can be attributed to GDM. GDM occurs more frequently in certain racial or ethnic groups than others and this influence of ethnicity on risk of GDM is very important and has long been established. The risk of GDM increases with age, obesity, previous pregnancy with large babies, and any previous history of impaired glucose tolerance or GDM. Furthermore, GDM has been associated with an increased lifetime risk of developing T2DM.

Maturity onset diabetes of the young (MODY)

MODY is a rare form of diabetes which is different from both type 1 and type 2 diabetes, and runs strongly in families. MODY is caused by a mutation in a single gene. If a parent has this gene mutation, any child they have, has a 50 per cent chance of inheriting it from them. If a child does inherit the mutation, they will generally go on to develop MODY before they're 25, whatever their weight, lifestyle, ethnic group etc. Genetic studies have defined a number of subtypes of MODY. Mutations in the genes encoding hepatic nuclear factor 4 (HNF4), glucokinase (GCK), hepatic nuclear factor 1 alpha and 1 beta (commonly known as HNF1A and HNF1B, but official symbols are TCF1 and TCF2, respectively), insulin promoter factor 1 (IPF-1), and NEUROD1 are the cause of the six known forms of MODY

MODY1

(Caused by a Mutation in Transcription Factor HNF4A). The HNF4A gene encodes a transcription factor that is found in the liver and pancreas. HNF4A is found in a region of chromosome 20 that is linked with type 2 diabetes, and mutations of this gene cause a rare form of autosomal dominant diabetes (MODY1).

Pathophysiology of MODY1

Hepatocyte nuclear factors (HNFs) are a heterogeneous class of evolutionarily conserved transcription factors that are required for cellular differentiation and metabolism. HNF4A is an orphan receptor; the ligand(s) that binds to this receptor is unknown. A BLAST search using human HNF4A as a query finds proteins in 47 different species, which are all multicellular species (metazoans). However, potential true homologous genes have thus far been identified in only three species: the mouse, rat, and the nematode *Caenorhabditis elegan*. The HNF4A gene maps to chromosome 20. It has 11 exons (coding regions) that span over 30,000 bases. There are at least three different transcript variants of this gene, which encode three different protein isoforms (a, b, and c). The longest mRNA transcript, NM_000457, encodes the longest HNF4A protein (isoform b), containing over 450 amino acids.

MODY2

(Caused by a Mutation in the Enzyme Glucokinase). Glucokinase, encoded by the GCK gene, catalyses the first step of glucose metabolism in the liver. It may also be an important "glucose sensor" in the pancreas. Mutant glucokinase causes a rare autosomal dominant form of diabetes (MODY2) and may also play a role in type 2 diabetes.

Pathophysiology of MODY2

The hexokinase family consists of several enzymes that are all evolutionarily related. In vertebrates, there are four hexokinases named I to IV. Glucokinase is a distinct member of this family with a different kinetic profile.

A BLAST search using human GCK as a query finds proteins in 46 different species, which range from metazoan (multicellular organisms), fungi, plants, and other eukaryotes. Potential true homologous genes have thus far been identified in the mouse, rat, fly, mosquito, nematode worm, and the plant "mouse ear cress".

The GCK gene maps to chromosome 7. It has 12 exons (coding regions) that span about 46,000 bases. There are three GCK transcript variants that differ in their first exons and their expression is tissue specific. One isoform predominates in the pancreatic beta cells; the other two isoforms are found in the liver.

MODY3

(Caused by a Mutation in Transcription Factor TCF1). The TCF1 gene encodes a transcription factor that is found in the liver and pancreas and is important in the development of these and other organs. A mutation of TCF1 causes a rare form of autosomal dominant diabetes (MODY3).

Pathophysiology of MODY3

The TCF1 gene is a member of the homeobox family of genes. In the early 1980s, important developmental genes were identified in the fruit fly. These master control genes lay out the body plan, and if they are mutated, the development of the fly is disrupted. These genes were called homeobox genes after "homeotic", the description for a shift in structural development. Homeobox genes contain a conserved DNA motif of 180 base pairs that encodes a domain (a homeodomain) of about 60 amino acids. Homeodomains bind to certain regions of DNA and regulate the transcription of many other genes, several of which in turn play a key role in the control of embryogenesis.

MODY4

(Caused by a Mutation in Transcription Factor IPF1). Insulin promotor factor-1 (IPF1) is responsible for the development of the pancreas in the embryo and is also a key regulator of insulin gene expression. Mutations of IPF1 cause a rare form of autosomal dominant diabetes (MODY4) and may play a role in susceptibility to type 2 diabetes.

Pathophysiology of MODY4

The IPF1 gene is a member of the homeobox family of genes. In the early 1980s, important developmental genes were identified in the fruit fly. These master control genes lay out the body plan, and if they are mutated, the development of the fly is disrupted. These genes were called homeobox genes after "homeotic", the description for a shift in structural development. Homeobox genes such as IPF1 are important in determining cell fates; in the embryo, the presence of IPF1 ensures that pancreatic precursor cells develop into their destined mature pancreatic cells. Homeobox genes contain a conserved DNA motif of 180 base pairs that encodes a domain (a homeodomain) of about 60 amino acids. Homeodomains bind to certain regions of DNA and regulate the transcription of many other genes, several of which in turn play a key role in the control of embryogenesis

MODY5

(Caused by a Mutation in Transcription Factor TCF2). TCF2 encodes a transcription factor that is found in the liver and pancreas and is important in the development of these and other organs. A mutation of TCF2 causes a rare form of autosomal dominant diabetes (MODY5).

Pathophysiology of MODY5

The TCF2 gene is a member of the homeobox family of genes. In the early 1980s, important developmental genes were identified in the fruit fly. These master control genes lay out the body plan, and if they are mutated, the development of the fly is disrupted. These genes were called homeobox genes after "homeotic", the description for a shift in structural development. In the embryo, the presence of TCF2 is needed for the correct development of the kidneys and genital system. Homeobox genes contain a conserved DNA motif of 180 base pairs that encodes a domain (a homeodomain) of about 60 amino acids. Homeodomains bind to certain regions of DNA and regulate the transcription of many other genes, several of which in turn play a key role in the control of embryogenesis.

MODY6

(Caused by a Mutation in Transcription Factor NEUROD1). The transcription factor NEUROD1 can directly activate the transcription of the insulin gene. It is also needed in the development of the pancreas beta cells and the nervous system. Mutations of this gene cause MODY6, the most recently discovered form of autosomal dominant diabetes, and may also play a role in type 1 and type 2 diabetes.

Pathophysiology of MODY6

NEUROD1 belongs to a group of transcription factors called basic helix-loop-helix (bHLH) proteins. The bHLH proteins contain a conserved sequence of amino acids that binds to DNA. This sequence is also known as a DNA-binding motif, and the HLH motif consists of a short alpha helix connected by a flexible loop to a second, longer alpha helix. bHLH proteins are classified into two groups based on how they bind to DNA and in what tissues they are found. Class A members tend to be expressed in all tissues, whereas class B members, such as NEUROD1, are found only in specific tissues, mainly in the nervous system and the pancreas. bHLH proteins can function as transcription factors only when two bHLH monomers complex to form a dimer. The two-helix structure of HLH binds both to DNA and to the HLH motif of a second HLH protein. The second HLH protein can be the same (resulting in a homodimer) or different (resulting in a heterodimer), and alpha helices extending from the dimerization interface make specific contacts with DNA.

The NEUROD1 gene maps to chromosome 2. It has two exons (coding regions) that span about 4,860 bases; only exon 2 is translated. The gene encodes a protein of 356 amino acids.

Others types of MODY

The other types of MODY in this category include MODY7 (KLF11 MODY), which results from the mutations in Kruppel-like factor 11 (KLF11) gene located on chromosome 2p25 and MODY8 (CEL MODY), which arises from the mutations in carboxyl ester lipase (CEL) gene located on chromosome 9q34. This category also includes MODY9 (PAX4 MODY), caused due to the mutations in PAX family transcription factor, Paired box gene 4 (PAX4) gene located on chromosome 7q32 and MODY10 (INS MODY), which results from the mutations in the INS located on chromosome 11p15 also, MODY11 (BLK MODY), which arises due to the mutations in the human homolog of a B-lymphocyte-specific protein tyrosine kinase (BLK) gene located on chromosome 8p23.1.

Furthermore, there is MODY12 (ABCC8-MODY), which results from the mutations in ATP-binding cassette transporter subfamily C member 8 (ABCC8) gene located on chromosome 11p15 and ABCC8 which encodes sulfonylurea receptor-1 (SUR1) protein, a subunit of ATP-sensitive potassium (KATP) channel. MODY12 is responsive to sulfonylureas.

The remaining types include MODY13 (KCNJ11-MODY) and MODY14 (APPL1-MODY). MODY13 (KCNJ11-MODY) is caused due to the mutations in potassium inwardly rectifying channel subfamily J member 11 (KCNJ11) gene located on chromosome 11p15.1 which encodes β-cell inward rectifier, BIR (inwardly rectifying potassium channel Kir6.2), a subunit of ATP-sensitive potassium (KATP) channel. MODY14 (APPL1-MODY)

results from the mutations in Adaptor Protein, Phosphotyrosine Interacting with PH Domain and Leucine Zipper 1 (APPL1) or DCC-interacting protein 13-α (DIP13-α) gene located on chromosome 3p14.3

Neonatal diabetes

Neonatal diabetes is a form of diabetes that is diagnosed under the age of six months. It's a different type of diabetes than the more common type 1 diabetes as it's not an autoimmune condition (where the body has destroyed its insulin producing cells).

Wolfram Syndrome

Wolfram Syndrome is a rare genetic disorder which is also known as DIDMOAD syndrome after its four most common features (Diabetes Insipidus, Diabetes Mellitus, Optic Atrophy and Deafness)

Alstrom Syndrome

Alstrom Syndrome is a rare genetically inherited syndrome which has a number of common features.

Latent autoimmune diabetes in adults (LADA)

LADA is a type of diabetes which seems to straddle type 1 and type 2 diabetes. It is more like type 1, and other are more like type 2. That's why some people call it type 1.5 diabetes or type 1 ½ diabetes. It's not actually classified as a separate type of diabetes, but there's some medical research going on to try and pinpoint exactly what makes it different from type 1 and type 2 diabetes

Steroid-induced diabetes

Some people who take steroids can develop diabetes. This is known as steroid-induced diabetes, and is more common in people who are at higher risk of type 2 diabetes.

Cystic fibrosis diabetes

Cystic fibrosis diabetes is the most common type of diabetes in people with cystic fibrosis. Although it has both type 1 and type 2, it is a different condition.

Lipoatrophic Diabetes

Lipoatrophy is the atrophy of fat tissue. In the syndrome Berardinelli-Seip, lipoatrophy is so severe that from birth adipose tissue is almost absent. From early infancy severe insulin resistance causes diabetes. Other features include acanthosis nigricans, increased production of androgen hormones, an enlarged liver, and increased muscle mass. Berardinelli-Seip Congenital Lipodystrophy syndrome in OMIM. At least two mutations on different chromosomes have been identified as a cause of Berardinelli syndrome, mutations in AGPAT2 on chromosome 9 and mutations in BSCL2 mutation on chromosome 11. In many cases, disruption of the structure and the function of the insulin receptor cannot be found. For this reason, it is assumed that the problem lies at the post-receptor level, involving signal transduction.

Chemical or Drug induced Diabetes

Many medications can impair insulin secretion. Such drugs not directly cause diabetes but precipitate diabetes in individuals with pre-existing insulin resistance and deficiency. In addition, certain hormones, when given as a therapy, can impair the action of insulin, e.g., glucocorticoids, thyroid hormone. Although rare, particular toxins such as rat poison and specific drugs can permanently destroy the beta cells of the pancreas. This results in the abrupt onset of diabetes that requires insulin treatment.

Infections

A genetic predisposition to type 1 diabetes has been well established. However, many lines of evidence also point to the existence of environmental risk factors that may act as the trigger for the autoimmune attack on the pancreas. Viruses have been suspected to contribute to the onset of type 1 diabetes because new cases of diabetes occur more frequently at certain times of the year. More recently, virus-specific IgM antibodies have been isolated from patients with new-onset diabetes, and pancreatic extracts from patients who died from new-onset diabetes cause diabetes in animals by the destruction of beta cells.

Several viruses have been associated with inducing certain cases of diabetes and include the following:

- rubella virus
- Coxsackie B virus
- mumps virus
- cytomegalovirus

Causes of Type 1 DM [4]

Environmental and Genetic Causes

The environmental trigger is an autoimmune phenomenon (i.e., a condition where immune/defensive system recognizes body's own healthy cells as being foreign to the body and starts attacking these healthy cells) via producing autoantibodies.

Probably, this autoimmune reaction in type 1 DM is the result of a viral trigger, most commonly the coxsackievirus B (CVB).

Studies reveal that when women encounter this infection during pregnancy, their children develop autoantibodies to the β-cells of the pancreas. Since these cells secrete insulin that tends to lower the blood glucose levels, the autoantibody-induced destruction of β-cells ends up in early-onset DM (also called as juvenile or childhood-onset DM).

This viral-provoked damage to the cells of pancreas specifically occurs in genetically susceptible children.

Causes of Type2 DM

Type 2 DM also occurs because of an interaction of genetic and environmental factors, the environmental causes differ in that it has no viral association.

Genetic factors

Family history is established as a cause for type 2 DM, as opposed to type 1 DM. The estimated risk of developing diabetes is 70% when both parents are diabetic. The probability increases to about 3 times with a first-degree diabetic relative.

Additionally, if an identical twin has diabetes, the risk is about 70%.

Environmental Factors

Chronic Inflammation, Obesity, and Insulin Resistance

Type 2 DM has a link to obesity, which decreases the synthesis of the insulin receptor.

Hence, insulin cannot bind to its receptor to exert its effects, called as insulin resistance in the medical world.

It is, however, important to note that it is not merely insulin resistance (IR) that is a prominent feature in type 2 DM, impaired beta-cell function, and insulin secretion is as essential as IR in the progression to T2D.

Studies show that the genes that confer the risk for obesity also increase the risk for type 2 DM.

As a matter of fact, not all obese persons develop T2D. Hence, studies demonstrate various mechanisms via which obesity causes type 2 DM. For instance, there appears to be a relationship between adipokine dysregulation (a cell-signalling protein associated with obesity) and type 2 DM. Obese people who have this type of genetic variation will acquire diabetes.

Symptoms of diabetes [4][5]:

- increased thirst and urination
- increased hunger
- fatigue
- blurred vision
- numbness or tingling in the feet or hands
- sores that do not heal
- unexplained weight loss
- Have very dry skin
- Have sores that heal slowly
- Have more infections than usual

Symptoms of type 1 diabetes can start fastly, within a week. Symptoms of type 2 diabetes often develop slowly over the course of several years and can be so mild that it might not even notice them. Many people with type 2 diabetes have no symptoms. Some people do not find out they have the disease until they have diabetes-related health problems, such as blurred vision or heart trouble.

Symptoms in men

In addition to the general symptoms of diabetes, men with diabetes may have a decreased sex drive, erectile dysfunction (ED), and poor muscle strength.

Symptoms in women

Women with diabetes can also have symptoms such as urinary tract infections, yeast infections, and dry, itchy skin**.**

Gestational diabetes symptoms

Most women with gestational diabetes don't have any symptoms. The condition is often detected during a routine blood sugar test or oral glucose tolerance test that is usually performed between the 24th and 28th weeks of gestation.

In rare cases, a woman with gestational diabetes will also experience increased thirst or urination.

Some symptoms appear Suddenly, they are

In Individuals with type 1 diabetes, the onset of symptoms can be very sudden, while in type 2 diabetes, they tend to come about more gradually, and sometimes there are no signs at all. Symptoms sometimes occur after a viral illness. In some cases, a person may reach the point of diabetic ketoacidosis (DKA) before a type 1 diagnosis is made. DKA occurs when blood glucose is dangerously high and the body can't get nutrients into the cells because of the absence of insulin. The body then breaks down muscle and fat for energy, causing an accumulation of ketones in the blood and urine. Symptoms of DKA include a fruity odour on the breath, heavy, taxed breathing and vomiting. If untreated, DKA can result in stupor, unconsciousness, and even death

Risk Factors for Diabetes Mellitus

The risk factors for DM can be divided into modifiable versus non-modifiable risk factors [10]:

Modifiable Risk Factors

- Obesity (for type 2 DM): A body mass index (BMI) of ≥30 defines obesity.
- Cigarette smoking: According to CDC, cigarette smoking put at a significant risk of acquiring diabetes, approximately a 30-40% chance of than non-smokers.
- Sedentary lifestyle: Combining physical activity with a healthy diet attenuates the incidence of DM.
- Diet (for T2D): junk foods like chips, French fries, sugary or high-carb or high GI (glycaemic index) diet, like white bread, white rice, GI is a measure of how a carbohydrate-containing food will raise the blood sugar levels.
- Dyslipidaemia (deranged lipid profile such as raised LDL/bad cholesterol, raised triglycerides, or low HDL/good cholesterol).
- Prediabetes: Prediabetes is another risk factor for acquiring diabetes sooner or later.
- Gestational diabetes: Children born to diabetic mothers have a strong inclination to develop type 2 diabetes later in life.
- Medication-induced DM: Glucocorticoids, diuretics, β-blockers cause DM.
- Insulin resistance serves as another risk factor for prediabetes, which can progress to type 2 DM.
- Sleep apnoea: A sleeping disorder manifests as interrupted breathing during sleep. Sleep apnoea alters glucose metabolism, enhancing the risk for type 2 diabetes.
- Polycystic_ovarian_syndrome: This is a condition strongly associated with insulin resistance, obesity, and type 2 DM.

Non-modifiable Risk Factors

These are inherited, genetic, or developmental features that are irreversible and are not modifiable by dietary or other lifestyle changes.

- Family history: There is an increased risk of prediabetes if your parents are diabetic.
- Race: People of varying ethnic origins have an increased prevalence of developing type 2 DM. According to ADA, among all the Americans, the African Americans, Mexicans, American Indians, and Pacific Islanders are more prone to develop diabetes than other populations.
- Age: Age is a high risk of hypertension, diabetes, cardiac diseases, and stroke. It cannot reverse the age-related changes, however, it can get into the groove by adopting healthy lifestyles, such as eating healthy, exercising, watching out weight, and monitoring the blood glucose levels at timely intervals.
- Gender: The prevalence of diabetes based on gender varies widely. A study showed that single women of 35-64 years were more prone to develop DM.

Pathophysiology of type 1 diabetes (IDDM)[2][6]

The autoimmune destruction of pancreatic β-cells, leads to a deficiency of insulin secretion which results in the metabolic derangements associated with IDDM. In addition to the loss of insulin secretion, the function of pancreatic α-cells is also abnormal and there is excessive secretion of glucagon's in IDDM patients. Hyperglycaemia leads to reduced glucagon's secretion, however, in patients with IDDM, glucagon's secretion is not suppressed by hyperglycaemia. The resultant elevated glucagon's levels exacerbate the metabolic defects due to insulin deficiency. The most pronounced example of this metabolic disruption is that patients with IDDM rapidly develop diabetic ketoacidosis in the absence of insulin administration. Although insulin deficiency is the primary defect in IDDM, there is also a defect in the administration of insulin. There are many biochemical mechanisms that cause impairment of tissue's response to insulin. Deficiency in insulin leads to uncontrolled lipolysis and elevated levels of free fatty acids in the plasma, which suppresses glucose metabolism in peripheral tissues such as skeletal muscle. This impairs glucose utilization and insulin deficiency also decreases the expression of a number of genes necessary for target tissues to respond normally to insulin such as glucokinase in liver and the GLUT 4 class of glucose transporters in adipose tissue. Which explains the major metabolic derangements, which result from insulin deficiency in IDDM are impaired glucose, lipid and protein metabolism.

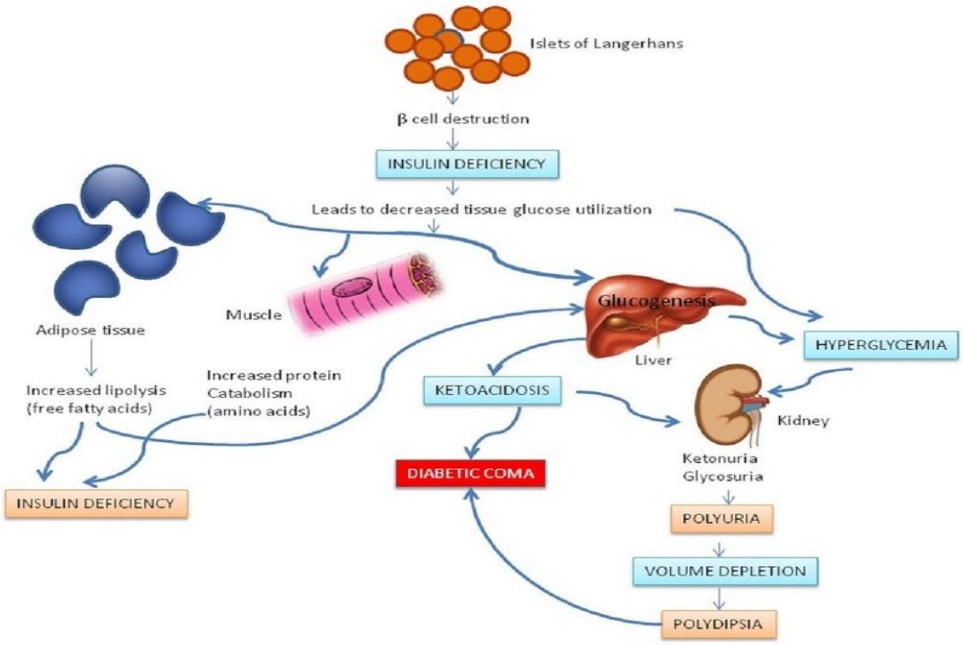

Fig 1: Pathophysiology of Type 1 Diabetes

Pathophysiology of type 2 diabetes (NIDDM)

Individuals with NIDDM have levels of circulating insulin, unlike patients with IDDM. On the basis of oral glucose tolerance testing the essential elements of NIDDM can be divided into four distinct groups:

i) Those with normal glucose tolerance.
ii) Chemical diabetes (called impaired glucose tolerance).
iii) Diabetes with minimal fasting hyperglycaemia (fasting plasma glucose less than 140 mg/dl).
iv) Diabetes mellitus with fasting hyperglycaemia (fasting plasma glucose greater than 140 mg/dl).

People with impaired glucose tolerance have hyperglycaemia in spite of having highest levels of plasma insulin, indicating that they are resistant to the action of insulin. In the progression from impaired glucose tolerance to diabetes mellitus, the level of insulin declines indicating that patients with NIDDM have decreased insulin secretion. Insulin resistance is the primary cause of NIDDM; however, some researcher contend that insulin deficiency is the primary cause because a moderate degree of insulin resistance is not sufficient to cause NIDDM. Most patients with the common form of NIDDM have both defects. Recent proofs have demonstrated a role for a member of the nuclear hormone receptor super family of proteins in the etiology of type 2 diabetes. Relatively new classes of drugs used to increase the sensitivity of the body to insulin are the thiazolidinedione drugs. These compounds bind and alter the function of the peroxisome proliferators-activated receptor g (PPARg). PPARg is also a transcription factor and when activated, binds to another transcription factor known as the retinoid x receptor (RXR).

When these two proteins are complexed a specific set of genes becomes activated. PPARg is a regulator of adipocyte differentiation; it can induce the differentiation of fibroblasts or other undifferentiated cells into mature fat cells. PPARg is also involved in the synthesis of biologically active compounds from vascular endothelial cells and immune cells.

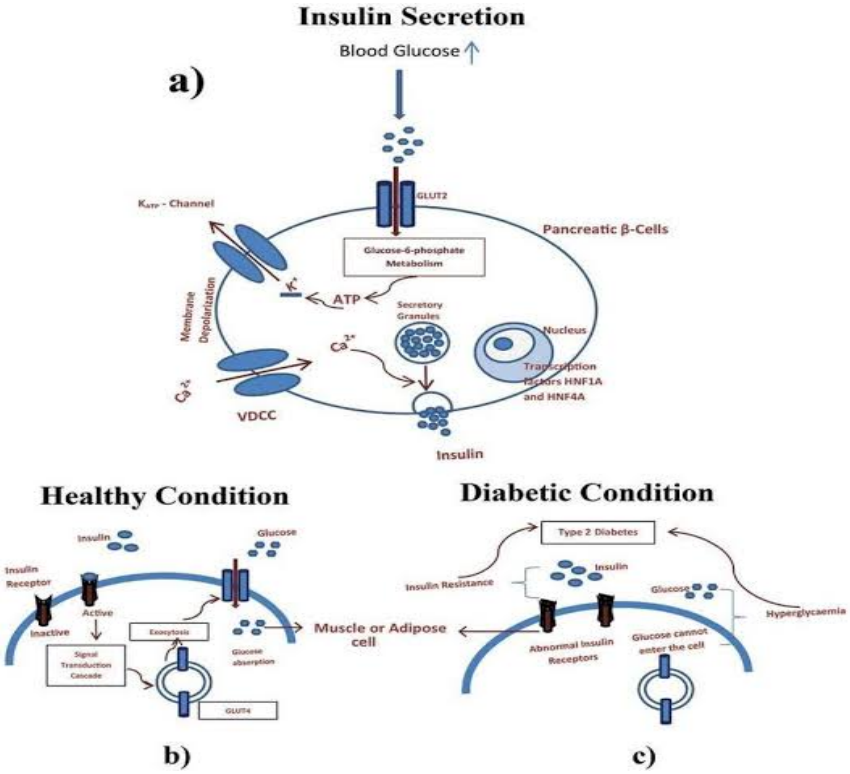

Fig 2: Pathophysiology of type 2 Diabetes

Treatment for Diabetes Mellitus

Pharmacologic Treatment [7]

When considering appropriate pharmacologic therapy, it is important to determine whether the patient is insulin-deficient, insulin-resistant, or both. Treatment options are divided into noninsulin therapies—insulin sensitizers, secretagogues, alpha-glucosidase inhibitors, incretins, pramlintide, bromocriptine, and sodium-glucose cotransporter 2 (SGLT-2) inhibitors—and insulin therapies.

Table 1: Classification of Antidiabetic agents

Types of drugs	How they work	Example(s)
Alpha-glucosidase inhibitors	Slow your body's breakdown of sugars and starchy foods	Acarbose and miglitol
Biguanides	Reduce the amount of glucose that liver makes	Metformin
DPP-4 inhibitors	Improves blood sugar without making it drop too low	Linagliptin, saxagliptin and sitagliptin
Glucagon-like peptides	Change the way the body produces insulin	Dulaglutide, exenatide and liraglutide
Meglitinides	Stimulate your pancreas to release more insulin	Nateglinide and repaglinide
SGLT2 inhibitors	Release more glucose into the urine	Canagliflozin and dapagliflozin
Sulfonylureas	Stimulate the pancreas to release more insulin	Glyburide , glipizide, and glimepiride
Thiazolidinediones	Help insulin work better	Pioglitazone and rosiglitazone

Mechanism of action of Metformin [8]

Metformin is a widely-used drug to glucose metabolism and diabetes-related complications. The mechanisms underlying these benefits are complex and still not fully understood. Physiologically, metformin has been shown to reduce hepatic glucose production, yet not all of its effects can be explained by this mechanism and there is increasing evidence of a key role for the gut. At the molecular level the findings vary depending on the doses of metformin and duration of treatment, with differences between acute and chronic administration. Metformin has been shown to act via both AMP-activated protein kinase (AMPK)-dependent and AMPK-independent mechanisms; by inhibition of mitochondrial respiration but also perhaps by inhibition of mitochondrial glycerophosphate dehydrogenase, and a mechanism involving the lysosome. In the last 10 years, it have moved from a simple picture, that metformin improves glycaemia by acting on the liver via AMPK activation, to a much more complex picture reflecting its multiple modes of action.

Table 2: Natural sources which are used to treat Diabetes mellitus [9]

Apple Cider Vinegar	The primary compound in ACV is acetic acid. There are many evidence-based approaches to using ACV. Taking 2 tablespoons before bedtime can reduce your morning fasting sugar levels. Even better, 1-2 tablespoons of ACV taken with meals can decrease the glycaemic load of a carbohydrate rich meal. Patients to either consume ACV alone, prior to a meal or mix it into salad dressings or teas.
Fibre and Barley	Eating fibre decreases blood sugar and insulin concentrations. The recommended

	amount of fibre is around 30 grams per day. Take fibre supplements like Metamucil, the best way to reach your goal is to eat veggies. Barley is a high-fibre, high-protein grain which has lots of data to support its role in helping improve blood sugar, insulin, cholesterol and general inflammation. Barley does not require soaking and usually can cook in less than 15 minutes on the stove top with just some water and salt.
Chromium	Mainly found in brewer's yeast, deficiency in chromium impairs the metabolism of glucose. Evidence supports chromium for lower blood sugar. Be careful in kidney disease with this supplement.
Zinc	Those with diabetes are commonly found to be zinc deficient. Studies have shown zinc supplementation can reduce blood sugar, have an antioxidant effect, lower blood sugar and even help treat some of the complications related to diabetes. Large doses of zinc can inhibit the absorption of other minerals like copper.
Aloe Vera	The aloe vera is known for its laxative effect. There is increasing evidence for use of the gel, which is the mucilaginous material inside the leaves.
Berberine	These botanicals found in plants such as goldenseal, barberry, Oregon grape root and Coptis. Its use for decreasing blood sugar. Be aware that this herb can interfere with metabolism of traditional pharmaceuticals and should never be taken while pregnant
Cinnamon	A medically beneficial indulgence to help lower your blood sugar and cholesterol levels.
Fenugreek	A seed commonly used as a food spice has been used abroad for centuries for its medical benefits to lower cholesterol. If urine smells like maple syrup, this is a known side effect and is harmless.
Gymnema	Its medical use showing benefits for glucose metabolism, insulin levels and as an adjunct to improve the results of traditional pharmaceuticals. Be aware, because this botanical works synergistically with your meds, you must monitor your blood sugar closely to avoid having hypoglycaemia

CONCLUSION

Diabetes mellitus (DM) is a chronic metabolic disorder caused by an absolute or relative deficiency of insulin. This high blood glucose produces the symptoms of frequent urination, increased thirst, and the increased hungry. Diabetes is due to either the pancreas not producing enough insulin, or because cells of the body do not respond properly to the insulin. Diabetes is not only the three main types (i.e., type 1, type 2 and gestational diabetes) but also other types such as MODY (maturity onset diabetes of the young 1-6), Neonatal diabetes, latent autoimmune diabetes in adults, Chemical induced diabetes, Steroid induced diabetes, Cystic fibrosis diabetes etc. Early Detection of metabolic complications is vital for full recovery. Self-glucose monitoring will prevent these conditions.

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