

## Review

## Diabetes mellitus: Classification, mediators, and complications; A gate to identify potential targets for the development of new effective treatments



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## ARTICLE INFO

## ABSTRACT

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Nowadays, diabetes mellitus has emerged as a significant global public health concern with a remarkable increase in its prevalence. This review article focuses on the definition of diabetes mellitus and its classification into different types, including type 1 diabetes (idiopathic and fulminant), type 2 diabetes, gestational diabetes,

**Abbreviations:** DM, Diabetes Mellitus; T1D, Type 1 diabetes; T2D, Type 2 diabetes; LADA, Latent autoimmune diabetes in adults; LADY, Latent autoimmune diabetes in youth; GAD, Glutamic Acid Decarboxylase; MODY, Maturity-onset diabetes of the young; HNF-1, Hepatic transcription factor-1; FPG, Fasting Plasma Glucose; OGTT, Oral glucose tolerance test; HbA1c, Hemoglobin A1c; TNF- $\alpha$ , Tumor Necrosis Factor-alpha; NF- $\kappa$ B, Nuclear factor kappa B; JNKs, Janus kinase pathways; IRS-1, Insulin receptor substrate 1; c-RP, C-reactive protein; MCP-1, Monocyte chemoattractant protein; IL-6, Interlukin-6; IFN- $\gamma$ , Interferon- $\gamma$ ; PAI-1, Plasminogen activator inhibitor 1; AGEs, Advanced Glycation End Products; ROS, Reactive Oxygen Species; RAGE, Receptor advanced glycation end product; NK, Natural killer; iNOS, Inducible nitric oxide synthase; CVD, Cardiovascular diseases; AT, Adipose tissue; MCP-1, Monocyte chemoattractant protein-1; LDL, Low-density lipoprotein; PPAR- $\gamma$ , Peroxisome proliferator-activated receptor gamma; NSAIDs, Non-steroid anti-inflammatory drugs; BAT, Brown adipose tissue; WAT, White adipose tissue; GSIS, Glucose-stimulated insulin secretion; FFAs, Free fatty acids; CAT, Catalase; GLT, Glutathione; SOD, Superoxide dismutase; ROOH, Reactive hydroperoxides; MDA, Malondialdehyde; ETC, Electron transport chain; MAM, Mitochondria-associated ER membranes; TLRs, Toll-like receptors; CEB/Ps, CCAAT enhancer-binding proteins; MEF2, Myocyte enhancer factor 2; HIF-1, Hypoxia-inducible factors alpha; IST, Insulin signal transduction; IRS-1, Insulin receptor substrate-1; IKK-B, Inhibitor of nuclear factor kappa B; GSK-3, Glycogen synthase kinase 3; AMPK, AMP-activated protein kinase; mTOR, Mammalian target of rapamycin; p38 MAPK, p38 mitogen-activated protein kinases; MRC, Mitochondrial Respiratory Chain; DAG, Diacylglycerol; IST., Insulin signal transduction.; LPS, Lipopolysaccharides; SCFAs, Short-chain fatty acids; IP-10, IFN-inducible protein 10; Imp, Imidazole propionate; BCAA, Branched-chain amino acids; TMAO, Trimethylamine-N-oxide; NAFLD, Non-alcoholic fatty liver disease; HCV, Hepatitis C virus; NASH, Nonalcoholic steatohepatitis; CIN, Contrast-induced nephropathy; GFR, Glomerular filtration rate; TGF- $\beta$ 1, Transforming growth factor-beta 1; JAK-STAT, Janus kinase-signal transducer and activator of transcription; SMPDL3b, Sphingomyelin phosphodiesterase acid-like 3b; JAML, Junctional adhesion molecule-like protein; CaMKII, Nitric oxide (NO) Ca2+/calmodulin-dependent protein kinase II; SERCA2a, Sarcoplasmic/endoplasmic reticulum Ca2+ ATPase 2a; HDACs, Histone deacetylases; PBMCs, Peripheral blood mononuclear cells; TIRAP, Toll/IL-1R domain-containing adaptor protein; HIF1 $\alpha$ , Hypoxia-inducible factor 1 alpha; VEGF-1, Vascular endothelial growth factor-1; Sema4d, Semaphorin 4d; VE-Cadherin, Vascular endothelial cadherin; Ang1, Angiopoietin 1; EPA, Eicosapentaenoic acid; DHA, Docosahexaenoic acid; 12-HETE, Hydroxyeicosatrienoic acids; DPP4i, Dipeptidyl peptidase 4 inhibitors; HCN2, Hyperpolarization-activated cyclic nucleotide-gated 2; ApoE, Apolipoprotein E; NTR, p75 neurotrophin receptor; NT-3, Neurotrophic factor-3; NGF, Nerve growth factor.

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Treatment

hybrid forms, slowly evolving immune-mediated diabetes, ketosis-prone type 2 diabetes, and other special types. Diagnostic criteria for diabetes mellitus are also discussed. The role of inflammation in both type 1 and type 2 diabetes is explored, along with the mediators and potential anti-inflammatory treatments. Furthermore, the involvement of various organs in diabetes mellitus is highlighted, such as the role of adipose tissue and obesity, gut microbiota, and pancreatic  $\beta$ -cells. The manifestation of pancreatic Langerhans  $\beta$ -cell islet inflammation, oxidative stress, and impaired insulin production and secretion are addressed. Additionally, the impact of diabetes mellitus on liver cirrhosis, acute kidney injury, immune system complications, and other diabetic complications like retinopathy and neuropathy is examined. Therefore, further research is required to enhance diagnosis, prevent chronic complications, and identify potential therapeutic targets for the management of diabetes mellitus and its associated dysfunctions.

## 1. Introduction

### 1.1. Definition of diabetes mellitus (DM)

Chronic hyperglycemia is a metabolic disorder caused by either a lack of insulin secretion, impaired insulin action, or both. Notably, insulin plays an important role as an anabolic hormone, affecting the metabolism of carbohydrates, lipids, and proteins [1]. The metabolic abnormalities associated with diabetes mainly affect tissues such as adipose tissue, skeletal muscles, and the liver due to insulin resistance. The severity of symptoms can vary depending on the duration and type of diabetes. Individuals with high blood sugar levels, particularly those with a complete lack of insulin, such as children, may experience symptoms such as increased appetite, polydipsia, dysuria, weight loss, increased appetite, and vision problems. Some people with diabetes may not experience any symptoms, especially type 2 diabetic patients in their early stages [2]. Without proper treatment, uncontrolled diabetes can lead to various complications such as coma, confusion, and in rare cases, death from ketoacidosis or nonketotic hyperosmolar syndrome not treated [1].

In 2014, the WHO announced that 8.5% of adults aged 18 and above were affected by diabetes. In 2019, diabetes was responsible for 1.5 million deaths, with 48% of these occurring before the age of 70. Additionally, diabetes led to another 460,000 deaths due to kidney disease, and roughly 20% of cardiovascular-related deaths were attributed to elevated blood glucose levels. From 2000–2019, there was a 3% rise in standardized mortality rates related to diabetes. In lower-middle-income countries, the mortality rate associated with diabetes increased by 13%. In contrast, the likelihood of succumbing to any of the four primary non-communicable diseases (which include cardiovascular diseases, cancer, chronic respiratory diseases, or diabetes) between the ages of 30 and 70 declined by 22% worldwide from 2000 to 2019 [3].

Herein, the search criteria were based on the screening of all the respected and available research and review articles in the literature about diabetes. The authors screened over 500 scientific articles from different databases like PubMed and Google Scholar. Fig. (1).

### 1.2. Classification of DM

#### 1.2.1. Type 1 diabetes

Type 1 diabetes (T1D) can be detected well before abnormal insulin secretion starts, with a steady decline starting at least two years before diagnosis [4]. Around the same time, there is a decline in  $\beta$ -cell sensitivity to glucose. As the first insulin response decreases, the last insulin response rises, potentially indicating a compensation mechanism. Early in the post-diagnosis phase, the decline in insulin responsiveness keeps speeding up. Within the first few years after diagnosis, a biphasic decline in insulin secretion has been seen, with the first year being steeper than the second. Once a diagnosis is made, the decrease in insulin secretion may continue for years, eventually leaving little to no insulin production. Higher glucose levels are a sign of T1D even when they are within the normal range. When T1D develops, there are significant glucose variations. It may be possible to anticipate the development of diabetes more accurately in at-risk persons by using metabolic markers, such as

dysglycemia. Alteration in glucose and C-peptide levels can be utilized in risk ratings to further improve prediction [5].

**1.2.1.1. Idiopathic T1D.** A rare variant of T1D has been reported and known as “idiopathic diabetes”, which is not caused by autoimmunity having lesser severity than autoimmune T1D. People with idiopathic diabetes may experience episodic ketoacidosis as well as insulin insufficiency. This variant is more common in individuals of Asian or African heritage [6].

**1.2.1.2. Fulminant T1D.** This is a unique kind of T1D that was originally identified in 2000. It shares certain characteristics with idiopathic T1D, including not being immune-mediated [7]. Keto-acidosis occurs shortly after the initiation of hyperglycemia, and serum C-peptide levels, which is a marker of the endogenous release of insulin, are undetectable while blood glucose levels are high (288 mg/dL). About 20% of Japanese people with acute-onset T1D (5000–7000 instances) have this condition, which has been mostly characterized in East Asian nations. It causes an incredibly quick and practically complete  $\beta$ -cell death that leaves almost no residual insulin output. This condition is mainly attributed to some environmental and hereditary causes. Through an increased immune response without discernible formation of autoantibodies attacking pancreatic  $\beta$ -cells, an antiviral immune response may cause the loss of pancreatic  $\beta$ -cells. There have also been reports of this type of diabetes and pregnancy [8].

#### 1.2.2. Type 2 diabetes

A key component of type 2 diabetes (T2D) pathogenesis is defective insulin secretion [9]. Insulin secretion varies widely in response to insulin sensitivity to maintain adequate glucose levels. The disposition index is a measure of the curvilinear relationship between the sensitivity of insulin and the secretion of insulin. Besides, type 2 diabetic patients have a low disposition index; therefore, they are unable to appropriately enhance their insulin production to combat insulin resistance. Even when the absolute insulin levels in insulin-resistant obese T2D patients are higher than in insulin-sensitive lean control subjects, the levels are still too low given the severity of their insulin resistance. Insulin production (first phase) is significantly reduced or eliminated due to glucose stimulation. T2D patients have a high ratio of proinsulin to insulin (C-peptide). The maximal insulin production and hyperglycemia-induced potentiation of insulin responses to non-glucose stimuli are substantially diminished [10]. Hyperglycemia tends to worsen and become more challenging to cure over time. The continuing decline in  $\beta$ -cell function is another feature of T2D progression [11].

#### 1.2.3. Gestational diabetes

Pregnancy-related hyperglycemia increases the risk of bad outcomes for the mother, fetus, and newborn [12]. This risk is present whether the hyperglycemia adopts the T2D form diagnosed before or during pregnancy. Newborns born to mothers with gestational diabetes are at an elevated risk of developing diabetes in adulthood [13]. The increased incidence of pregnancy-related complications, such as premature birth, large-for-gestational-age births, macrosomia (birth weight  $>$  4.5 kg),

cesarean delivery, and preeclampsia is primarily due to hyperglycemia during pregnancy, which leads to larger neonates. Gestational diabetes can be influenced by several risk factors, such as having a family history of the condition, being obese, advanced maternal age, having polycystic ovarian syndrome, leading a sedentary lifestyle, and exposure to environmental pollutants. [14]. The identification of gestational diabetes relies on specific criteria, which involve evaluating fasting blood sugar levels, blood sugar levels after a 75 g oral glucose load, and other relevant parameters, as mentioned previously [15].

#### 1.2.4. Hybrid forms of diabetes

**1.2.4.1. Slowly evolving immune-mediated diabetes (LADA).** Slowly evolving immune-mediated diabetes, also known as latent autoimmune diabetes in adults (LADA) resembles type 2 diabetes clinically but is characterized by the presence of pancreatic autoantibodies associated with autoimmune diabetes. Initially, individuals with LADA can be managed with oral medications and lifestyle modifications like those with type 2 diabetes [16]. However, they tend to progress to requiring insulin therapy at a faster rate compared to typical type 2 diabetes patients. LADA is more prevalent in certain regions than rapid-onset type 1 diabetes. There is a comparable subtype known as latent autoimmune diabetes in youth (LADY) observed in children and adolescents with clinical type 2 diabetes and pancreatic autoantibodies. The criteria used to diagnose LADA typically involve positive glutamic acid decarboxylase (GAD) autoantibodies, age older than 35 years at the time of diagnosis, and no immediate need for insulin therapy in the first 6–12 months after diagnosis. The prevalence of GAD autoantibodies in clinically diagnosed type 2 diabetes individuals varies between ethnic and regional groups, ranging from 5% to 14% [17].

**1.2.4.2. Ketosis-prone type 2 diabetes.** Ketosis-prone type 2 diabetes is a unique clinical condition primarily seen in young African Americans and populations in sub-Saharan Africa. It is characterized by episodes of ketosis and severe insulin deficiency at the initial presentation, resembling type 1 diabetes or diabetic ketoacidosis. However, individuals with this condition eventually enter remission and do not require insulin treatment. Nonetheless, around 90% of these individuals experience further episodes of ketosis within 10 years. Ketosis-prone type 2 diabetes is less common in populations of European descent but can be observed in various ethnic groups. The exact underlying cause is not fully understood, and no genetic evidence or markers of autoimmunity have been identified. It is believed that glucose toxicity may play a role in

acute and phasic  $\beta$ -cell failure in this condition. Interestingly, after insulin therapy and restoration of normal blood glucose levels, there is a significant and prolonged improvement in insulin secretory function in  $\beta$ -cell [18].

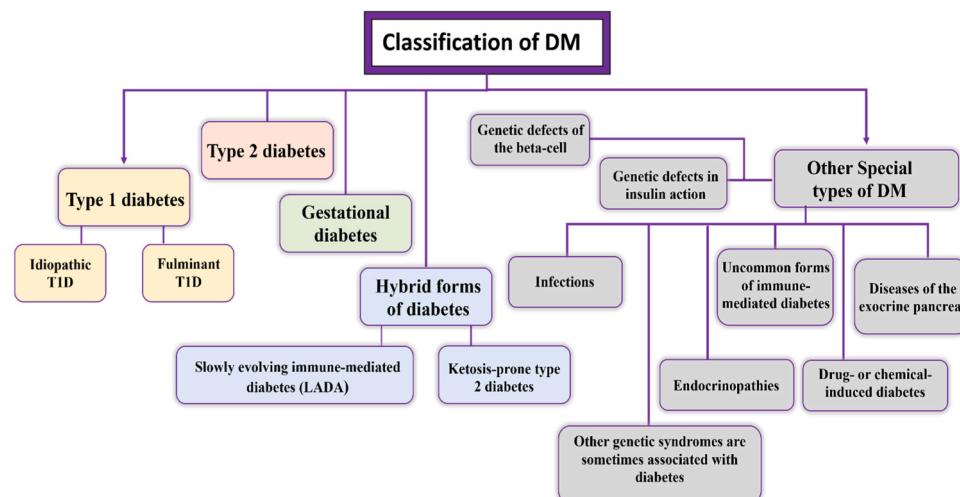
#### 1.2.5. Other special types of DM

**1.2.5.1. Genetic defects of the beta-cell.** Maturity-onset diabetes of the young (MODY): This type of diabetes is associated with abnormal monogenetic  $\beta$ -cell function. It typically appears at a young age, usually before 25 years old, and is characterized by reduced insulin secretion with little to no abnormalities in insulin action. The condition is inherited in an autosomal dominant manner, meaning that only one copy of the affected gene from either parent is sufficient to cause the condition. Mutations in several genes, including hepatic transcription factor (HNF)-1, glucokinase, HNF-4, HNF-1 $\alpha$ , IPF-1, and NeuroD1, have been identified as causes of MODY [19].

**1.2.5.2. Genetic defects in insulin action.** Genes mutations of insulin receptors: Certain gene mutations of insulin receptors can lead to abnormalities in insulin action. These mutations associated with insulin can cause a variety of metabolic abnormalities, ranging from elevated insulin levels and mild high blood sugar to severe diabetes. In some cases, individuals with these mutations may display additional symptoms such as acanthosis nigricans (skin darkening), virilization (development of male characteristics), and enlarged cystic ovaries in women. Despite the presence of mutant insulin, the impaired binding of these molecules to the insulin receptor can lead to either mild or even normal glucose metabolism [20].

**1.2.5.3. Diseases of the exocrine pancreas.** Diabetes can arise from several conditions that lead to widespread damage to the pancreas. Such conditions include infection, pancreatitis, pancreatic carcinoma, trauma, and pancreatectomy (surgical removal of the pancreas). Typically, significant damage to the pancreas is necessary for diabetes to develop, but even small, affected portions of the pancreas due to adenocarcinomas can be linked to diabetes. Additionally, certain diseases like cystic fibrosis, hemochromatosis, and fibrocalculus pancreatopathy can also disrupt insulin secretion and harm  $\beta$ -cells [21].

**1.2.5.4. Endocrinopathies.** Excess amounts of certain hormones can antagonize insulin action and lead to diabetes. Conditions such as acromegaly (excess growth hormone), glucagonoma that is



**Fig. (1).** The newest classification of DM represents the different types and subtypes of diabetes, including Type 1 Diabetes, Type 2 Diabetes, Gestational Diabetes, Hybrid Forms of Diabetes (LADA and Ketosis-prone Type 2 Diabetes), and Other Special Types of Diabetes.

(excess glucagon) pheochromocytoma that is (excess epinephrine), and Cushing's syndrome that is (excess cortisol) can cause diabetes, indeed, diabetes can be exacerbated, especially in individuals who have preexisting defects in secretion of insulin. Conditions like somatostatinomas and aldosteronomas can induce hypokalemia, which further contributes to the development and progression of diabetes in affected individuals [20].

**1.2.5.5. Drug- or chemical-induced diabetes.** Certain drugs and toxins have the potential to interfere with insulin secretion or action, either on their own or by triggering diabetes in individuals who already have insulin resistance. For instance, drugs like nicotinic acid and glucocorticoids can impact insulin action. Additionally, specific toxins like Vacor and intravenous pentamidine could permanently damage  $\beta$ -cells. However, it's important to note that drug-induced reactions leading to diabetes are relatively rare occurrences [19].

**1.2.5.6. Infections.** Some viruses have been linked to the destruction of beta-cells and the emergence of diabetes. These viruses include coxsackievirus B, congenital rubella, mumps, adenovirus, and cytomegalovirus. Their role in inducing diabetes is especially notable in individuals who have genetic predispositions or markers associated with type 1 diabetes. In susceptible individuals, these viruses can trigger an autoimmune response, leading to the destruction of beta-cells and the development of diabetes [21].

**1.2.5.7. Uncommon forms of immune-mediated diabetes.** In this category, two known conditions are mentioned:

**1.2.5.7.1. Stiff-man syndrome.** This is an autoimmune condition affecting the central nervous system, which is characterized by painful spasms and stiffness in the axial muscles. Individuals with this syndrome typically show elevated levels of glutamic acid decarboxylase (GAD) autoantibodies and are at an elevated risk of developing diabetes [20].

**1.2.5.7.2. Anti-insulin receptor antibody-related diabetes.** Antibodies against the insulin receptor can interfere with insulin binding, leading to diabetes. In certain instances, these antibodies can function as insulin agonists, leading to hypoglycemia instead of hyperglycemia. Individuals diagnosed with systemic lupus erythematosus and other autoimmune disorders may show the presence of antibodies that target the insulin receptor. Acanthosis nigricans are often present in individuals with this condition [22].

**1.2.5.8. Other classifications.** To classify diabetic subtypes rationally based on the information provided by the given articles, we can summarize the following key points [23–25]:

#### a) Comorbidities and risk factors:

Diabetic patients may have a range of associated comorbidities and risk factors that should be considered when classifying subtypes. These comorbidities can include cardiovascular diseases (CVDs), genetic factors, GI symptoms, fasting incretin tone, and trajectories of HbA1c levels.

#### b) Variable selection:

The optimal number of variables for classification is essential. Some studies have used a limited set of variables (e.g., age, BMI, HbA1c), while others employed more extensive datasets. The choice of variables should balance validity and economic efficiency.

#### c) Clustering methods:

Various clustering methods were employed, including k-means clustering, hierarchical clustering, PCA (Principal Component Analysis), and TBA (Tree-based algorithm). The choice of method can impact the results, and it's essential to consider outliers and missing data when using these methods.

#### d) Validation:

Validating clustering results is critical. External validation on

independent samples or cross-validation within the dataset helps ensure the quality of the clustering analysis.

#### e) Standardization:

Standardizing data is necessary to enable the comparison of variables with different scales. Standardization ensures that variables contribute equally to the clustering results.

#### f) Limitations:

Common limitations include small sample sizes, issues affecting generalizability, and short follow-up periods. Additionally, some studies may group medications, potentially affecting the results.

In a rational classification of diabetic subtypes, one could consider these factors and conduct a comprehensive analysis of a large and diverse diabetic population. This analysis would involve selecting relevant variables, applying appropriate clustering methods, validating results, standardizing data, and addressing common limitations. The goal would be to identify clinically meaningful subgroups that may guide personalized treatment and prevention strategies for diabetic patients, taking into account their unique characteristics, risk factors, and comorbidities.

There are several subtypes of DM, each with its characteristics and severity. We will summarize the subtypes and their relative seriousness:

#### a) Severe Autoimmune Diabetes (SAID) - Cluster 1:

- Type 1 diabetes.
- Typically affects younger individuals.
- An autoimmune condition where the immune system attacks beta cells.
- Low BMI, insulin deficiency, and poor blood sugar control.
- Requires insulin treatment.
- Seriousness: This type can be serious, especially if not managed properly, as it involves an autoimmune response that can lead to insulin dependence and complications.

#### b) Severe Insulin-Deficient Diabetes (SIDD) - Cluster 2:

- Similar to Cluster 1 but lacks GADA antibodies.
- Younger individuals with low BMI.
- Defective beta cell function.
- Seriousness: Like Cluster 1, it can be serious due to insulin deficiency, but the absence of GADA antibodies distinguishes it.

#### c) Severe Insulin-Resistant Diabetes (SIRD) - Cluster 3:

- Overweight individuals with high insulin resistance.
- Cells produce insulin, but they do not respond to it.
- Higher risk of non-alcoholic fatty liver disease.
- Seriousness: This type is serious because it can lead to complications, especially related to insulin resistance and obesity.

#### d) Mild Obesity-Related Diabetes (MOD) - Cluster 4:

- Occurs in obese or overweight individuals.
- Not associated with significant insulin resistance.
- Milder form of diabetes.
- Seriousness: Generally, less serious than the severe subtypes, but obesity-related health risks may still apply.

#### e) Mild Age-Related Diabetes (MARD) - Cluster 5:

- Typically affects older individuals.
- Mild difficulty with blood sugar control.
- The most common type accounts for about 40% of cases.
- Seriousness: While it may be less severe in terms of immediate symptoms, long-term management is important, especially in older

individuals.

#### Prediabetes:

- This is not a subtype but a condition where blood glucose levels are higher than normal but not in the diabetic range.
- Individuals with prediabetes have an increased risk of developing DM but can reverse it with lifestyle changes.

In terms of seriousness, the severity of each subtype depends on various factors, including how well it is managed and the individual's overall health. However, Cluster 3 (SIRD) is highlighted as being at the highest risk of developing kidney disease, which is a severe complication of diabetes. Cluster 2 has the greatest risk of diabetic retinopathy, which can lead to vision problems [26].

It's important to note that early detection and appropriate treatment are crucial for managing the seriousness of diabetes, regardless of the subtype. Proper management can help prevent or delay complications and improve the prognosis [27].

#### 1.2.5.9. Other genetic syndromes are sometimes associated with diabetes.

Certain genetic syndromes are accompanied by an increased incidence of diabetes. Examples like Wolfram's syndrome, Klinefelter syndrome, Turner syndrome, and Down syndrome. Wolfram's syndrome is a genetic disorder inherited in an autosomal recessive manner. It is characterized by insulin-deficient diabetes, with a complete absence of  $\beta$ -cells observed during autopsy. In addition to diabetes, affected individuals may exhibit other manifestations as part of the syndrome [19, 20] as shown in Table (1).

### 1.3. Diagnostic criteria for DM

The diagnosis of DM is commonly made through the measurement of hemoglobin (HbA1c) plasma glucose levels or oral glucose tolerance test (OGTT) or fasting plasma glucose (FPG). These values are used to estimate the correlation between HbA1c or FPG and retinopathy, which helps in setting cut-off values for glucose and HbA1c to diagnose diabetes [28]. DM is diagnosed when the level of fasting plasma glucose is less than 126 mg/dL (7.0 mmol/L), the 2 h OGTT plasma glucose level is more than 200 mg/dL (11.1 mmol/L), or the HbA1c level is less than 6.5% (48 mmol/mol), or random plasma glucose level is higher than 200 mg/dL (11.1 mmol/L) [29]. The International Expert Committee in 2009 proposed the adoption of HbA1c as a diagnostic and treatment monitoring tool in cases of diabetes, a recommendation that has gained widespread support from numerous organizations and experts globally. HbA1c has advantages over FPG for diagnosing diabetes, including better correlation with microvascular complications, higher pre-analytical stability, and a lower coefficient of variation (3.6%) compared to FPG (5.7%) and after 2 h of OGTT (16.6%). HbA1c has been found to have a stronger association with microvascular complications, especially retinopathy, and serves as a marker for protein glycation and glycemic control, which are related directly to the diagnosis and development of diabetes-related complications [30]. If HbA1c is used as the sole diagnostic test, the test must be repeated within two weeks with asymptomatic patients [31]. However, ethnicity can influence the cutoff values for diagnosing diabetes, with different cutoff values adopted by various nations and ethnic groups [32]. For example, a Japanese study measured the cutoff values at 5.5% (37 mmol/mol) and 6.5% (48 mmol/mol), while an Egyptian study reported a cutoff value of 6.3% (45 mmol/mol). Australian researchers suggested using two cutoff values, 5.5% to "rule out" diabetes and 7.0% to "rule in". Ethnicity can also affect the prevalence of diabetes and prediabetes [33]. HbA1c was used in most trials to identify diabetes in fewer patients than FPG or OGTT. However, other research found that using HbA1c, more people were diagnosed with diabetes [34].

**Table (1)**  
Other special types of DM.

Other specific types of DM	Brief description	Examples	Reference
The genetic defect of $\beta$ -cell function	This condition arises due to specific genetic mutations and presents with multiple clinical manifestations that necessitate diverse treatment approaches. Some of these manifestations manifest during the neonatal period, while others become apparent during early adulthood.	<ul style="list-style-type: none"> <li>• Chromosome 20, HNF-4 <math>\alpha</math>(MODY1)</li> <li>• Chromosome 7, glucokinase (MODY2)</li> <li>• Chromosome 12, HNF-1 <math>\alpha</math>(MODY3)</li> <li>• Chromosome 13, insulin promoter factor-1 (IPF-1; MODY4)</li> <li>• Chromosome 17, HNF-1<math>\beta</math> (MODY5)</li> <li>• Chromosome 2, NeuroD1 (MODY6)</li> <li>• Mitochondrial DNA</li> <li>• Others</li> </ul>	[20]
Genetic defects in insulin action	This condition is caused by specific genetic mutations and is characterized by profound insulin resistance, even in the absence of obesity. Diabetes develops when $\beta$ cells are unable to effectively compensate for the resistance of insulin present in the body.	<ul style="list-style-type: none"> <li>• Type A insulin resistance</li> <li>• Leprechaunism</li> <li>• Rabson-Mendenhall syndrome</li> <li>• Lipoatrophic diabetes</li> <li>• Others</li> </ul>	[20,21]
Diseases of the exocrine pancreas	Hyperglycemia can be caused by various conditions that impact the pancreas, such as trauma, tumors, inflammation, and other related factors.	<ul style="list-style-type: none"> <li>• Cystic fibrosis</li> <li>• Trauma &amp; pancreatectomy</li> <li>• Fibrococalculus pancreatopathy</li> <li>• Neoplasia</li> <li>• Pancreatitis</li> <li>• Hemochromatosis</li> <li>• Others</li> </ul>	[19,21]
Endocrinopathies	It is observed in diseases characterized by the excessive secretion of hormones that antagonize the action of insulin.	<ul style="list-style-type: none"> <li>• Glucagonoma</li> <li>• Hyperthyroidism</li> <li>• Cushing's syndrome</li> <li>• Acromegaly</li> <li>• Pheochromocytoma</li> <li>• Aldosteronoma</li> <li>• Somatostatinoma</li> <li>• Others</li> </ul>	[20,21]
Drug- or chemical-induced diabetes	Certain medications and chemicals can interfere with the secretion or function of insulin, while others have the potential to cause damage to $\beta$ cells.	<ul style="list-style-type: none"> <li>• Vacor</li> <li>• Glucocorticoids</li> <li>• Pentamidine</li> <li>• Thyroid hormone</li> <li>• Thiazides</li> <li>• Alpha-adrenergic agonists</li> <li>• Beta-adrenergic agonists</li> <li>• Dilantin</li> <li>• Nicotinic acid</li> <li>• Pyrinuron</li> <li>• Interferon-alpha</li> <li>• Others</li> </ul>	[21]
Infections	Certain viruses have been linked to the direct destruction of $\beta$ cells.	<ul style="list-style-type: none"> <li>• Congenital rubella</li> <li>• Cytomegalovirus</li> <li>• Others</li> </ul>	[20,21]
Uncommon forms of immune-	Rare immune-mediated diseases have been	<ul style="list-style-type: none"> <li>• Anti-insulin receptor antibodies</li> <li>• "Stiff man" syndrome</li> </ul>	[19,21]

(continued on next page)

**Table (1) (continued)**

Other specific types of DM	Brief description	Examples	Reference
mediated diabetes	associated with this condition.	• Others	
Other genetic syndromes are sometimes associated with diabetes	The risk of diabetes is elevated in individuals with various genetic disorders and chromosomal abnormalities.	• Down syndrome • Turner syndrome • Klinefelter syndrome • Wolfram syndrome • Huntington chorea • Friedreich ataxia • Laurence-Moon-Biedl syndrome • Porphyria • Myotonic dystrophy • Prader-Willi syndrome • Others	[19–21]

## 2. The effect of chemicals and toxins in DM

There are several mechanisms through which long-term exposure to environmental toxins, such as arsenic (As) and other heavy metals, can contribute to the progression of diabetes mellitus (DM). Here's an explanation of how these toxins may lead to the development and progression of DM [35]:

- Increased oxidative stress: Environmental toxins like arsenic can induce oxidative stress in the body. Oxidative stress refers to an imbalance between the production of harmful reactive oxygen species (ROS) and the body's ability to detoxify them. Prolonged exposure to these toxins can overwhelm the body's antioxidant defense systems, leading to oxidative damage to various cells and tissues.
- Beta-cell dysfunction: The pancreas contains beta cells responsible for producing insulin, which regulates blood glucose levels. Oxidative stress and the disruption of mitochondrial function caused by toxins like arsenic can impair the function of these beta cells. This dysfunction can result in decreased insulin production or secretion.
- Insulin resistance: Toxins can also contribute to insulin resistance, a condition where the body's cells become less responsive to insulin. This often occurs in the context of obesity and metabolic dysfunction, which are associated with chronic exposure to environmental toxins.
- Inflammation: Oxidative stress and mitochondrial dysfunction triggered by toxins can lead to chronic inflammation. Inflammation can further exacerbate insulin resistance, disrupt insulin signaling pathways, and impair the overall ability of cells to respond to insulin.
- Mitochondrial dysfunction: Toxins like arsenic can disrupt mitochondrial function, which plays a critical role in energy metabolism. Impaired mitochondrial function can lead to decreased ATP production, causing a shift from oxidative phosphorylation to glycolysis for energy generation. This metabolic shift can affect the ability of beta cells to couple insulin secretion with glucose levels.
- Selenium deficiency: Selenium is an essential nutrient for the body and is involved in antioxidant defense mechanisms. Some toxins, like arsenic, can deplete selenium levels in the body, potentially reducing the activity of selenoproteins like glutathione peroxidase 1 (GPx-1). Lower GPx-1 activity can lead to an increased burden of hydrogen peroxide ( $H_2O_2$ ) and oxidative stress.
- Combined effects of multiple toxins: Humans are often exposed to various toxins simultaneously, and these toxins may have additive or synergistic effects on diabetes risk. This means that the combined impact of exposure to multiple environmental contaminants can be more detrimental than exposure to each toxin individually.

In summary, long-term exposure to environmental toxins can contribute to the progression of diabetes mellitus through a complex

interplay of mechanisms involving oxidative stress, beta-cell dysfunction, insulin resistance, inflammation, and mitochondrial dysfunction. These factors collectively disrupt glucose homeostasis and contribute to the development and worsening of diabetes. It's essential to understand and mitigate the impact of environmental toxins on metabolic health to reduce the risk of diabetes-related complications.

## 3. The role of inflammation in diabetes

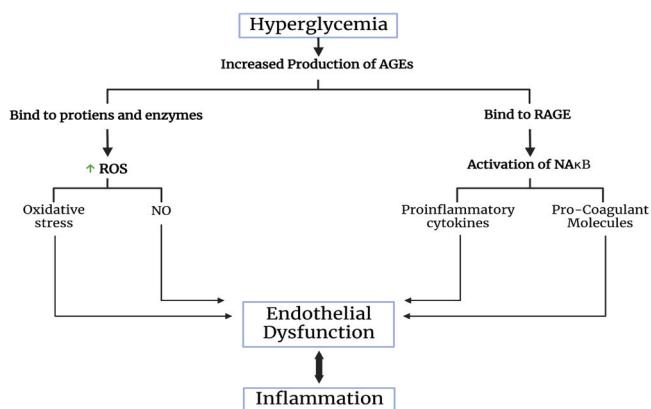
The resistance of Insulin and its related complications are partly driven by the inflammatory response, which is a primary molecular mechanism underlying their pathophysiology [36]. Insulin resistance and the onset of DM are connected to the presence of chronic low-grade inflammation. That can trigger other pathophysiologic mechanisms, such as  $\beta$ -cell dysfunction and impairment of insulin signaling. The relationship between DM and inflammation is not understood, but cytokines such as tumor necrosis factor-alpha (TNF- $\alpha$ ) and nuclear factor kappa B (NF- $\kappa$ B) can induce Janus kinase pathways (JNKs) that lead to an impairment in insulin signaling by stimulating insulin receptor substrate 1 (IRS-1) serine phosphorylation. Patients with diabetes have been found to have elevated levels of various circulatory mediators such as TNF- $\alpha$ , c-reactive protein (c-RP), monocyte chemoattractant protein (MCP-1), Interlukin-6 (IL-6), IL-1 $\beta$ , IL-18, E-selectin, Interferon- $\gamma$  (IFN- $\gamma$ ), and plasminogen activator inhibitor 1(PAI-1) [37–39]. Therefore, managing these inflammatory processes could be beneficial for treating diabetes. Studies have approved the significance of anti-inflammatory agents in maintaining the homeostasis of glucose. Oxidative stress can be associated with insulin resistance as it triggers monocytes and macrophage activation, leading to inflammatory responses responsible for insulin resistance and DM.

### 3.1. Inflammation in T1D

Type 1 diabetes (T1D) is an autoimmune disorder characterized by the targeted destruction of insulin-producing pancreatic  $\beta$  cells, while other cells in the pancreas remain unaffected [40]. However, T1D displays significant variation in terms of severity of the autoimmune response, age of onset, and response to treatment [41]. It has been established that both humoral (related to antibodies) and cellular (involving immune cells) immunity contribute to the development of T1D [42]. Early theories regarding predisposition suggest that environmental factors, such as infections, nutrition, and certain chemicals, may trigger the activation of self-directed immune reactions. These theories remain relevant, although the exact initial trigger for T1D is still not fully understood [43,44].

#### 3.1.1. Inflammatory infiltrates in T1D

Patients with T1D experience insulitis, an inflammation produced by the condition that affects the  $\beta$ -cell pancreatic islets [45]. Mechanisms of peripheral and central immunological tolerance that result in the production of reactive T cells in the peripheral blood [46]. Furthermore, findings from animal models reveal that both CD4+ and CD8+ T cells (also known as Effector T-cells/Teff) play a role in the initiation of type 1 diabetes (T1D) by targeting various  $\beta$ -cell autoantigens and related peptide epitopes. Moreover, research has shown that regulatory T cells (Tregs) become dysfunctional in the context of this autoimmune disease. Adoptive T-cell transfer models of T1D have demonstrated that different T-cell subtypes can lead to an unfavorable peri-islet infiltrate, ultimately resulting in overt diabetes. [47]. Notably, the immunological profile of B cells (CD20+) changes as the disease progresses, and early research indicates a close correlation with the migration patterns of CD8+ T cells, which may exhibit high or low islet infiltration. Macrophages also play a crucial role in islet inflammation as they release cytokines like TNF- $\alpha$  and IL-1 and produce reactive oxygen species (ROS). [48,49] as shown in Fig. (2). Additional research has revealed that the pancreatic exocrine tissue of patients with T1D

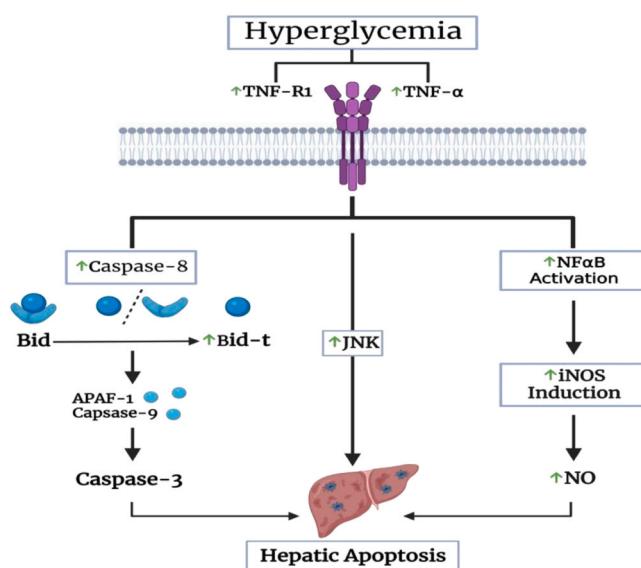


**Fig. (2).** Mechanism of hyperglycemia in promoting vascular complications through enhancing the production of the advanced glycation end products (AGEs), NO, ROS, NF- $\kappa$ B, and Receptor advanced glycation end product (RAGE).

contains a significant presence of neutrophils and lymphocytes. This finding further supports the hypothesis that these cells could play a role in the development of the disease. [50]. While the intricate interplay of various cell types appears to contribute to the progression of diabetes, some studies have also identified the presence of natural killer (NK) cells, dendritic cells, and natural killer T (NKT) cells in the islet infiltration. However, it is suggested that these cells might only play a minor role in the overall process of diabetes development [51,52].

### 3.1.2. Mediators of inflammation in T1D

Inflammation of pancreatic  $\beta$ -cells is caused by IFN- $\gamma$  interaction with some inflammatory cytokines, like IL-1 and TNF- $\alpha$  in T1D patients [53,54]. The combined effects of these inflammatory substances culminate in an increase in inducible nitric oxide synthase (iNOS), which produces NO [55] as shown in Fig. (3). Additionally, studies have demonstrated that the biology of the  $\beta$ -cell can directly affect how the body reacts to an inflammatory environment by influencing the  $\beta$ -cell death that is induced by IFN- $\gamma$  and PTPN2. The methods described above strongly suggest that there may be a variety of ways in which pancreatic  $\beta$ -cells can die. The regulation and management of local inflammatory cytokine production during this phase will likely play a significant role



**Fig. (3).** Schematic mechanisms of NF- $\kappa$ B activation induced by TNF- $\alpha$  signaling pathways.

in determining how the autoimmune process proceeds. The harmful effects of the attack on pancreatic islets through inflammation and autoimmune response can result in a cycle where initial stress caused by cytokines can worsen  $\beta$ -cell function, leading to further metabolic stress [56].

### 3.1.3. Anti-inflammatory trials on T1D

Since T1D has a strong genetic component, the immune cell pattern, and type present in each patient are important factors to consider when designing clinical studies aimed at delaying or stopping the progression of the disease (Table 2).

### 3.2. Inflammation in T2D

Various pathophysiological studies have provided significant insights into the development and progression of diabetes concerning insulin secretion and resistance. In individuals at risk of developing T2D, insulin resistance is initially observed, but it is compensated for by an increase in insulin secretion from the  $\beta$  cells. However, as the disease advances, the pancreatic functional reserve becomes inadequate to meet the rising demand for insulin secretion, leading to a point where, at the time of diabetes diagnosis, the beta cells are no longer capable of producing sufficient insulin. While the extent of insulin resistance and beta cell dysfunction may vary among individuals with T2D, it is widely recognized that abnormal insulin sensitivity can occur up to 15 years before the clinical diagnosis of diabetes. Therefore, apart from investigating the mechanisms behind insulin resistance, recent research has also focused on understanding the pathways that contribute to  $\beta$  cell failure. This research aims to develop a better understanding of the disease progression and identify potential targets for intervention to reduce the risk of developing diabetes [74].

In recent times, mounting evidence has highlighted the significance of low-grade inflammation in the pathogenesis of T2D. Individuals who eventually develop T2D often show indications of inflammation even before the disease's onset. Research studies have established a robust link between inflammatory markers and abnormalities in lipid and carbohydrate metabolism, as well as associations with atherosclerosis and obesity. A sedentary lifestyle and obesity are recognized as major factors contributing to insulin resistance and the development of T2D. Chronic low-grade inflammation has been observed in obesity, insulin resistance, early stages of atherosclerosis, and T2D. Adipose tissue (AT), previously thought to be passive, has been found to have an active endocrine function, expressing pro-inflammatory mediators that are increased in obesity and linked to insulin resistance. Macrophages play a role in the inflammatory pathways within AT and are associated with adipocyte dysfunction. Macrophages in AT secrete pro-inflammatory factors and can modulate adipocyte activity [58,75].

Moreover, in obese individuals, peripheral blood mononuclear cells demonstrate an inflammatory state, showing elevated levels of pro-inflammatory cytokines. The dysregulation of AT in insulin resistance conditions results in chronic low-grade systemic inflammation, as AT serves as a significant source of inflammatory factors. These research findings underscore the role of AT dysfunction and inflammation in the development of insulin resistance and T2D. The interaction between inflammation and insulin signaling pathways further contributes to insulin resistance and endothelial dysfunction, thereby increasing the susceptibility to cardiovascular disorders [75].

### 3.2.1. Mediators of inflammation T2D

In T2D, chronic low-grade inflammation is one of the diabetic pathogeneses. Various mediators of inflammation contribute to  $\beta$ -cell dysfunction, insulin resistance, and the improvement of T2D. The key mediators of inflammation in T2D include cytokines, adipokines, chemokines, and inflammatory signaling molecules [75].

**Table (2)**

Reported anti-inflammatory mediators in T1D.

Drug	Mechanism of Action	Main Findings	Side Effects	References
Rituximab	Monoclonal anti-CD20 antibody	Moderate effectiveness in the initial two clinical trials Rate of C peptide ↓, insulin requirements↓, HbA1c ↓	Common side effects may include infusion reactions, infections, and infusion-related symptoms.	[57–59]
Teplizumab Otelixizumab	Two humanized anti-CD3 monoclonal antibodies (mAbs)	The decreased loss rate of β-cell functions in individuals recently diagnosed with T1D	Common side effects may include infections, gastrointestinal symptoms, and rash.	[60]
Etanercept	TNF antagonism	Improved metabolic control and increased endogenous insulin production in young T1D patients. HbA1c ↓, endogenous insulin production ↑	Common side effects may include injection site reactions, infections, and headaches.	[61,62]
Alpha-1 antitrypsin (AAT)	Anti-inflammatory serum protein	Improved β-cell function and decreased IL-1β response in monocytes and dendritic cells in T1D patients IL-1β response to monocytes and dendritic monocytes ↓, β-cell function ↑	Side effects are generally rare but may include fever, rash, and injection site reactions.	[63,64]
Vitamin D analogue	Alfacalcidol	β-cell preservation especially in male subjects Potential therapeutic target with anti-inflammatory properties, but limited β-cell protection demonstrated in recent T1D cases	Common side effects may include gastrointestinal symptoms, headache, and fatigue.	[65–67]
Vitamin D analogue	Calcitriol	In the treatment group, there was an ↑ in fasting C peptide levels from the time of diagnosis to one year, while the daily insulin dosage showed a significant ↓.		[68]
Proinsulin peptide	Human leukocyte antigen-DR4 (DRB1 *0401)	↑ C-peptide, ↑ Proinsulin induces the production of IL-10, which is a favorable outcome for β-cell health, as indicated by the proinsulin/C-peptide ratio, a marker of β-cell stress.	Side effects are generally rare but may include injection site reactions and hypersensitivity reactions.	[69]
Engineered DNA plasmid encoding proinsulin	BHT-3021	↓ CD8 + T cells reactivity to proinsulin, C peptide level maintained, no change can be observed to Interferon-γ, IL-10, IL-4		[70]
IL-1beta antagonism	Canakinumab	No C peptide response	Common side effects may include infections, upper respiratory tract infections, and gastrointestinal symptoms.	[71]
IL-1 receptor blockade	Anakinra	↓ insulin requirements compared with controls, ↓ insulin dose adjusted. No C peptide response.	Common side effects may include injection site reactions, infections, and gastrointestinal symptoms.	[72]
IL-1 receptor blockade IL-1β antagonism (plasma↑ transcriptional meta-analysis)	Anakinra/canakinumab	The relationship between C peptide ↑ & inflammation is immunomodulation or reverse.		[73]

**3.2.1.1. Cytokines.** The primary cytokines implicated in T2D are IL-1β, IL-6, TNF-α, and leptin. IL-1β is a crucial inflammatory cytokine that may contribute to the dysfunction and apoptosis of beta cells. IL-6 and TNF-α are significant cytokines produced by adipocytes that can impair insulin action and promote insulin resistance. TNF-α is particularly abundant in adipose tissue and is associated with obesity, insulin resistance, and beta-cell dysfunction. IL-6 exerts multiple effects on glucose metabolism and insulin sensitivity, and elevated levels are observed in obese individuals, predicting future T2D risk. Leptin, produced by adipocytes, plays a role in regulating energy homeostasis and has various actions. It is involved in insulin resistance, appetite regulation, and modulation of the immune system. Leptin levels are positively correlated with obesity and insulin levels [76].

These cytokines have been associated with several aspects of T2D development, including inflammation, insulin resistance, dysfunction of beta cells, and metabolic abnormalities. They play roles in promoting adipose tissue dysfunction, impairing insulin signaling, inducing oxidative stress, and contributing to chronic low-grade inflammation. Understanding the roles and interactions of these cytokines is crucial for unraveling the mechanisms underlying T2D and developing potential therapeutic strategies for its prevention and treatment [77].

**3.2.1.2. Adipokines.** Adipokines are cytokines that are released by adipose tissue, and they play a role in the development of insulin resistance and T2D. One such adipokine is adiponectin, which possesses anti-inflammatory properties. However, its levels are reduced in individuals with insulin resistance and obesity. This deficiency is linked to insulin resistance and an increase in the production of pro-inflammatory cytokines. Conversely, leptin, another adipokine, is elevated in obesity and has been associated with inflammation and insulin resistance [78].

**3.2.1.3. Chemokines.** Chemokines are chemotactic cytokines that attract immune cells to sites of inflammation. In T2D, chemokines such as interleukin-8 (IL-8) and monocyte chemoattractant protein-1 (MCP-1) are involved in the recruitment of immune cells, particularly macrophages, to adipose tissue. The infiltration of macrophages into adipose tissue further promotes inflammation and contributes to insulin resistance [79–81].

**3.2.1.4. Inflammatory signaling molecules.** Inflammatory signaling molecules, such as c-Jun N-terminal kinase (JNK) and nuclear factor-kappa B (NF-κB), are activated in the presence of obesity and metabolic dysfunction. These signaling pathways are involved in the production of pro-inflammatory cytokines and the activation of inflammatory responses, leading to impaired glucose metabolism and insulin resistance [75].

**3.2.1.5. Adiponectin.** Adiponectin is a protein produced by fat cells that has anti-inflammatory and potentially antiatherogenic properties. Its levels are reduced in individuals with insulin resistance, heart disease, and T2D. Adiponectin improves insulin sensitivity, inhibits liver glucose production, promotes fatty acid oxidation in muscles, and has positive effects on blood vessel function. It also reduces inflammation by inhibiting certain signaling pathways and the production of inflammatory molecules. Additionally, adiponectin protects against atherosclerosis by preventing the accumulation of cholesterol in immune cells besides reducing the adhesion of these cells to blood vessel walls. On the other hand, IL-6, another molecule, decreases the expression and release of adiponectin [82,83].

**3.2.1.6. Resistin.** Resistin is a hormone generated by fat cells, mainly in

white adipose tissue, and is involved in insulin resistance. Interestingly, resistin administration has been shown to significantly increase the expression of a specific protein called SOCS-3 in fat cells [84,85].

**3.2.1.7. CD40 ligand (CD40L).** CD40 ligand (CD40L) is a mediator of inflammation that is present in certain immune cells and activated platelets. It plays a role in promoting blood clotting processes and inflammation that contribute to the improvement of atherosclerosis [86].

In T2D, inflammation plays a crucial role in both its development and progression. Multiple mediators of inflammation, including cytokines, adipokines, chemokines, and inflammatory signaling molecules, contribute to beta cell dysfunction, insulin resistance, and the exacerbation of T2D. Adiponectin, resistin, and CD40L are particularly involved in the inflammatory processes linked to insulin resistance, obesity, and T2D. Gaining a comprehensive understanding of these inflammatory pathways and their interactions can offer valuable insights into the underlying mechanisms of T2D, potentially leading to knowledge of therapeutic targets for the prevention and management of the disease [75] as shown in Fig. (4).

### 3.2.2. Current knowledge of T2D treatments

In addition to their primary modes of action, the current treatment methods for T2D also contain anti-inflammatory qualities [87]. As measured by circulating c-reactive protein (c-RP) and IL-6 concentrations, non-pharmacological therapy for weight loss, such as lifestyle changes, as well as pharmacological and bariatric surgery procedures, appear to lower inflammation and improve cardiovascular and all-cause mortality, Table 3.

### 3.2.3. Anti-inflammatory drugs in T2D

Over the past few years, numerous medicinal strategies targeting specific inflammatory pathways have been developed to support the idea of anti-inflammatory therapy for cardiometabolic disorders such as atherosclerotic, CVD, and diabetes Table 4 [74].

## 4. Role of some organs in T2D related to inflammation

### 4.1. Role of adipose tissue and obesity in T2D

The liver and muscles contribute significantly to systemic insulin resistance [105]. Steatosis is expected to have a main role in impaired hepatic insulin sensitivity that results in fasting hyperglycemia. Steatosis is the accumulation of fats in the liver that happens before T2D and is frequently associated with obesity [106]. Furthermore, excessive calorie intake leads to the buildup of fat in subcutaneous tissue, followed by the deposition of fat in other tissues like the liver, pancreas, muscles, and perivascular tissue [107]. While pancreatic fat buildup increases tissue insulin resistance, it also serves to further define  $\beta$ -cell failure. The presence of inflammatory biomarkers is inversely correlated with insulin resistance, the prevalence of T2D and CVD, and obesity-related illnesses such as metabolic syndrome, hypertension, and dyslipidemia. Particularly, eating too much and not moving enough can lead to diseases like obesity and metabolic syndrome. Activation of at least two key inflammatory pathways, such as the transcription factor NF- $\kappa$ B, and the stress-activated JNK as well as subacute chronic inflammation serve as common and potentially unifying mechanisms for these diseases. Numerous studies have demonstrated that adipokines enhance obesity-induced metabolic and cardiovascular diseases and stimulate additional inflammatory responses; however, they have also demonstrated that adipokines amplify this inflammatory state by stimulating the production of pro-inflammatory cytokines [108]. Studies have indicated that brown adipose tissue (BAT) plays a crucial role in regulating energy and glucose homeostasis, as evidenced by its association with peripheral insulin resistance and blood sugar levels in animal models. In contrast, white adipose tissue (WAT), particularly visceral WAT located in the trunk, upper body, or abdomen, is the primary origin of inflammatory markers in T2D. [107]. However, white adipose tissue (WAT) is also a target of the inflammatory response in diabetic patients. WAT generates numerous bioactive substances associated with inflammatory pathways, including TNF- $\alpha$ , IL-6, IL-1, IL-10, adiponectin, leptin, chemokines, monocyte chemoattractant protein, resistin, angiotensinogen, and serum amyloid protein. The infiltration of macrophages and immune cells (B & T cells) into adipose tissue leads to chronic low-grade

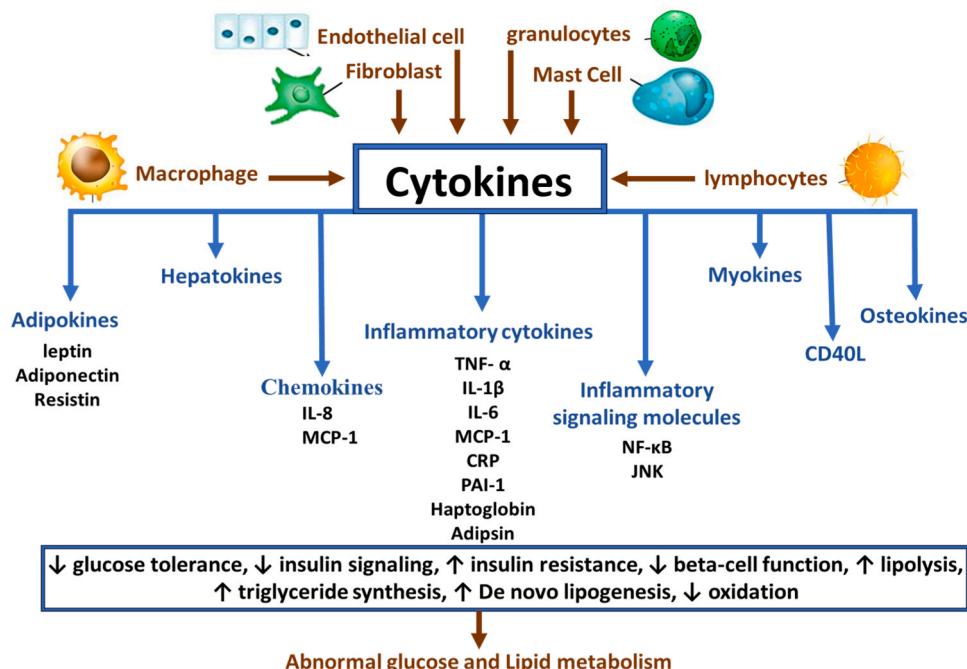


Fig. (4). The key Mediators of inflammation in type 2 diabetes.

**Table (3)**

Current treatments of T2D.

Drugs	Mechanism of action and main funding	Receptors targeted	Side effects	References
Rosuvastatin	Lowered high-sensitivity of c-RP along with low-density lipoprotein (LDL) and cholesterol; however, effects of statins on glycaemic control are inconsistent, indicating that they do not improve glycemic control and do not, therefore, offer an integrated anti-inflammatory therapy for diabetes and cardiovascular diseases (CVD).	HMG-CoA Reductase	Common side effects may include muscle pain, liver enzyme abnormalities, and gastrointestinal symptoms.	[61]
Insulin	Can cause ↓ levels of inflammatory markers. Reduced inflammation by insulin is achieved through lowering NF-κB activity in mononuclear cells of the blood.	Insulin Receptor	Common side effects may include hypoglycemia, injection site reactions, and weight gain.	[88]
Thiazolidinediones	Have anti-inflammatory properties through ↑ the peroxisome proliferator-activated receptor gamma (PPAR-γ), associated with decreased expression of NF-κB targets and trans-repression of NF-κB.	PPAR-γ	Common side effects may include weight gain, edema, and an increased risk of fractures.	[89]
Metformin	Has metabolic and anti-inflammatory effects on the immune cells and vascular tissues that could be independent of glycemia.	AMPK	Common side effects may include gastrointestinal symptoms (diarrhea, nausea), vitamin B12 deficiency, and lactic acidosis (rare).	[90]
Sodium-glucose cotransporter-2 inhibitors (SGLT2 inhibitors)	A novel family of anti-diabetic medications works by enhancing the renal excretion of glucose. The circulating indicators of inflammation may be improved by SGLT2 inhibitors in people, according to preliminary evidence; nevertheless, more research is required.	SGLT2	Common side effects may include urinary tract infections, genital yeast infections, and increased urination.	[91]

**Table (4)**

Anti-inflammatory drugs in T2D.

Drugs	Mechanism of action	Main findings	Side Effects	References
Anakinra	IL-1 receptor blockade	studies on their use in the prevention of atherosclerosis and CVD have HbA1c, leukocyte ↓, CR↓ insulin secretion↑, insulin requirement ↓, and Insulin sensitivity ↑.	Common side effects may include injection site reactions, infections, and headaches.	[92,93]
Gevokizumab	IL-1beta antagonism	studies on their use in the prevention of atherosclerosis and CVD have HbA1c ↓, CRP > ↓, and insulin secretion ↑.	Common side effects may include upper respiratory tract infections, injection site reactions, and gastrointestinal disturbances.	[94]
Canakinumab	IL-1beta antagonism	T2D patients with high CVD risk have CRP ↓, HbA1c ↓, insulin secretion ↑, fibrinogen ↓, IL-6 ↓.	Common side effects may include infections, injection site reactions, and gastrointestinal symptoms.	[95,96]
Salsalate	IKKbeta-NF-kappaB inhibition	FBG ↓, CRP ↓, insulin sensitivity ↑, adiponectin ↑, HbA1c ↓, insulin secretion ↑, triglyceride ↓, leukocyte ↓, and uric acid ↓.	Common side effects may include gastrointestinal symptoms, headache, and dizziness.	[97,98]
Soluble TNF receptor-Fc fusion protein (etanercept)	TNF antagonism	insulin secretion ↑, FBG ↓, CRP ↓, LDL ↓, adiponectin ↑, no effect on sensitivity of insulin	Common side effects may include injection site reactions, infections, and headaches.	[99]
Infliximab	TNF antagonism	Fasting glucose ↑, ratio of high molecular weight to total adiponectin ↑, no effect on CRP.	Common side effects may include infections, gastrointestinal symptoms, and infusion reactions.	[100]
Diacerein	Decrease in TNF and IL-1β levels by an unknown mechanism of action	HbA1c ↓, FBG ↓, insulin secretion ↑	Common side effects may include gastrointestinal symptoms, skin reactions, and liver enzyme abnormalities.	[101]
Methotrexate	DHFR inhibitor – antimetabolite	No effects on CRP, IL-1beta or IL-6	Common side effects may include nausea, fatigue, and liver function abnormalities.	[102]
Methotrexate + Sulphasalazine	DHFR inhibitor & (DMARD) combination	HbA1c ↓	Side effects may vary depending on the specific drugs used in the combination.	[103]
Salicylates; aspirin	Non-steroid anti-inflammatory drugs (NSAIDs)	Treat thrombosis in rheumatoid disorders and primary and secondary CVD prevention.	Common side effects of methotrexate include nausea and fatigue.	[104]

inflammation due to an elevation in the production of chemokines and cytokines, establishing a pathological link between diabetes, obesity, and insulin resistance [107] as shown in Fig. (5).

#### 4.2. Role of pancreatic β-cell in T2D

T2D is significantly influenced by β-cells found within the pancreatic islets of Langerhans. These cells play a vital role in regulating insulin release through glucose-stimulated insulin secretion (GSIS), triggered by glucose stimulation. The function and quantity of β-cells are modulated by different transcription factors, which are regulated by pancreatic pericytes and macrophages. [109].

Inceptor, an inhibitory receptor for insulin, aids in the internalization of the insulin receptor (IR) through a process called clathrin-mediated endocytosis. In T2D, β-cells undergo exhaustion as they proliferate in number and enlarge to enhance insulin secretion into the bloodstream. However, challenged beta-cells can undergo dedifferentiation or apoptosis, leading to dysfunction. These dysfunctional beta-cells have cytotoxic effects that worsen the symptoms of T2D [109].

Inflammation in the pancreatic Langerhans β-cell islets (insulitis) is a common pathway observed in different types of diabetes, regardless of the underlying cause. Insulitis leads to a decline in the function and number of β-cells [110]. According to some theories, the "stressed" β-cell may change the ratio of β-cell mass in Langerhans islets, resulting in

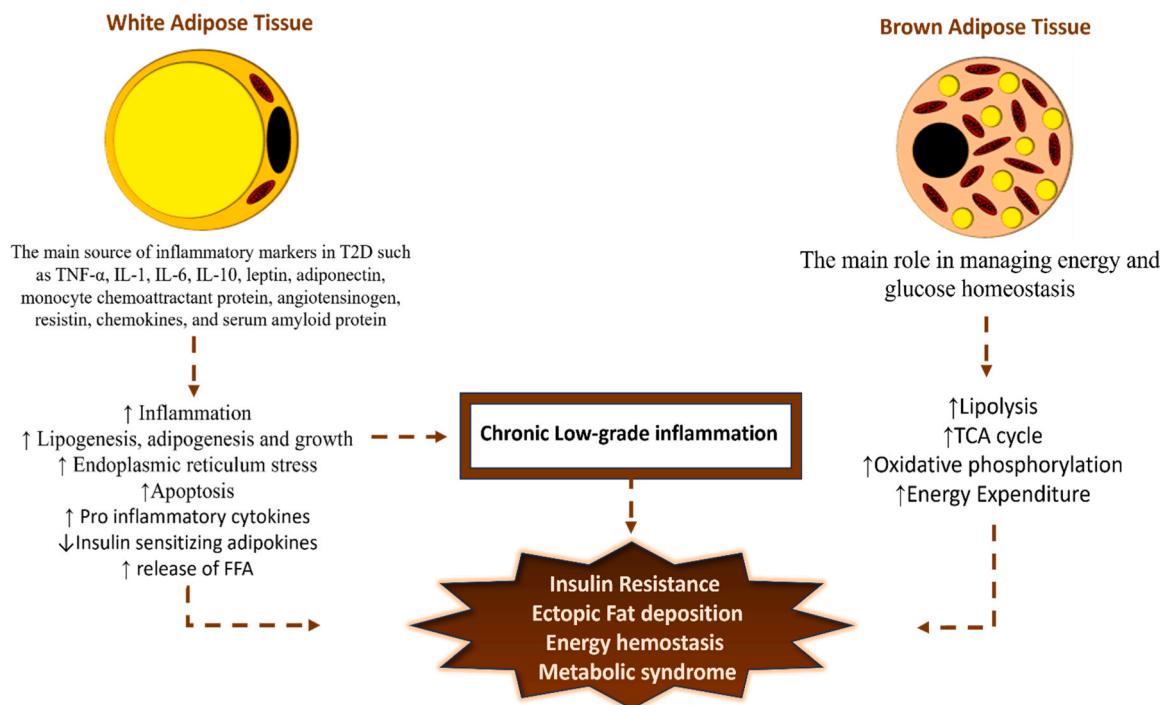


Fig. (5). Role of Adipose Tissue (WAT) & (BAT) in T2D related to inflammation.

localized inflammation in people with a hereditary predisposition. Numerous experimental models and observational human studies have revealed that macrophages are the major cause of islet inflammation in T2D patients [111]. The inflammasome/IL-1 $\beta$  signaling is the major and most common pathway that is active in the islets of various T2D models and causes  $\beta$ -cell loss. Although it has also been suggested that islet autoimmunity contributes to the decline in  $\beta$ -cell activity throughout T2D, other immune cells could also be involved in the inflammation of

the islets in this condition. Free fatty acids (FFAs), endocannabinoids, and amyloid polypeptides are a few of the stimuli that induce islet macrophages to release IL-1 in human islets as shown in Fig. (6).

However, it has been hypothesized that the primary cause of hyperglycemia is inflammation in pancreatic  $\beta$ -cells, which results in apoptotic processes. In addition, after being initially produced, IL-1 regulates the generation of insulin by activating the pancreatic  $\beta$ -cells on their own. This method also increases the synthesis of NO, which

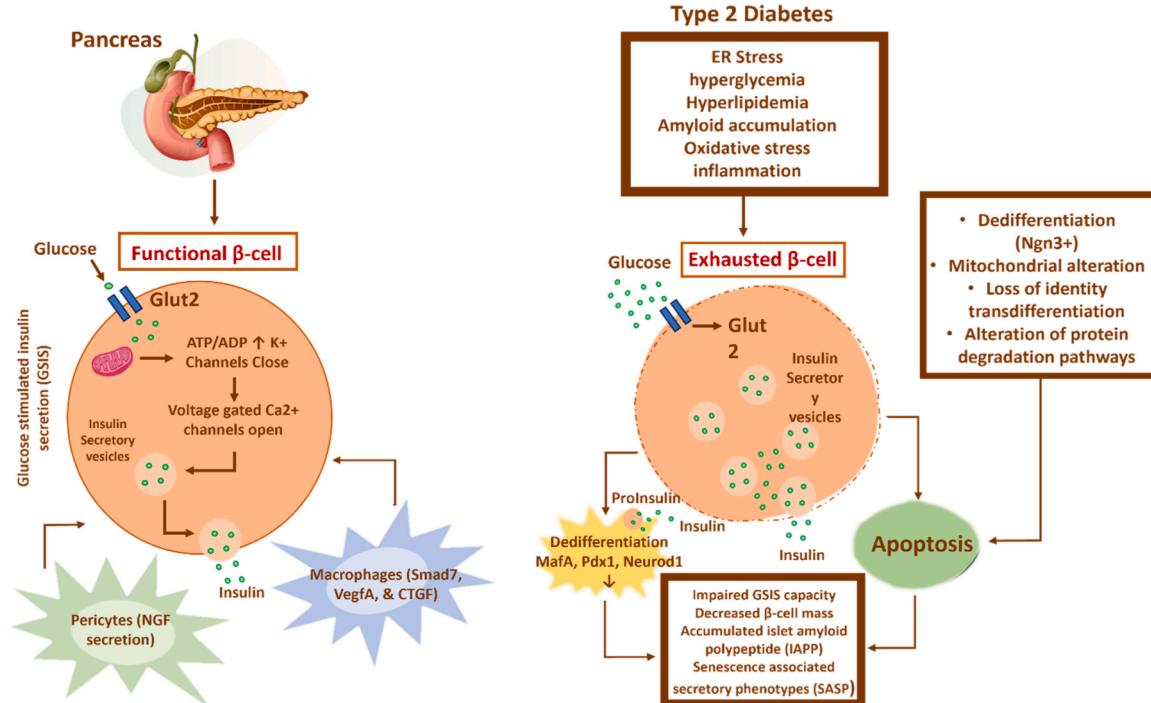


Fig. (6). The Integral Role of Pancreatic  $\beta$ -Cells in the Pathogenesis of Type 2 Diabetes: Regulation, Dysfunction, and Inflammatory Mechanisms Leading to  $\beta$ -Cell Loss and Hyperglycemia.

reduces the amount of ATP in the mitochondria [112]. Oxidative stress may ↑ the  $\beta$ -cells' production of ROS and other proinflammatory cytokines and chemokines, which would damage their blood supply and render them ineffective. Along with other inflammatory cytokines, IL-6 initiates pancreatic islet apoptosis, hence it acts as a pathologic marker for monitoring T2D [113]. By establishing a connection between islet inflammation, insulin resistance, and obesity, TNF- $\alpha$  is also thought to play a crucial role.  $\beta$ -cell inflammation and death appear to be fueled by their overproduction in adipose tissue, and this leads to more insulin resistance in peripheral tissues [112,114].

#### 4.2.1. Manifestations of pancreatic Langerhans $\beta$ -cell islets inflammation in people with T2D

T2D incidence and development are closely correlated with immune system activation, and inflammation of adipose tissue is mediated by both innate and adaptive immunity [115]. A key factor in the beginning and intensification of islet inflammation is the phenotypic flip of macrophages from primarily anti-inflammatory M2-type to higher proportions of pro-inflammatory M1-type macrophages. Studies revealed that activation of  $\beta$ -cell and T-cell recruitment is followed by macrophage invasion to adipose tissue. Other organs, such as the liver, nervous system, and skeletal muscle, are also involved in the regulation of inflammatory state and metabolic homeostasis in T2D. However, more studies are still required to support that claim [116].

#### 4.2.2. Oxidative stress and antioxidant defense system in $\beta$ -cells

Active biomolecules known as free radicals are produced physiologically during metabolic processes and/or by immune cells [117]. Free radicals play important physiological functions in a wide range of molecular processes, like cell-cell communication, synaptic plasticity, defense against pathogen invasion, memory formation, cell-cell interactions, apoptosis, cell proliferation, aging, and autophagy [118]. However, oxidative stress is generated when free radical levels exceed the natural antioxidant defense capacity. Catalase (CAT), glutathione (GLT), and superoxide dismutase (SOD) are just a few of the several enzymes that most biological cells use as part of their inherent defense system to shield them from free radical damage. Free radicals are reactive derivatives of either oxygen or nitrogen molecules, such as ROS: hydrogen peroxide, hydroperoxyl, and hydroxyl radicals as well as superperoxides [119]. Due to the unpaired electrons in the molecules that make up the outer layer of these hyperactive components, they can bind to and alter other biomolecules. They can oxidize nucleic acids, proteins, and lipids, producing toxic byproducts that cause tissue malfunction [120]. Additionally, they change and sometimes even destroy the architecture of biological molecules. One well-known consequence of oxidative stress, which has an impact on gene expression in general and cell survival, is DNA damage [121]. In addition to their harmful direct effects, free radicals can also harm cells indirectly by activating several stress-sensitive intracellular signaling pathways, including the JNK/SAPK (stress-activated protein kinase/c-Jun NH (2)-terminal kinase), p38, mitogen-activated protein kinases (MAPK), NF- $\kappa$ B, PKC (protein kinase PKC (protein kinase C), AGE/RAGE (advanced glycation end product/receptor for AGE) interactions, hexosamine pathways, and sorbitol synthesis. Biomarkers such as total cholesterol, reactive hydroperoxides (ROOH), and malondialdehyde (MDA) are used to monitor oxidative stress in diabetic patients. Oxidative stress plays a crucial role in the pathogenesis of numerous problems of diabetes by altering lipid peroxidation and inducing mitochondrial malfunction and DNA damage [122]. Additionally, it plays various roles in pathological situations as well as age-related illnesses like cancer, chronic renal disease, chronic obstructive lung disease, and CVD. The steady loss of tissue function brought on by a variety of causes, including increasing free radical species, is known as aging and the illnesses that it is associated with. The oxidative stress theory is widely accepted as the primary explanation for aging and the difficulties associated with it. Therefore, maintaining a normal state of redox biology is crucial to preventing difficulties brought

on by oxidative stress as well as insulin resistance [123].

#### 4.2.3. Insulin production and secretion because of $\beta$ -cell dysfunction

Normal glucose homeostasis requires healthy and functional pancreatic  $\beta$ -cells. Therefore, DM is associated with variable degrees of  $\beta$ -cell malfunction [124]. A significant factor in the improvement of diabetes mellitus (DM) is the progressive loss of  $\beta$ -cell mass and function. This leads to impaired and reduced production of glucose-induced insulin, resulting in elevated postprandial glucose levels. The initial phase of insulin release is affected, followed by a decline in postprandial insulin secretion, leading to defects in steady-state and basal insulin release. Ultimately, this process culminates in total  $\beta$ -cell failure. The dysfunction or failure of  $\beta$ -cells is influenced by oxidative stress and various pathogenic mechanisms. Chronic hyperglycemia in islets triggers the production of free radicals through biochemical processes, such as elevated cytosolic calcium levels and activated protein kinase.  $\beta$ -cells are particularly susceptible to oxidative stress as they lack a specialized antioxidant defense mechanism. Consequently, oxidative stress is a common occurrence in both T1D and T2D, significantly contributing to the loss of function observed in these conditions [125]. Several biochemical pathways underlie the impairment of  $\beta$ -cell function by oxidative stress. It leads to a substantial reduction in insulin synthesis and impairs the insertion of proinsulin vesicles into the plasma membrane. Additionally, it diminishes their exocytosis in response to changes in blood glucose levels. Additionally, it can cause the pancreatic cells to undergo apoptotic processes that result in death and the loss of  $\beta$ -cells. Several proapoptotic substances are extremely reactive to oxidative stress and can cause pancreatic cells to undergo apoptosis [126]. A surplus of free radical species also affects  $\beta$ -cells' metabolic processes negatively and damages KATP channels, which reduces insulin production. According to studies showing that genetic knockout models of  $\beta$ -cell KATP channels protected them from oxidative stress, free radicals damage KATP channels by attaching to their SH residues [127]. Higher levels of free radicals prevent Pdx-1 (the insulin promoter factor 1) and MafA (a transcription factor) from regulating insulin gene expression, which lowers insulin synthesis at the DNA level [128]. Wang showed in 2017 that oxidative stress caused NF- $\kappa$ B, p38 MAPK, JNK/SAPK, and hexosamine pathways to be activated. These stress-activated signaling pathways are crucial in the malfunctioning of  $\beta$ -cells. TLRs (toll-like receptors) can also be activated by free radicals, which in turn impairs  $\beta$ -cell activity [129]. Another potential biological link between  $\beta$ -cell dysfunction and oxidative damage is oxidative stress-induced mitochondrial malfunction [130].

#### 4.2.4. Glucose transporter type 4 (GLUT-4) expression and/or localization

A GLUT-4 controls the amount of glucose that enters insulin-dependent cells including myocytes and adipocytes [131]. Any factor that lowers insulin sensitivity is mainly altered through GLUT-4 expression because it limits the amount of glucose that enters target cells, which results in decreased insulin sensitivity in tissues. Clinical investigations demonstrate that T2D patients with insulin resistance have reduced GLUT-4 expression and/or location. Localization and Normal expression of GLUT-4 are important to control insulin sensitivity in tissues because GLUT-4 controls glucose entry into insulin-dependent cells including myocytes and adipocytes. Any factor that reduces the expression of GLUT-4 has a considerable impact on the sensitivity of target tissues to insulin, as it restricts the amount of glucose that can enter the cells. The mechanisms listed below help oxidative stress to produce this pathophysiologic condition; the mitochondria-targeted paraquat was used to cause mitochondrial oxidative stress in mouse adipocytes and myotubes. It was noticed that GLUT-4 trafficking was markedly suppressed and led to insulin resistance in tissues. The transcriptional regulators of GLUT-4 expression, including NF- $\kappa$ B, PPAR- $\gamma$ , nuclear factor-1, p85, CEB/Ps (CCAAT enhancer-binding proteins), MEF2 (myocyte enhancer factor 2), and HIF-1 (hypoxia-inducible factors alpha), can be suppressed by persistent oxidative stress.

Additionally, oxidative damage activates a variety of factors and byproducts that are caused by oxidative stress, including p38 MAPK, PKC, JNK/SAPK, hexosamine, and sorbitol, which can all inhibit GLUT-4 expression. Therefore, localization and/or lowering expression of GLUT-4 is the substantial molecular mechanism through which DM could be developed due to insulin resistance resulting from oxidative stress [127].

#### 4.2.5. Insulin signaling pathways

Malfunctioning of insulin signaling pathways may affect how quickly insulin resistance and diabetes develop. Insulin signal transduction (IST) regulation has been suggested as a potential therapeutic target for improving insulin sensitivity. Oxidative stress deteriorates the proper IST at several levels, including IRS, IRS-1 and IRS-2, Akt signaling pathways, and PI3K enzyme. When T2D-induced oxidative stress was created in diabetic rats, researchers found IST components in the brains of those animals. They found that *Nigella sativa* oil might stop these changes and return insulin signaling to normal [132]. In brain tissues, oxidative stress drastically reduced the expression of IST components such as p-IRS, p-AKT, and GSK-3. They can also disrupt normal IST via p38 MAPK-dependent molecular pathways; *in vitro* and *in vivo* models of diabetes, blocking this pathway restored normal IST. The oxidative stress brought on by hyperglycemia activates IKK-B, a stress-sensitive serine/threonine (Ser/Thr) kinase, which then phosphorylates a variety of substrates, including the IRS, IRS-1, and IRS-2 [127]. As a result, there are negative knock-on effects such as insulin resistance and ↓ PI3K activation. *In vitro*, research has shown that the IKK-inhibitor salicylates can restore the normal IST in oxidative stress. Other serine/threonine kinases that are vulnerable to oxidative stress that may impair insulin signaling include Akt (or PKB), AMPK, mTOR, and GSK-3. By causing the proteins required for typical IST function to be downregulated, oxidative stress can also harm IST. Free radicals have an impact on the main IST components, including GSK-3, IRS, IRS-1, and Akt, and are downregulated by oxidative stress. As a result, there will be an increase in DM and insulin resistance. As a result, the disruption of the normal IST is due to oxidative stress and insulin resistance [133] as shown in Fig. (7).

#### 4.2.6. Systemic mitochondrial dysfunction

Mitochondria are double-membrane organelles that are responsible for energy production, calcium storage, the creation of fatty acids and heat, as well as cell survival. They also participate in cellular signaling networks [134]. It has been established that insulin resistance and DM have a pathogenesis that includes mitochondrial dysfunction. Most cases of mitochondrial dysfunction result from oxidative stress, which disrupts mitochondrial function. Disruption of mitochondrial function

occurs due to a reduction in the respiratory capacity of mitochondria, alteration in the normal function of the Mitochondrial Respiratory Chain (MRC), increased levels of proton leak in the MRC, and alteration in the potential difference through the inner mitochondrial membrane resulting in disruption of mitochondrial membranes integrity [135]. These processes can take place in either pancreatic islets (locally) or adipocytes and muscle tissues (systemically). Healthy mitochondria generating the energy required for glucose uptake are essential for maintaining normal processes of glucose uptake in peripheral tissues via GLUT-4. As a result, mitochondrial dysfunction significantly lowers the capacity of cells to produce ATP and inhibits the absorption of glucose caused by insulin in adipocytes and muscle cells [136]. Insulin resistance results from the cells' inability to take up blood glucose for insulin response under these circumstances. Furthermore, oxidative stress may adversely affect mitochondrial function by promoting the synthesis of DAG (diacylglycerol) and fatty acid oxidation within the mitochondria. This process can lead to the activation of additional serine/threonine kinases and the impairment of insulin signal transduction (IST). As a consequence, oxidative stress-induced mitochondrial dysfunction presents another biological mechanism through which free radicals contribute to insulin resistance [137].

#### 4.3. Role of gut microbiota in T2D

Studies have indicated that there are various factors involved in weight loss following bariatric surgery, apart from just malabsorption or physical limitations. Changes in gut hormones after bariatric surgery have been found to have positive metabolic effects in the short- and long-term and offer potential new therapeutic approaches for treating insulin resistance and obesity [138]. Recent studies have also shown that there is a connection between the body's energy balance and immune system, and the bacteria in the gut. Transplanting gut bacteria from lean donors to insulin-resistant individuals has been found to have beneficial metabolic effects. The composition of gut bacteria is influenced by metabolic status and diet and differs between obese and lean individuals. The onset of obesity and diabetes is believed to be linked to low-grade inflammation generated from a metabolic change in the body triggered by an interaction between the immune system and products from gut microbiota [139].

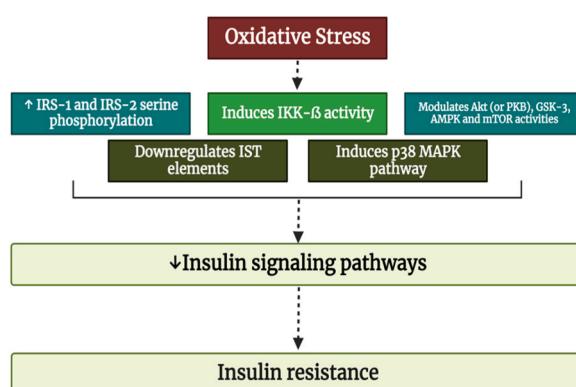
Lipopolysaccharides (LPS) can induce inflammation by triggering the sensation of inflammatory cytokines. Conversely, Short-chain fatty acids (SCFAs) have the opposite effect, as they can reduce the production of pro-inflammatory cytokines and chemokines while promoting the growth of regulatory T cells. Additionally, SCFAs inhibit the activity of inflammatory T cells and prevent the release of IFN-inducible protein 10 (IP-10) in human colonic sub-epithelial myofibroblasts. This indicates that SCFAs play a role in dampening the inflammatory response and promoting immune regulation [140].

Organ impairment can result from a range of harmful compounds that an unbalanced gut flora can create. The bacterial metabolites imidazole propionate (ImP) and branched-chain amino acids (BCAA) can develop insulin resistance by inhibiting insulin signaling [141]. Trimethylamine (TMA) is transformed by the liver into trimethylamine-N-oxide (TMAO), which hastens the onset of diabetic nephropathy. Furthermore, increased levels of some nephrotoxic metabolites such as indoxyl sulfate and P-cresyl sulfate could worsen kidney damage. Increased ethanol- and phenylacetate-producing bacteria in the intestines encourage the growth of non-alcoholic fatty liver disease (NAFLD) and further liver damage [142] as described in Fig. (8).

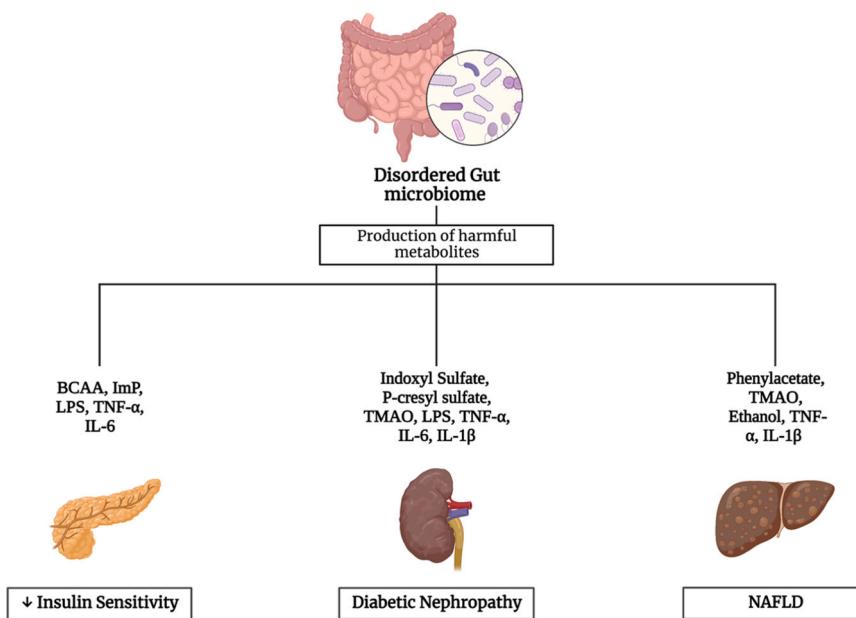
### 5. Complications associated with DM

#### 5.1. Liver cirrhosis

The liver plays a crucial role in carbohydrate metabolism because it regulates blood glucose levels through the processes of glycogenesis and



**Fig. (7).** Insulin signal transduction (IST), insulin receptor substrate-1 (IRS-1), an inhibitor of nuclear factor kappa B (IKK-B), glycogen synthase kinase 3 (GSK-3), AMP-activated protein kinase (AMPK), mammalian target of rapamycin (mTOR), and p38 mitogen-activated protein kinases are some of the molecular pathways that are damaged by oxidative stress (p38 MAPK).



**Fig. (8).** A schematic illustration shows how having more bacteria in the intestines causes NAFLD to proceed more quickly and cause more liver damage.

glycogenolysis [143]. However, diseases such as insulin resistance, glucose intolerance, and diabetes can disrupt the metabolic balance of glucose in the liver. In cases of liver disease, both muscle and adipose tissue exhibit insulin resistance, and along with hyperinsulinemia, these factors are believed to be key underlying causes of diabetes [144]. Additionally, as hepatitis C virus (HCV), alcohol, hemochromatosis, and NAFLD are frequently linked to DM, the liver disease etiology is significant in determining the occurrence of the condition. Since FBG levels may be normal in people with compensated liver cirrhosis, DM may be subclinical in these cases. Hepatogenous diabetes is a condition of impaired glucose regulation owing to loss of liver functions as a consequence of cirrhosis which means DM develops after the cirrhosis onset. Hepatogenous diabetes has a distinct natural history than inherited T2D because microangiopathy is less common. In contrast, patients with diabetes and cirrhosis have cirrhosis consequences more frequently, which can be fatal. DM causes more severe liver failure by accelerating liver fibrosis and inflammation [145]. Secondly, DM may ↑ the incidence of bacterial infections in individuals with cirrhosis, leading to higher mortality rates. One mechanism behind this is that insulin resistance increases the production of adipokines, including TNF- $\alpha$  and leptin, which activate inflammatory pathways that worsen liver damage. Adiponectin is a different cytokine responsible for modulating insulin sensitivity and tissue inflammation. Reduced adiponectin levels are reported in cases with insulin resistance in the liver and peripheral tissues. Some theories suggest that the development of liver disease is linked to low levels of adiponectin. The second pathway involves DM exacerbating immunodepression in cirrhotic patients, which increases the likelihood of life-threatening infections that can damage liver function [146].

#### 5.1.1. NAFLD

NAFLD refers to several liver conditions, such as cirrhosis, fibrosis, and simple steatosis [147]. Fatty liver, considered to be the most benign form of NAFLD, is thought to affect one-third of adult Americans. The main fatty liver brought on by the buildup of fat is predominantly composed of triglycerides because of a metabolic syndrome caused by T2D, obesity, and dyslipidemia. Nonalcoholic steatohepatitis (NASH) is considered one of the severe manifestations of NAFLD that also causes tissue inflammation, cell death, and fibrosis. NASH is the most frequent make of cryptogenic cirrhosis currently. It is categorized as a condition that can lead to liver failure and cirrhosis [148].

#### 5.1.2. NASH

NASH is a complex manifestation of NAFLD [149]. NASH is predisposed by obesity in visceral, hypertriglyceridemia, and insulin resistance [150]. It is known that enlarged adipose tissue in a state of chronic inflammation linked to obesity secretes more adipokines [151]. Cytokines released from the liver can induce some systemic effects such as hyperglycemia, hyperinsulinemia, and insulin resistance. These abnormalities prevent the liver from properly metabolizing lipids [152]. The most studied cytokine (TNF) directly stimulates the liver stellate cells leading to fibrosis of the liver. Losing body weight aids in the treatment of metabolic syndrome disorders like hyperlipidemia and fatty liver [153].

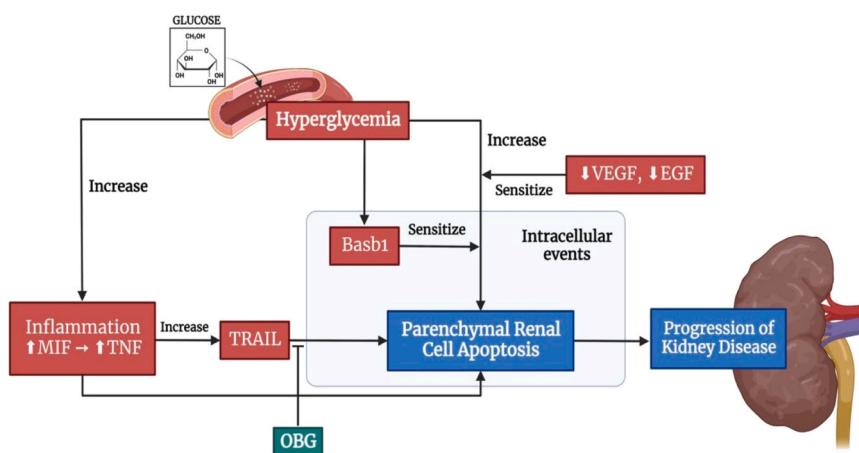
#### 5.1.3. Alcohol-related liver disease

In persons with alcoholic liver disease, diabetes is most likely to occur [154]. This risk is inversely correlated with the amount of alcohol ingested, rising by a factor of two in patients who consume more than 270 g of alcohol per week as opposed to those who consume lower than 120 g/wk. After acute alcohol consumption, there is a considerable decrease in insulin-mediated glucose absorption. Contrarily, those who are chronic alcoholics frequently get chronic pancreatitis and lose their pancreatic islet cells, which leads to DM [155].

#### 5.2. Diabetic kidney disease

DM may have a significant negative influence on the kidneys and urine system leading to end-stage renal failure in Western Europe and the US [156]. The underlying problem in about 40% of all patients who consistently require dialysis is diabetes mellitus. Chronic renal insufficiency is caused by glomerular damage brought on by diabetes, extra-renal and intrarenal atherosclerosis, and other factors [157,158]. Diabetes also causes severe interstitial inflammation in the kidneys. Individuals are more likely to develop contrast-induced nephropathy (CIN) and frequently encounter bacterial infections of the urinary system and renal tissue as described in Fig. (9). Acute kidney injury (AKI), however, is still a significant problem for patients who are hospitalized all over the world. The number of instances has steadily increased in recent years, reaching 20% in middle Europe. According to a 2013 meta-analysis of more than 300 studies, the average AKI incidence for people worldwide is substantially more than 30% [159].

Despite efforts to control levels of blood glucose can still develop



**Fig. (9).** Diabetic nephropathy and renal long-term complications of DM.

kidney disease, suggesting that additional factors like lipotoxicity, oxidative stress, and hyperglycemic memory play a role. Hyperglycemic memory refers to the phenomenon where previous episodes of high blood glucose levels can have long-lasting effects on the development of complications, even when glucose levels are subsequently well controlled. The exact mechanisms underlying metabolic memory are not fully understood but involve epigenetic, genetic, cellular, and tissue-level alterations that occur during periods of hyperglycemia [160,161].

Diabetic kidney disease is marked by significant changes in the structure and function of the kidneys. These alterations include impaired podocyte function, resulting in the detachment of podocytes from the glomerular basement membrane. Moreover, there is a thickening of the glomerular basement membrane due to the accumulation of extracellular matrix components. These changes lead to tubule-interstitial fibrosis, glomerular sclerosis, and a decline in kidney function, manifested as albuminuria and reduced glomerular filtration rate (GFR) [162].

Transforming growth factor-beta 1 (TGF- $\beta$ 1) plays a crucial role in promoting fibrogenesis in the kidney. It facilitates the accumulation of extracellular matrix, inhibits its breakdown, and triggers cell dedifferentiation, all of which contribute to the development of fibrosis. Both hyperglycemia and insulin resistance enhance the signaling of TGF- $\beta$ 1, further promoting its effects in the kidney. Additionally, abnormal signaling of Janus kinase-signal transducer and activator of transcription (JAK-STAT) pathways also plays a role in the activation of TGF- $\beta$ 1, exacerbating its fibrogenic actions [163,164]. Although therapies targeting active TGF- $\beta$ 1 have shown limited efficacy, targeting the latent form of TGF- $\beta$ 1 holds promise for future treatments [165]. Lipid signaling and lipotoxicity are emerging as important factors in diabetic kidney disease. Abnormal lipid metabolism and the excessive accumulation of lipids in the kidney lead to renal lipotoxicity and podocyte dysfunction. Certain molecules and pathways that play a role in lipid metabolism, such as sphingomyelin phosphodiesterase acid-like 3b (SMPDL3b) and junctional adhesion molecule-like protein (JAML), have been implicated in the development and progression of kidney disease. These molecules and pathways are potential targets for interventions aimed at improving kidney health. Inhibition of these targets shows promise in ameliorating diabetic kidney injury [166].

VEGF-B and mTORC1 signaling have also been a critical role in diabetic kidney disease [165,167]. Inhibition of VEGF-B and mTORC1 signaling pathways has shown beneficial action in animal models, reducing glomerular lipid content, insulin resistance, and renal damage. SGLT2 inhibitors, commonly used antidiabetic drugs, have been shown to have dual benefits. They not only help in lowering blood glucose levels but also demonstrate the ability to slow down the progression of kidney disease associated with diabetes [168,169]. The protective effects of SGLT2 inhibitors may be attributed to various mechanisms,

including improved ketone body production, anti-inflammatory effects, decrease of oxidative stress, blood pressure lowering, and inhibition of kidney fibrosis [161,167].

### 5.3. Cardiovascular disease

Cardiovascular disease (CVD) stands as the primary cause of morbidity and mortality among patients with diabetes, particularly T2D [170]. Atherosclerosis, characterized by plaque formation in the arteries, is a common form of CVD in diabetes [171]. Hyperglycemia plays a role in contributing to endothelial dysfunction and the activation of vascular smooth muscle cells (VSMCs) through the production of advanced glycation end products (AGEs). Additionally, it contributes to the formation of fatty streaks in the arterial wall [172].

Recently, novel signaling molecules have been linked to the pathogenesis of CVD in individuals with T2D. QKI-7, an RNA-binding protein, is elevated in the vessels of diabetic patients and promotes endothelial dysfunction by degrading mRNAs essential for endothelial cell function. Inhibition of QKI-7 may hold promise for treating vascular complications. Nitric oxide (NO) is a beneficial molecule in atherosclerosis, and its regulation involves signaling pathways that include PI3K/Akt, Ca<sup>2+</sup>/calmodulin-dependent protein kinase II (CaMKII), and PKA. Dysregulated calcium signaling in diabetic hearts, caused by AGEs and hyperglycemia, disrupts the balance of calcium release and uptake, leading to reduced expression and activity of sarcoplasmic/endoplasmic reticulum Ca<sup>2+</sup> ATPase 2a (SERCA2a) and heart failure [173,174].

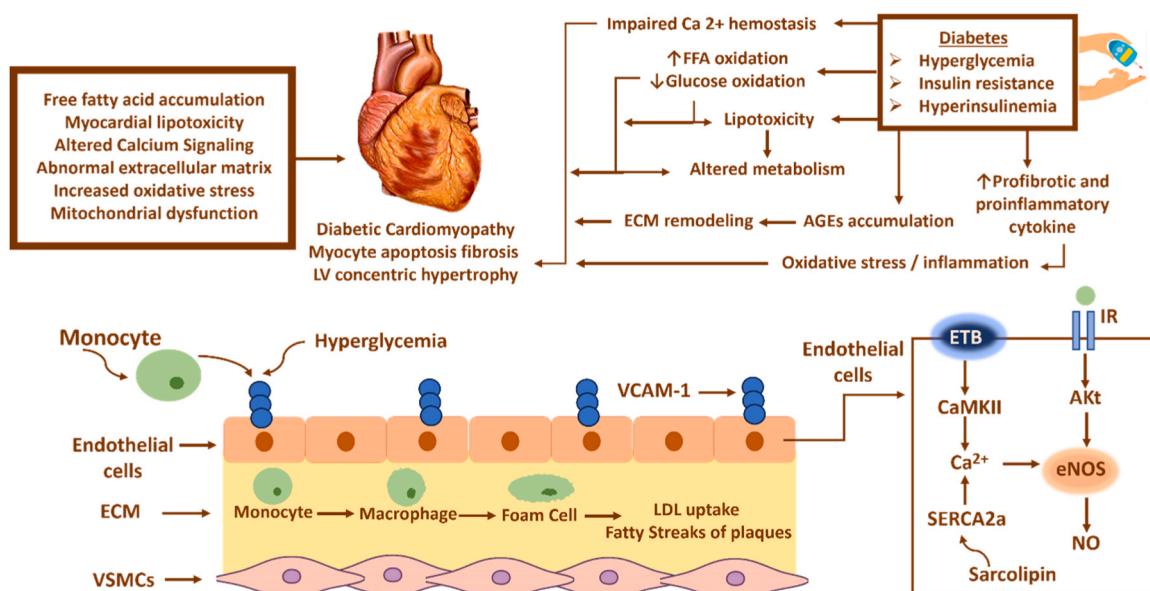
Epigenetic changes mediated by histone deacetylases (HDACs) and other regulators play an important role in diabetic CVD. HDAC4, in response to CaMKII and PKA signaling, regulates  $\beta$ -adrenergic signaling and protects against diabetic heart failure. Sarcolipin, a negative regulator of SERCA2a, is increased in diabetic cardiomyocytes, further impairing calcium regulation [175,176].

Exophers, structures involved in cellular waste disposal, have been discovered in the heart and play a key role in maintaining cardiac function. Cardiomyocytes utilize exophers to remove dysfunctional mitochondria, and their dysregulation may contribute to cardiomyopathy and other diabetic complications [177] as shown in Fig. 10.

### 5.4. Complications associated with immune disease

#### 5.4.1. Hyperglycemia and susceptibility to infection

The human body has powerful defense mechanisms against various microorganisms, such as bacteria, viruses, parasites, and fungi. Normally, these defense mechanisms make it difficult for viruses to penetrate and cause illness. However, some diseases cause deterioration of the immune system. For example, an open wound can allow bacteria to enter and cause infection. Healthy skin, mucosal surfaces, ROS,



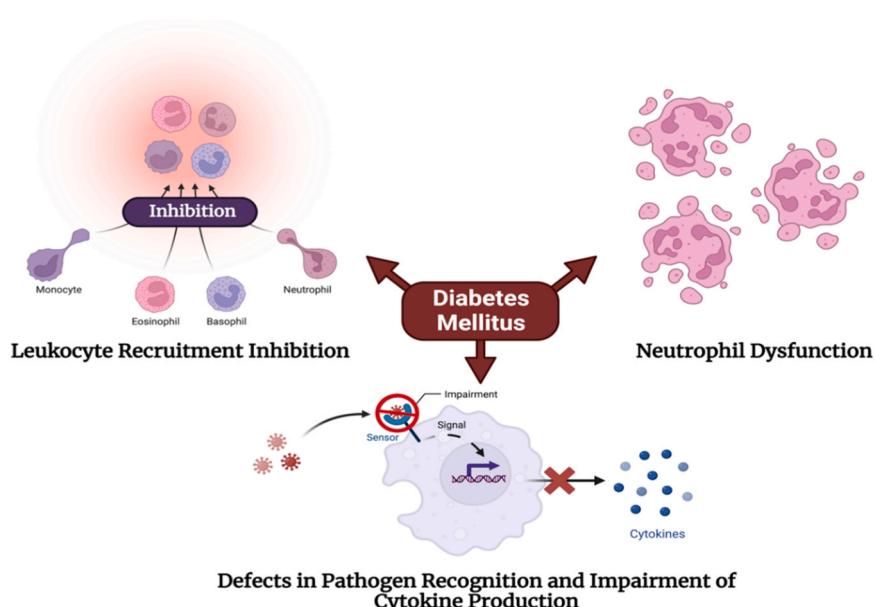
**Fig. (10).** Cardiovascular complications result from the hyperglycemia pathway that causes endothelial cell impairment by inducing VCAM-1 expression on the cell membrane [109].

cytokines, and chemokines act as natural barriers and assist our defense mechanisms in preventing the infiltration of harmful pathogens as described in Fig. (11). Unfortunately, diabetes disrupts the host's immunological response [178,179]. In addition to the possibility of natural barrier deterioration caused by neuropathy, cellular immunity is suppressed due to T2D. Both a lack of insulin and high blood sugar are the main contributors. Infections are a concern for individuals with diabetes as their immune systems are unable to adequately defend against foreign invaders. Numerous studies have investigated the mechanisms related to diabetes that compromise the defense mechanism of the host against infections [180,181].

#### 5.4.2. Impairment of cytokine production

Monocytes and Peripheral blood mononuclear cells (PBMCs) in T1D & T2D patients release less IL1 $\beta$  than LPS controls after stimulation with LPS [178]. When compared to healthy donors, T1D participants'

monocytes from PBMCs emitted less IL-6 and IL-1. Anti-CD3 antibodies activated non-diabetic participants' PBMCs, and when those cells were then subjected to high glucose levels, the production of the cytokines IL-2, IL-6, and IL-10 was suppressed. Inhibition of cytokines may suppress the immune response in hyperglycemic patients because IL-6 is crucial for protection against pathogens as well as for the adaptive immune response through the induction of antibody production and development of effector T-cells. Studies revealed that dextro octreotide-induced PBMCs from healthy patients showed lower IL-17A and IL-6 mainly in the CD16+ and CD14+ intermediate monocytes expression, indicating compromised immunological responses due to the elevated level of blood glucose. The increased glycation caused the inhibition of IL-10 secretion by myeloid cells. Production of TNF- $\alpha$  and IFN- $\gamma$  was also reduced by T cells [182]. In comparison to normal mice, mice with high-fat diet-induced hyperglycemia and leptin-receptor-deficient had decreased levels of the cytokine IL-22.



**Fig. (11).** Diabetes mellitus effects on the immune system and its major associated complications.

Following infection with *Burkholderia pseudomallei*, PBMC cultures from individuals with diabetes produced a decrease in levels of IFN and IL-12 compared to PBMCs from healthy donors. The administration of recombinant IFN- $\gamma$  and IL-12 significantly reduced bacterial load in PBMCs from individuals with diabetes, indicating that the reduced production of IFN- $\gamma$  and IL-12 in diabetes decreases the ability of immune cells to control bacterial growth during infection [183]. Therefore, diabetic hyperglycemia is suggested responsible for inhibiting leukocytes and macrophage activity against infections [184]. Diabetic mice have decreased expression of some proteins involved in pathogen recognition like the Toll/IL-1R domain-containing adaptor protein (TIRAP) and Toll-like receptor (TLR)-2 [185]. Several investigations have revealed that diabetic subjects' neutrophils and monocytes have higher TLR expression [178]. TLR expression increased in patients with well-managed hyperglycemia but decreased in diabetic patients with bad glycemic control besides other complications [186].

### 5.5. Diabetic retinopathy

Diabetic retinopathy is a major complication of diabetes, with approximately 20% of patients at the time of diabetes diagnosis and approximately 40–45% during the disease. This condition is marked by the dysfunction of two key cell types present in the retina: endothelial cells, responsible for forming blood vessels in the retinal microvasculature, and pericytes, which offer support and regulate the activities of the endothelial cells. [187].

Hyperglycemia, the presence of harmful substances like advanced glycation end products (AGEs), and oxidative stress collectively contribute to the disruption of tight junctions between endothelial cells in the retina's blood vessels. Consequently, pericytes, which support and regulate these endothelial cells, become detached and undergo cell death (apoptosis). This early loss of pericytes is a significant factor in diabetic retinopathy, a condition that affects the eyes in people with diabetes. The detachment and apoptosis of pericytes result in increased permeability of the blood-retina barrier, allowing harmful substances to leak into the retina and contributing to the progression of the disease. Therefore, targeting pericytes for early interventions becomes crucial in preventing the advancement of diabetic retinopathy. [187,188].

Various signaling pathways contribute to the loss of pericytes in diabetic retinopathy, and these pathways include Notch 1, Notch 3, hypoxia-inducible factor 1 alpha (HIF1 $\alpha$ ), and vascular endothelial growth factor-1 (VEGF-1). VEGF-1 signaling plays a major role in the advancement of diabetic retinopathy by promoting abnormal and disorganized growth of new blood vessels (neovascularization) from endothelial cells. While therapies targeting VEGF-1 have been effective in inhibiting the advancement of diabetic retinopathy, individual patient responses to these treatments vary. Recent research indicates that the levels of Semaphorin 4d (Sema4d) in body fluids can serve as a predictive biomarker for how patients will respond to anti-VEGF-1 therapy. Higher levels of Sema4d are associated with a poorer response to anti-VEGF-1 treatment. Moreover, Sema4d itself plays a significant role in the progression of diabetic retinopathy. Combining therapies that target both VEGF-1 and Sema4d may offer a more effective approach compared to using anti-VEGF-1 treatment alone. Addressing both these factors simultaneously could lead to better treatment outcomes for diabetic retinopathy patients. [189,190].

Effective communication between pericytes and retinal glial cells is vital for the proper function of blood vessels in the eye. This communication involves the release of a membrane-bound protein called Sema4d by retinal glial cells. Once released, Sema4d triggers signaling pathways in both pericytes and endothelial cells. As a result of this signaling, the vascular endothelial cadherin (VE-Cadherin), which helps maintain tight junctions between cells, undergoes internalization and phosphorylation. This process weakens the tight junctions between cells and contributes to increased vascular permeability, leading to the leakage of blood vessels in diabetic retinopathy. Maintaining the

crosstalk between glial cells and pericytes is crucial for preserving a healthy vascular system in the eye and preventing complications associated with diabetic retinopathy [190].

Src, a crucial signaling protein, is regulated by other factors, including angiopoietin 1 (Ang1) and Ang2. Pericytes release Ang1, which binds to the Tie2 receptor on endothelial cells, triggering signaling pathways that enhance intercellular interactions and strengthen cell-cell junctions. In contrast, Ang2 acts as an antagonist to Ang1/Tie2 signaling, promoting increased permeability of the blood-retina barrier. [191].

Crosstalk between pericytes and endothelial cells is essential for a healthy retinal vasculature. Circular RNAs, such as cPWWP2A and cZNF532, have been identified as mediators of this crosstalk. They regulate the expression of target microRNAs. Subsequently, these interactions influence the expression of genes related to pericyte function and vascularization. [192,193] as shown in Fig. (12).

Diabetic retinopathy is characterized by persistent inflammation, marked by increased levels of oxidized lipoproteins, AGEs, and free radicals. This ongoing inflammatory state significantly contributes to the development of the condition. Proinflammatory cytokines like IL-6, IL-17A, IL-1 $\beta$ , TNF $\alpha$ , and MCP-1 play a crucial role in the pathogenesis of diabetic retinopathy, leading to harmful effects such as vascular leakage, apoptosis of endothelial cells, and capillary degeneration. Another contributing factor is Prostaglandin E2 and its receptor EP2, which induce the expression of IL-1 $\beta$  and NLRP3 signaling in diabetic retinopathy, further intensifying the inflammatory response and disease progression. In summary, chronic inflammation and the involvement of various inflammatory molecules play a central role in the development and advancement of diabetic retinopathy, causing damage to the retinal vasculature and contributing to vision-related complications. [194–196].

Lipids are emerging as important signaling molecules that contribute to the progression of diabetic retinopathy. One example is ceramide 6, which triggers the expression of regulation in development and DNA damage responses 1 (REDD1). REDD1, in turn, helps prevent apoptosis by interfering with the function of JNK, a protein involved in cell death pathways. Certain lipids, such as eicosapentaenoic acid (EPA), and docosahexaenoic acid (DHA) appear to have protective roles in diabetic retinopathy. These lipids may offer beneficial effects in mitigating the disease's progression and related complications. On the other hand, some lipids can worsen the advancement of diabetic retinopathy. For instance, 12-hydroxyeicosatrienoic acids (12-HETE) and 15S-HETE have demonstrated that these factors worsen the progression of the disease, likely by promoting inflammatory processes and other detrimental effects on the retinal vasculature. The intricate interplay of these lipids as secondary messengers in diabetic retinopathy underscores the importance of lipid metabolism in the disease's pathogenesis and suggests potential therapeutic targets for managing the condition effectively. [197].

Dipeptidyl peptidase 4 inhibitors (DPP4i), mainly used to treat T2D, have been employed to treat diabetic retinopathy. However, their effects vary depending on the specific inhibitor used. For example, linagliptin shows GLP1R-independent anti-angiogenic effects mediated by the decrease of VEGFR signaling. Elevated levels of DPP4i can lead to aggravated permeability and promote a proangiogenic response in diabetic retinopathy [198].

Overall, understanding the complex cellular and molecular mechanisms involved in diabetic retinopathy opens possibilities for developing targeted interventions to prevent and treat this condition.

### 5.6. Diabetic neuropathy

Diabetic neuropathy, a more common complication in approximately half of diabetic patients, affects both the autonomic and peripheral nervous systems. It mainly affects the sensory nerve endings in the hands and lower limbs, causing a range of symptoms like pain,

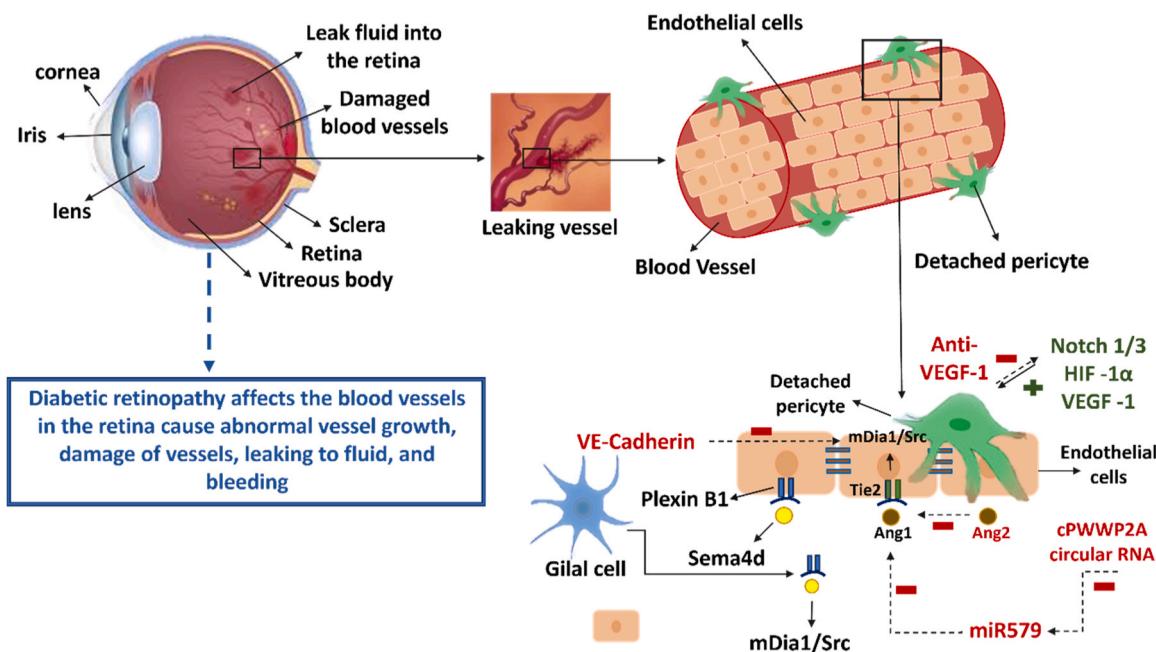


Fig. (12). Mechanisms of pericyte detachment and tight junction disruption in diabetic retinopathy [109].

burning sensations, tingling, and numbness. As the condition advances, it can also involve the motor nerve endings in the lower extremities, leading to problems with balance and a loss of sensation in the feet. Moreover, diabetic neuropathy can also appear proximally in regions such as the thighs or pelvic area, following a pattern of spreading from the more central parts of the body to the outermost areas. This primarily impacts the sensory nerve endings in the hands and lower limbs, resulting in symptoms such as pain, burning, tingling, and numbness. As the condition advances, motor nerve endings in the lower extremities can also be affected, leading to balance issues and loss of sensation in the feet. Additionally, diabetic neuropathy can manifest proximally in regions such as the thigh or pelvic area, following a pattern from proximal to distal [199,200].

The development of diabetic neuropathy is associated with the activation of the polyol pathway in diabetes, resulting in the accumulation of substances such as methylglyoxal (MG) and advanced glycation end products (AGEs), which impair nerve function. MG specifically targets the voltage-gated sodium channel  $\text{Na}(\text{v})1.8$ , leading to increased pain sensitivity, or hyperalgesia, in individuals with diabetes.  $\text{Na}(\text{v})1.8$  is involved in heightening pain perception. cAMP and PKA are other regulators of  $\text{Na}(\text{v})1.8$  that also elevate the levels of hyperpolarization-activated cyclic nucleotide-gated 2 (HCN2) ion channels in nerve fibers responsible for pain sensing. In mouse models of diabetic neuropathy, the hyperactivation of HCN2 in  $\text{Na}(\text{v})1.8$ -positive neurons is linked to pain, and inhibiting HCN2 has shown pain-relieving effects in both T1D and T2D models. Diabetic neuropathy is also associated with mechanical allodynia, where normally non-painful stimuli trigger pain. Recent research indicates that the CXCL12/CXCR4 signaling axis may play a significant role in the initiation of mechanical allodynia in diabetic neuropathy. Additionally, MG modification of the ligand-gated ion channel TRPA1 contributes to increased pain hypersensitivity in diabetic neuropathy. [201–203].

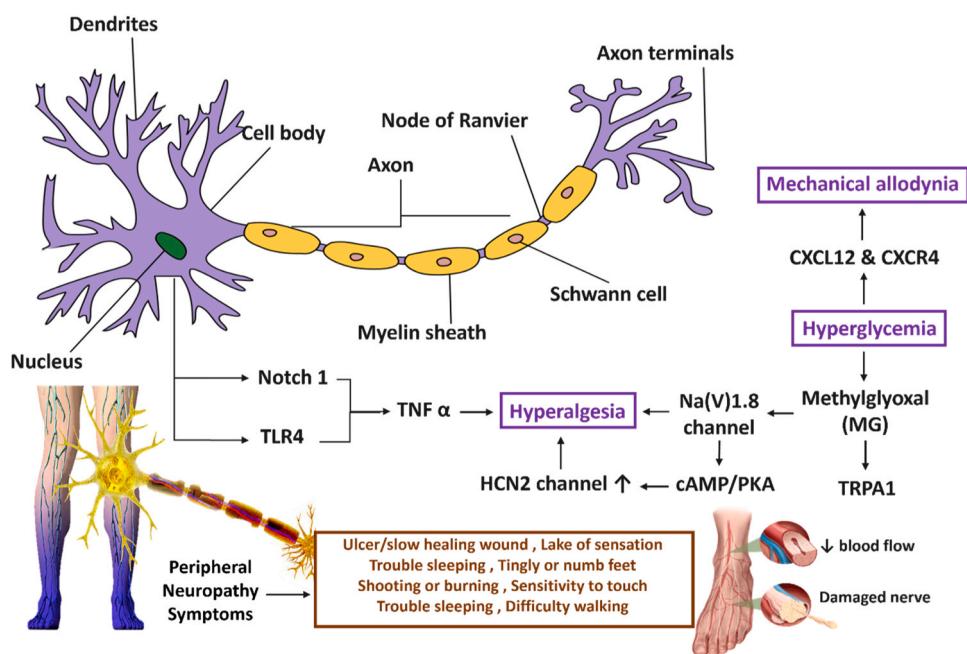
Neuronal oxidative/nitrosative stress triggers the stimulation of pathways like nuclear factor "kappa-light-chain-enhancer" of activated B-cells (NF $\kappa$ B), MAPK, and JNK promoting inflammation and cytokine production that contribute to diabetic neuropathy. High-throughput analyses have identified inflammation and lipid metabolism pathways, involving targets like PPAR $\gamma$ , Apolipoprotein E (ApoE), and leptin, as potentially critical in the development of this complication. T2D and

diabetic neuropathy have links to genetic factors, particularly specific variations in genes related to inflammation and lipid metabolism. Some of these genes include APOE, NF- $\kappa$ B, nitric oxide synthase 3 (NOS3), SREBP-1, Toll-like receptor 2 (TLR2), and TLR4. These genetic polymorphisms are associated with the improvement of T2D and diabetic neuropathy. Activation of Toll-like receptor 4 (TLR4) sets off a series of signaling processes that result in an increased production and release of TNF $\alpha$ , which contributes to neuroinflammation. Inhibiting Notch1 or TLR4 has been found to reduce TNF $\alpha$  levels, which in turn helps alleviate mechanical allodynia (pain from non-painful stimuli) and improve thermal hyperalgesia thresholds (increased sensitivity to heat). This suggests that targeting these pathways could be a potential approach for managing pain and inflammation associated with diabetic neuropathy [204–207].

Both insulin deficiency and resistance in sensory nerves are believed to be significant contributors to the development of diabetic neuropathy. Insulin plays a crucial role as a neurotrophic hormone, essential for maintaining normal nerve function. In diabetes, insufficient insulin signaling can lead to various issues, such as reduced nerve regeneration capacity, impaired neurochemical synthesis, and mitochondrial dysfunction. These factors collectively contribute to the development and progression of diabetic neuropathy. Hyperglycemia in diabetes also impacts Schwann cells, responsible for supporting and surrounding sensory axons in the peripheral nervous system. This Schwann cell dysfunction results in disrupted myelin, compromised axon conduction, and impaired nerve regeneration, further exacerbating diabetic neuropathy. Several molecular targets, such as MAPK, p75 neurotrophin receptor (NTR), neurotrophic factor-3 (NT-3), and  $\beta$ -nerve growth factor (NGF), are deregulated due to this Schwann cell dysfunction, adding to the pathophysiology of diabetic neuropathy [208,209] as shown in Fig. (13).

### 5.7. Other complications in DM

In addition to the well-known complications mentioned earlier, recent research suggests that individuals with diabetes may also develop restrictive lung diseases, including lung fibrosis, although studies are needed to understand the underlying mechanisms [210]. Present findings indicate that elevated blood glucose levels and oxidative stress



**Fig. (13).** Mechanisms of hyperalgesia and mechanical allodynia in diabetic neuropathy: Insights into Notch, TLR4, cAMP/PKA signaling, and CXCL12/CXCR4 pathways.

might have a role in causing DNA damage, which in turn contributes to the development of lung fibrosis in diabetes [211]. A protein called RAGE, implicated in the repair of damaged DNA, is involved in this process. In animal studies, introducing a hyperactive form of RAGE through a viral delivery system has shown promising results in reversing fibrosis in the kidneys and lungs of diabetic mice [212].

Approximately 13–24% of individuals with diabetes suffer from different types of cognitive dysfunction, including dementia, reduced verbal memory, impaired attention, and deficits in executive functioning. One potential cause of impaired neural function in diabetes is insulin resistance within the brain. Besides insulin resistance, other factors like neuroinflammation, disrupted iron metabolism, and the accumulation of hyperphosphorylated tau protein, leading to protein buildup, may also play a role in cognitive dysfunction. Intriguingly, there is a significant association between Alzheimer's disease and T2D. The two conditions appear to be connected, with individuals having diabetes facing a higher risk of developing Alzheimer's disease. These findings suggest the existence of shared underlying mechanisms between diabetes and Alzheimer's, contributing to the cognitive deficits observed in diabetic patients [213,214].

#### 5.7.1. Type 2 diabetes and conditions closely linked to it

- Alzheimer's disease: Some researchers refer to Alzheimer's disease as "type 3 diabetes" due to its close association with insulin resistance and impaired glucose metabolism [215].
- Polycystic ovary syndrome (PCOS): PCOS is a condition that affects women and is characterized by hormonal imbalances. It can impact fertility and is closely linked with insulin resistance, often leading to an increased risk of type 2 diabetes [216].
- Cushing's syndrome: Cushing's syndrome is characterized by an excess production of the hormone cortisol. Elevated cortisol levels can lead to insulin resistance, increasing the risk of type 2 diabetes [217].
- Pancreatic cancer: There is a debated link between pancreatic cancer and T2D. Some studies suggest that T2D may be both a consequence and a risk factor for pancreatic cancer, but the exact nature of this relationship is still being explored [218].

#### 5.7.2. Type 1 diabetes and associated autoimmune conditions

- Coeliac disease: Coeliac disease is an autoimmune disorder in which the immune system reacts to gluten, a protein found in wheat, barley, and rye. It is more common in individuals with T1D.
- Rheumatoid arthritis: Rheumatoid arthritis is another autoimmune disease that can co-occur with T1D. It primarily affects the joints and can cause inflammation and pain.
- Addison's disease: Addison's disease is a rare autoimmune condition that affects the adrenal glands, leading to a deficiency in hormones like cortisol and aldosterone. It can coexist with T1D, as both are autoimmune disorders.
- Autoimmune thyroid disease: Autoimmune thyroid diseases, such as Hashimoto's thyroiditis and Graves' disease, involve the immune system attacking the thyroid gland. These conditions are more common in individuals with T1D [219–221].

It's important to note that autoimmune diseases tend to share a common underlying mechanism of the immune system mistakenly attacking the body's tissues. This is why individuals with one autoimmune condition may have a higher risk of developing another. Regular medical check-ups and monitoring are crucial for individuals with diabetes to manage and address any associated conditions effectively.

#### 6. Link to pathways and treatment options

Understanding the molecular pathways involved in diabetic complications is essential for developing targeted therapies. Some pathways that have shown potential in treatment are:

##### • Inflammatory pathways:

Targeting pro-inflammatory cytokines like TNF- $\alpha$  and IL-1 $\beta$ , using drugs like Anakinra, Canakinumab, and Gevokizumab, can help reduce inflammation and improve glycemic control.

##### • Oxidative stress pathways:

Antioxidant therapies that target ROS production and enhance endogenous antioxidant defense, such as vitamin D analogs and alpha-1 antitrypsin (AAT), may mitigate oxidative damage.

- Epigenetic pathways and metabolic memory:**

Understanding the epigenetic changes involved in metabolic memory can lead to novel therapies aimed at reversing or preventing the long-term effects of hyperglycemia.

- Personalized medicine:**

Identifying genetic and phenotypic markers that predict an individual's susceptibility to specific complications can guide personalized treatment strategies.

- Lifestyle interventions:**

Encouraging lifestyle modifications, including healthy diet, exercise, and weight management, remains fundamental in diabetes management and preventing complications.

Combining therapies that target multiple pathways, such as anti-inflammatory agents, antioxidants, and metabolic modulators, holds promise for reducing the burden of diabetic complications. Additionally, advancements in diagnostics and early intervention can help detect complications at an early stage and improve patient outcomes. Overall, future research efforts should focus on developing personalized and targeted treatments, leveraging advancements in diagnostics, and understanding the intricate molecular pathways involved in diabetes and its complications. This approach can pave the way for more effective management of diabetes and better outcomes for patients.

## 7. Conclusion and future perspectives

DM is a complex metabolic disorder that affects multiple organ systems and leads to various complications, including kidney disease, cardiovascular disease, immune dysfunction, retinopathy, and neuropathy. The knowledge of the underlying mechanisms and pathways involved in these complications has opened new avenues for future perspectives and potential treatments to inhibit the burden of diabetes and its complications.

### a) Targeting inflammation:

Inflammation plays a vital role in the development of diabetes and its complications. Future research should focus on identifying specific targets within the inflammatory pathways to develop more effective anti-inflammatory therapies. Drugs that inhibit pro-inflammatory cytokines, like TNF- $\alpha$  and IL-1 $\beta$  have shown promise in reducing inflammation and improving glycemic control in diabetes patients.

### b) Oxidative stress and antioxidant therapies:

Oxidative stress is a main driver of diabetic complications. Future studies should explore the potential of antioxidant therapies to decrease oxidative damage and inhibit or prevent the progression of diabetic complications. Targeting pathways involved in reactive oxygen species (ROS) production and enhancing endogenous antioxidant defense mechanisms could be beneficial.

### c) Metabolic memory:

Metabolic memory, where previous episodes of hyperglycemia have long-lasting effects on complications even with subsequent glycemic control, requires further investigation. Understanding the underlying epigenetic and cellular changes involved in metabolic memory can provide insights into novel therapeutic strategies to mitigate complications.

### d) Personalized medicine:

Each individual's response to diabetes and its treatments can vary. Personalized medicine, based on genetic, epigenetic, and phenotypic characteristics, holds great potential for tailoring treatment strategies to individual patients. Precision medicine can help identify patients at higher risk of specific complications and target treatments accordingly.

### e) Advancements in diagnostics:

Early detection of diabetes and its complications is crucial for effective management. Developing more sensitive and specific

diagnostic tools can aid in identifying patients at risk of developing complications at an early stage, allowing for timely intervention.

### f) Lifestyle interventions:

While pharmacological treatments are essential, lifestyle modifications remain a cornerstone in diabetes management. Encouraging a balanced diet, maintaining a healthy weight, and engaging in regular physical activity are beneficial for enhancing glycemic control and lowering the risk of complications.

### g) Combination therapies:

Combining therapies that target different pathways implicated in diabetes and its complications may yield better outcomes than single-agent treatments. Combinations of anti-inflammatory agents, antioxidants, and drugs targeting metabolic pathways could have synergistic effects in reducing complications.

## CRediT authorship contribution statement

**Ahmed A. Al-Karmalawy:** Conceptualization, Design, Construction of the conceptual framework of the review, Supervision. **Samar A. Antar, Nada A. Ashour, Marwa Sharaky, Muhammad Khattab, Naira A. Ashour, Roaa T. Zaid, Ahmed A. Al-Karmalawy:** Literature search, Collection, Draft preparation. **Samar A. Antar, Nada A. Ashour, Ahmed A. Al-Karmalawy:** Data interpretation. **Samar A. Antar, Nada A. Ashour, Muhammad Khattab, Ahmed A. Al-Karmalawy:** Software. **Eun Joo Roh, Ahmed Elkamhaw:** Funding. **Samar A. Antar, Nada A. Ashour, Marwa Sharaky, Muhammad Khattab, Naira A. Ashour, Roaa T. Zaid, Eun Joo Roh, Ahmed Elkamhaw, Ahmed A. Al-Karmalawy:** Original draft writing. **Nada A. Ashour, Marwa Sharaky, Ahmed A. Al-Karmalawy:** Review and editing of the manuscript. All authors have read and agreed to the submitted final version of the manuscript.

## Declaration of Competing Interest

We wish to confirm that there are no known conflicts of interest associated with this publication and there has been no significant financial support for this work that could have influenced its outcome.

## Data availability

No data was used for the research described in the article.

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