Section A-Research paper

Brief Overview about Correlations with and influencing factors on Type 2 Diabetes Mellitus

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Abstract

Background: Currently, more than half a billion adults are affected by diabetes globally, and the number is foreseen to rise to nearly 800 million by 2045, with the majority being type 2 diabetes mellitus (T2D). Type 2 diabetes (T2DM) is a complex metabolic disease in which the pathophysiology involves an interaction between genetic predisposition and environmental triggers. Hyperglycemia develops as a result of pancreatic islet failure in lieu of systemic insulin resistance. Islet failure in T2DM is associated with a deficit in β-cell mass and function and increased glucagon secretion. Insulin resistance in T2DM primarily manifests at the level of skeletal muscle, liver, and adipose tissue, and is characterized by impaired insulin-stimulated glucose disposal, failure to suppress hepatic glucose production, and elevated adipose tissue lipolysis and inflammation. Although we have not completely elucidated the pathophysiology of T2DM so far, it is the case that the disease has a major genetic component. Higher concordance rates are found among monozygotic (96%) than dizygotic (DZ) twins in some. In addition to a considerable number of genetic components associated with T2DM, segregation analysis also suggests the polygenic nature of T2DM. The susceptibility loci of T2DM have been discovered by genome-wide association studies (GWAS) since early 2007. Then, numerous GWAS conducted in different countries and ethnic groups have reported linkage signals at the same or different chromosomes with T2DM, and have successfully identified approximately 75 susceptibility loci related to T2DM. Examples of candidate genes are KCNJ11 (potassium inwardly rectifying channel, subfamily J, member 11), TCF7L2 (transcription factor 7-like 2, the strongest T2D locus identified to date), IRS1 (insulin receptor substrate 1), MTNR1B (melatonin-receptor gene), PPARG2 (peroxisome proliferator-activated receptor gamma 2), IGF2BP2 (insulin-like growth factor two binding protein 2), CDKN2A (cyclin-dependent kinase inhibitor 2A), HHEX (hematopoietically expressed homeobox) and FTO (fat mass and obesity associated) gene. A previous study found that low IL-10 production capacity is also associated with T2DM.

Keywords: Type 2 Diabetes Mellitus

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Introduction

Type 2 diabetes mellitus (T2DM) is a persistent state of hyperglycemia and glucose intolerance that occurs when the body cannot respond fully to insulin, followed by an increase in insulin production and a subsequent insulin deficiency. **(1)**.

Currently, more than half a billion adults are affected by diabetes globally, and
the number is foreseen to rise to nearly 800 million by 2045, with the majority being type 2 diabetes mellitus (T2D). **(2).**

Moreover, the incidence of diabetes is expected to continue to rise and, in the U.S. alone, is projected to affect nearly one in three people by the year 2050. These alarming projections suggest that there is an urgent need for the development and implementation of novel preventative and treatment strategies to combat the rise in T2DM prevalence worldwide. T2DM manifests through the development of fasting and postprandial hyperglycemia, which is the primary contributor to the induction of numerous life-threatening complications and co-morbidities **(3)**

T2D is a multifactorial metabolic disorder marked by dysregulated glucose homeostasis, insulin resistance, and impaired insulin secretion. Poor glucose control in people with T2D results in micro and macrovascular complications, including retinopathy, neuropathy, nephropathy, and cardiovascular disorders **(2).** Risk factors that cause T2D development consist of unfavorable dietary patterns, lifestyle, and genetic influences, which by interacting with each other, make disease prevention and treatment rather complex **(4)** .

Allowing for enhancing the comprehension of the genetic makeup of T2D, over 700 T2D risk loci have been detected to be associated with T2D. However, the genetic factors identified through genome-wide association studies (GWAS) contribute to the risk of T2D to a limited extent. Identifying biomarkers for screening and predicting T2D and its complications can aid in personalized healthcare management. Furthermore, it can provide insights into the underlying pathways involved in the progression of T2D. **(5)**

Epidemiology and Incidence:

Diabetes is a major global health problem. In 2017, it was estimated that 451 million people globally had diabetes, with this number expected to rise to 693 million by 2045. Globally, the number of people with diabetes mellitus has quadrupled in the past three decades, and diabetes mellitus is the ninth major cause of death. About 1 in 11 adults worldwide now have diabetes mellitus, 90% of whom have type 2 diabetes mellitus (T2DM) **(6).**

According to the IDF, Egypt ranks ninth in the world in terms of diabetes prevalence, with 8,850,400 adult diabetic patients and a 15.2 % prevalence in early 2020.Although these numbers appear to be high, the truth is that 40-50% of patients with diabetes or pre-diabetes are undiagnosed. By 2035, this number is expected to rise to 13.1 million **(6).**

Egypt ranked ninth among countries with the highest number of adults (aged 20–79) with diabetes in 2019, but this is expected to rise to eighth in 2030 and seventh in 2045. Egypt ranked third in the Eastern Mediterranean Region (EMR) in 2019, with a diabetes prevalence of up to 17.2%. Multiple organs of the body are affected by hyperglycemia and its accompanying carbohydrate, lipid, and protein metabolic dysfunctions, which disturb their normal function **(6).**

Etiology and Pathophysiology of Type 2 Diabetes Mellitus :

The etiology of hyperglycemia in T2DM is a complex multifactorial process , it can be distilled to progressive impairments in insulin sensitivity (i.e., insulin resistance) and a corresponding failure of pancreatic islets to maintain appropriate insulin output to compensate for the decline in insulin sensitivity (i.e., islet failure**) (14)** . Pathophysiological manifestations of insulin resistance and islet failure are evidenced early in the evolution of the disease and are imperative for its full development **(3)**

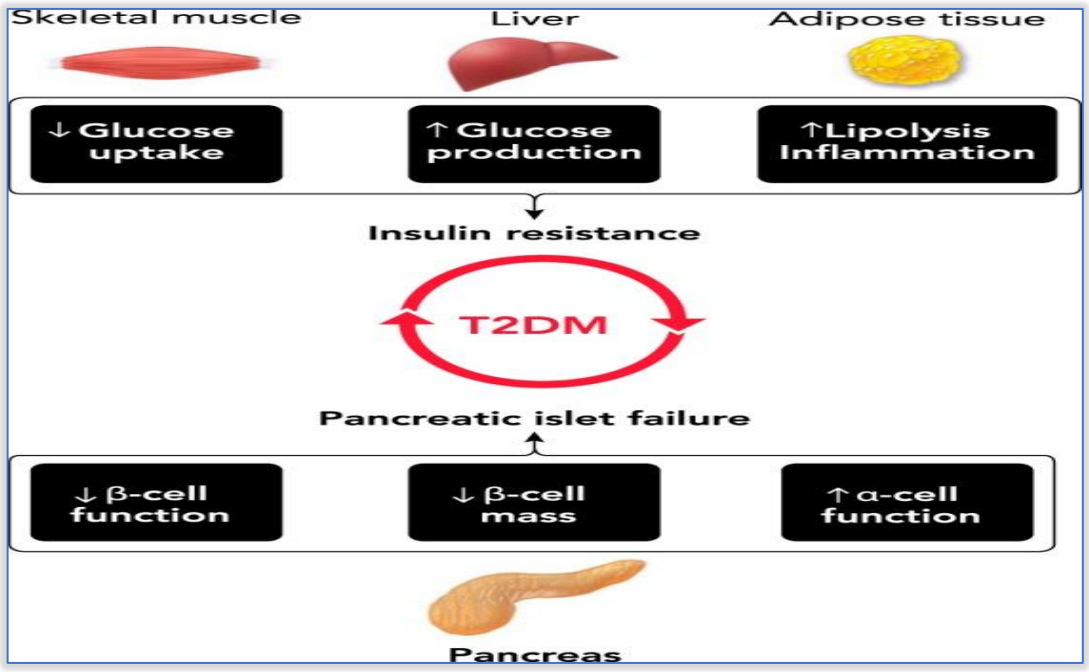

Figure 1: Pathophysiology of Type 2 diabetes mellitus **(3)**

Type 2 diabetes (T2DM) is a complex metabolic disease in which the pathophysiology involves an interaction between genetic predisposition and environmental triggers. Hyperglycemia develops as a result of pancreatic islet failure in lieu of systemic insulin resistance. Islet failure in T2DM is associated with a deficit in β-cell mass and function and increased glucagon secretion. Insulin resistance in T2DM primarily manifests at the level of skeletal muscle, liver, and adipose tissue, and is characterized by impaired insulin-stimulated glucose disposal, failure to suppress hepatic glucose production, and elevated adipose tissue lipolysis and inflammation **(3)**

Insulin resistance manifests as a reduction in insulin's ability to activate the cellular insulin signaling cascade and consequently stimulate insulin-mediated cellular processes. The pathophysiology of T2DM is primarily driven by induction of skeletal muscle, hepatic, and adipose tissue insulin resistance. Since skeletal muscle is the major organ responsible for postprandial glucose disposal, insulin resistance in skeletal muscle severely restricts the capacity for glucose clearance in patients with T2DM **(7).**

At the cellular level, muscle insulin resistance expresses due to 1) impaired insulin-mediated recruitment of GLUT4 (glucose transporter 4) proteins to the plasma membrane, 2) attenuated capacity for glycogen storage, 3) reduction in glucose oxidation, and 4) impaired mitochondrial function **(8)**.

In the liver, insulin resistance is associated with excessive rates of hepatic glucose production during fasting, attributed in part to failed insulin-mediated suppression of gluconeogenesis . Liver insulin resistance is also associated with failure to suppress hepatic glucose production in the postprandial state due to impaired suppression of gluconeogenesis and glycogenolysis **(9)**.

Finally, adipose tissue insulin resistance is characterized by defective insulin-mediated glucose transport, a decreased capacity for lipid uptake and a failure to suppress lipolysis and inflammation, resulting in elevated plasma free fatty acids (FFAs) and cytokines **(10).**

At the cellular level, induction of insulin resistance is largely attributed to ectopic lipid accumulation in insulin-sensitive tissues (i.e., liver, skeletal muscle, and adipose tissue) **(10).**

In muscle and liver, ectopic lipid deposition due to obesity-induced intracellular accumulation and consequent trafficking of lipid signaling intermediates (i.e., ceramides and diacylglycerols) plays a major contributory role in impaired activation of the cellular insulin signaling cascade **(10).**Specifically, intracellular diacylglycerols and ceramides contribute to insulin resistance through deleterious effects on activation of insulin signaling molecules such as insulin receptor substrate 1 and 2 (IRS-1 and -2). This process is mediated through activation of atypical serine/threonine kinases such as protein kinase C **(10).**

In addition, obesity in T2DM is also associated with impaired adipocyte metabolism resulting in 1) excessive lipolysis and consequent increase in plasma free fatty acid levels. 2) excessive production and secretion of pro-inflammatory cytokines (i.e., TNF-α, Il-6, etc.), which are thought to originate from activated adipose tissue macrophages **(11)** Thus aberrant adipose tissue metabolism in T2DM directly contributes to insulin resistance in target tissues through an increase in lipid accumulation or indirectly through cytokine-mediated disruption of the insulin signaling cascade in the liver and skeletal muscle **(11)**

Pancreatic islet failure together with insulin resistance is a characteristic pathology in T2DM and both are required for the establishment of hyperglycemia. The primary manifestation of islet failure in T2DM patients is the loss (or inappropriate activation) of glucose-stimulated insulin secretion and impaired suppression of glucagon release. Impaired glucose-stimulated insulin secretion is attributed to the induction of β-cell secretory dysfunction and loss of β-cell numbers (i.e., β-cell mass). Loss of β-cell mass in T2DM patients has been attributed to increased β-cell apoptosis and the development of β-cell dedifferentiation **(12).**

The etiology of β-cell secretory dysfunction and loss is highly complex as a Cumulative evidence points to induction of intracellular oxidative and/or endoplasmic reticulum stress brought on by increased exposure to toxicity associated with hyperglycemia/hyperlipidemia and/or islet amyloid peptide oligomers (IAPP). Mechanisms underlying impaired suppression of glucagon release are not well understood, with limited evidence pointing toward an increase in α-cell numbers and alterations in α-cell function in diabetes **(3)**

Correlations with and influencing factors on T2DM:

Heritable genetic correlation:

Genetic component:

Although we have not completely elucidated the pathophysiology of T2DM so far, it is the case that the disease has a major genetic component. Higher concordance rates are found among monozygotic (96%) than dizygotic (DZ) twins in some but not all.twin studies, which has been a compelling evidence of a significant genetic component in T2DM. Moreover, 40% of first-degree relatives of T2DM patients may develop diabetes, whereas the incident rate is only 6% in the general population **(13)**.

Susceptibility loci:

In addition to a considerable number of genetic components associated with T2DM, segregation analysis also suggests the polygenic nature of T2DM. The susceptibility loci of T2DM have been discovered by genome-wide association studies (GWAS) since early 2007 . Then, numerous GWAS conducted in different countries and ethnic groups have reported linkage signals at the same or different chromosomes with T2DM, and have successfully identified approximately 75 susceptibility loci related to T2DM. Examples of candidate genes are KCNJ11 (potassium inwardly rectifying channel, subfamily J, member 11), TCF7L2 (transcription factor 7-like 2, the strongest T2D locus identified to date), IRS1 (insulin receptor substrate 1), MTNR1B (melatonin-receptor gene), PPARG2 (peroxisome proliferator-activated receptor gamma 2), IGF2BP2 (insulin-like growth factor two binding protein 2), CDKN2A (cyclin-dependent kinase inhibitor 2A), HHEX (hematopoietically expressed homeobox) and FTO (fat mass and obesity associated) gene. A previous study found that low IL-10 production capacity is also associated with T2DM **(14).**

Lifestyle factor correlation:

A wide variety of lifestyle factors are also of great importance to the development of T2DM, such as sedentary lifestyle , physical inactivity , smoking and alcohol consumption **(13)**.

Substantial epidemiological studies have shown that obesity is the most important risk factor for T2DM, which may influence the development of insulin resistance and disease progression . Nearly 90% of diabetic patients develop T2DM mostly relating to excess body weight according to the World Health Organization (WHO, 2011). Furthermore, obesity is strongly inherited **(15)** .

Some studies demonstrated that obstructive sleep apnea (OSA), a treatable sleep disorder that is pervasive among overweight and obese adults, has become a novel, modifiable risk factor relevant to insulin resistance and glucose intolerance, and may influence on the development of prediabetes (20%-67%) and T2DM (15%-30%), independent of shared risk factors . Several studies have indicated that OSA in T2DM patients is much more prevalent (36%-60%) than in the general population **(16)** .

In addition, diet is considered as a modifiable risk factor for T2DM. Studies have shown that a low-fiber diet with a high glycemic index is positively associated with a higher risk of T2DM, and specific dietary fatty acids may affect insulin resistance and the risk of diabetes in varying degrees **(4)** . Total and saturated fat intake is associated with an increased risk of T2DM independently of BMI, but higher intake of linoleic acid has the opposite effect, especially among leaner and younger men . Frequent consumption of meat especially processed meat, may increase the risk of T2DM after adjustment for BMI, prior weight change, and alcohol and energy intake **(14).**Soft drinks have also been bounded up with increased risk of T2DM and metabolic syndrome , because they are directly associated with BMI **(17)** .

Gut metagenome correlation:

In some recent studies, gut metagenome was shown to be a factor for the development of T2DM . Different kinds of gut bacteria may play different roles in maintaining or interacting with their environment. Two-stage metagenome-wide association study (MGWAS) suggested that T2DM patients show a moderate degree of gut microbial dysbiosis, with various butyrate-producing bacteria being decreased (Clostridiales sp. SS3/4, Roseburia intestinalis, Roseburia inulinivorans, Eubacterium rectale and Faecalibacterium prausnitzii) and some opportunistic pathogens being increased (Bacteroides caccae, Clostridium hathewayi, Clostridium ramosum, Clostridium symbiosum, Eggerthella lenta and Escherichia coli) **(18).**

In T2DM patients, the gut microbiota presents enrichment in membrane transport of sugars, methane metabolism, branched-chain amino acid (BCAA) transport, xenobiotics degradation and metabolism, sulphate reduction; and reduction in the level of bacterial chemotaxis, flagellar assembly, butyrate biosynthesis and metabolism of cofactors and vitamins.

There is a T2D classifier system based on gut microbiota, in which the T2DM index is correlated with the ratio of T2DM patients and this system provides accurate classification of T2D individuals . For example, butyrate-producing bacteria may play a protective role against several types of diseases, and dysbiosis in T2DM patients may result from 'functional dysbiosis' rather than a specific microbial species **(19).**

Gut metagenomic markers show higher specificity for differentiation between T2DM cases and controls based on human genome variation, which may be a promising complementary approach to monitor gut health for risk assessment of this disease **(20)** .

Vitamins and type 2 Diabetes mellitus:

Vitamin D:

Accumulating evidence supports that vitamin D may have a potential role in the control of T2DM , as seasonal variation is found in glycemic status of T2DM patients, in which hypovitaminosis D frequently occurred in the winter is likely to be associated with the aggravation of T2DM. A recent research shows that vitamin D deficiency may have negative effects on glucose intolerance, insulin secretion and T2DM , either directly via vitamin D receptor (VDR) activation or indirectly via calcemic hormones and also via inflammation **(21)**.
As both 1-α-hydroxylase and VDR are present in pancreatic β cells, vitamin D has significant roles in the synthesis and release of insulin. Furthermore, vitamin D has influence on the insulin sensitivity by controlling calcium flux through the membrane in both β cells and peripheral insulin-target tissues **(22)**.
In addition, vitamin D supplementation is recognized as a promising and inexpensive therapy, which may decrease the risk of T2DM and improve glycemic parameters in T2DM patients . Therefore, it is seemingly that the positive effects of vitamin D are correlated with its action on insulin secretion and sensitivity as well as on inflammation. **(22)**.

Vitamin K:

Vitamin K has two naturally occurring forms, including phylloquinone (vitamin K1) and menaquinones.
Besides, a recent survey indicates that vitamin K1 provides benefits in glucose homeostasis, as higher intake of vitamin K1 is correlated with greater insulin sensitivity and glycemic status . Because poor glycemic control and bone quality may occur when vitamin K is deficient, it is cardinal to exclude vitamin K deficiency in T2DM patients. Several preclinical and clinical observations show that vitamin K2 has effects on bone quality and subsequent bone mechanical strength in T2DM patients independently of increasing BMD (bone mineral density) . It is also suggested that vitamin K2 may improve osteocyte density and lacunar occupancy by viable osteocytes in the cortical bone of glucocorticoid-treated or sciatic neurectomized rats **(23) .**
In addition, vitamin K2 may down-regulate bone turnover and stimulate lamellar bone formation, and prevent an increase in bone resorption with maintaince of bone formation and prevent a decrease in lamellar bone formation in glucocorticoid-treated rats **(23) .** Further studies are required for the comprehensive assessment of the role of vitamin K in the development of T2DM , the above-mentioned susceptibility loci and other influencing factors of T2DM

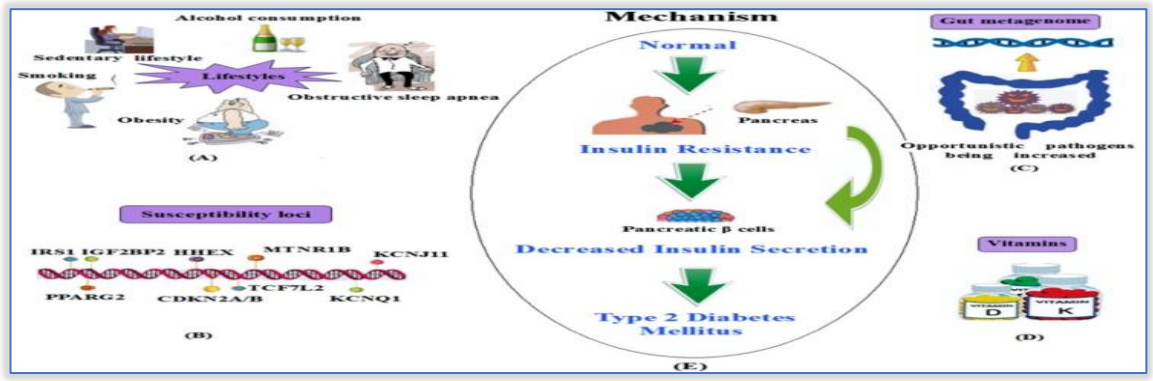

Figure 2:A summary of the influencing factors and mechanism of T2DM. (A) Lifestyles; (B) Susceptibility loci; (C) Gut metagenome association; (D) Vitamins. (E) The mechanism of T2DM.**(13)**

Signs and symptoms:

The classic symptoms of diabetes such as polyuria, polydypsia and polyphagia occur commonly in type 1 diabetes, which has a rapid development of severe hyperglycaemia and also in type 2 diabetes with very high levels of hyperglycaemia. Severe weight loss is common only in type 1 diabetes or if type 2 diabetes remains undetected for a long period. Unexplained weight loss, fatigue and restlessness and body pain are also

common signs of undetected diabetes. Symptoms that are mild or have gradual development could also remain unnoticed. Considering the asymptomatic nature of type 2 diabetes in the early stages, it is essential that the people are educated on its warning signs which include **:**Unexplained weight loss , Frequent fatigue , Irritability , Repeated infections especially in the Genital ereas ,Urinary tract ,Skin ,Oral cavity, Delayed wound healing , Dry mouth , Burning ,pain , numbness on feet, Itching , Reactive hypoglcemia , Acanthoses nigricans , Decreased vision **(24)**

Figure 3 : Overview of the most significant symptoms of diabetes **(24).**

Diagnosis and screening :

Diagnostic criteria for diabetes have traditionally relied on blood glucose levels. More recently, Glycosylated hemoglobin (HbA1c) has been added as an integrated measure of long-term glycaemia (the lifespan of a red blood cell is ~120 days) **(25).**

Criteria for the diagnosis of diabetes: (American Diabetes Association, 2022).

Fasting blood sugar (FBS) ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 h.

OR

Two hours post-prandial blood sugar (2-h PPBS) ≥200 mg/dL (11.1 mmol/L) during oral glucose tolerance test (OGTT). The test should be performed as described by World Health Organization (WHO), using a glucose load containing the equivalent of 75 g anhydrous glucose dissolved in water.

OR

HbA1C ≥6.5% (48 mmol/mol). The test should be performed in a laboratory using a method that is National Glycohemoglobin Standardization Program (NGSP) certified and standardized to the Diabetes Control and Complications Trial (DCCT) assay.

OR

In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

In the absence of unequivocal hyperglycemia, diagnosis requires two abnormal test results from the same sample or in two separate test samples.

Generally, FBS, 2-hPPBS during 75-g OGTT, and HbA1C are equally appropriate for diagnostic screening. It should be noted that the screening tests do not necessarily detect diabetes in the same individuals. The efficacy of interventions for primary prevention of type 2 diabetes has mainly been demonstrated among individuals who have impaired glucose tolerance (IGT) with or without elevated fasting glucose, not for individuals with isolated impaired fasting glucose (IFG) or for those with prediabetes defined by HbA1C criteria **(26).**

The same tests may be used to screen for , diagnose diabetes and to detect individuals with prediabetes**.** Diabetes may be identified anywhere along the spectrum of clinical scenarios—in seemingly low-risk

individuals who happen to have glucose testing, in individuals screened based on diabetes risk assessment, and in symptomatic patients. **(26).**

Diabetic complications and their pathogenesis :

Acute complications:

Diabetic complications include diabetic keto acidoses (DKA) and non-ketotic hyper-osmolar state (NKHS). While the first is seen primarily in individuals with type 1 DM, the latter is prevalent in individuals with type 2 DM. Both disorders are associated with absolute or relative insulin deficiency, volume depletion, and altered mental state **(27).**

In DKA

insulin deficiency is combined with counter-regulatory hormone excess (glucagon, catecholamines, cortisol, and growth hormone). The decreased ratio of insulin to glucagon promotes gluconeogenesis, glycogenolysis, and ketone body formation in the liver and also increases free fatty acid and amino-acid delivery from fat and muscle to the liver. Ketosis results from a marked increase in free fatty acid release from adipocytes due to increased lipolysis. In DKA, nausea and vomiting are often present , Lethargy and CNS depression may evolve into coma in severe DKA. Cerebral edema, an extremely serious complication, is seen most frequently in children**. (27).**

NKHS

is most commonly seen in elderly individuals with type 2 DM. Its most prominent features include polyuria, orthostatic hypotension, and a variety of neurological symptoms including altered mental state, lethargy, obtundation, seizure, and possibly coma. Insulin deficiency and inadequate fluid intake are the underlying causes of NKHS. Insulin deficiency leads to hyperglycemia, which induces an osmotic diuresis leading to profound intravascular volume depletion. **(27).**

Chronic complications :

The chronic complications of diabetes mellitus affect many organ systems and are responsible for the majority of morbidity and mortality. Chronic complications can be divided into vascular and nonvascular complications.

The vascular complications are further subdivided into: microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular complications (coronary artery disease, peripheral vascular disease, and cerebrovascular disease). **Nonvascular complications** include problems such as gastroporesis, sexual dysfunction, and skin changes.

Early in the course of diabetes, intracellular hyperglycemia causes abnormalities in blood flow and increased vascular permeability. This reflects decreased activity of vasodilators such as nitric oxide, increased activity of vasoconstrictors such as angiotensin II and endothelin-1, and elaboration of permeability factors such as vascular endothelial growth factor (VEGF). In diabetic arteries, endothelial dysfunction seems to involve both insulin resistance specific to the phosphotidylinositol–3-OH kinase pathway and hyperglycemia. **(27).**

Diabetic retinopathy

Diabetic retinopathy occurs in 3/4 of all persons having diabetes for
more than 15 years and is the most common cause of blindness. There is appearance of retinal vascular lesions of increasing severity, culminating in the growth of new vessels. Diabetic retinopathy is classified into two stages: nonproliferative and proliferative **(28)**.

Neuropathy

About half of all people with diabetes have some degree of neuropathy, which can be polyneuropathy, mono-neuropathy, and/or autonomic neuropathy.

In polyneuropathy there is loss of peripheral sensation which, when coupled with impaired microvascular and macrovascular junction in the periphery, can contribute to non-healing ulcers, the leading cause of non-traumatic amputation.

Mono-neuropathy is less common than polyneuropathy and includes dysfunction of isolated cranial or peripheral nerves. **Autonomic neuropathy** can involve multiple systems, including cardiovascular, gastrointestinal, genitourinary, sudomotor, and metabolic systems (**29).**

Nephropathy

This is a major cause of end-stage renal disease. There are glomerular hemodynamic abnormalities resulting in glomerular hyper-filtration, leading to glomerular damage as evidenced by microalbuminurea. There is overt proteinuria, decreased glomerular filtration rate, and end-stage renal failure. **(30)**.

Cardiovascular morbidity and mortality

In diabetes mellitus there is marked increase in several cardiovascular diseases, including peripheral vascular disease, congestive heart failure, coronary artery disease, and myocardial infarction, and a one- to five fold increase in sudden death. The absence of chest pain (silent ischemia) is common in individuals with diabetes, and a thorough cardiac evaluation is indicated in individuals undergoing major surgical procedures. In addition to coronary artery disease, cerebrovascular disease is increased in individuals with diabetes mellitus (threefold increase in stroke). Individuals with DM have increased incidence of congestive heart failure (diabetic cardiomyopathy). **(31)**.

Hypertension

Hypertension can accelerate other complications of diabetes mellitus, particularly cardiovascular disease and nephropathy. Antihypertensive agents should be selected based on the advantages and disadvantages of the therapeutic agent in the context of the individual patient's risk-factor profile. **(27).**

Infections

Individuals with diabetes mellitus exhibit a greater frequency and severity of infection. The reasons for this include incompletely defined abnormalities in cell-mediated immunity and phagocyte function associated with hyperglycemia as well as diminished vascularization secondary to long-standing diabetes. Many common infections are more frequent and severe in the diabetic population, whereas several rare infections are seen almost exclusively in the diabetic population (e.g. rhinocerebral mucormycosis and malignant otitis externa, which is usually secondary to P. aeruginosa infection in the soft tissue surrounding the external auditory canal). Pneumonia, urinary tract infection, and skin and soft tissue infections are all more common in the DM population. Gram-negative organisms, e.g. S. aureus and Mycobacterium tuberculosis, are more frequent pathogens in patients of DM. Diabetic patients have an increased rate of colonization of S. aureus in skin folds and nares and also have a greater risk of postoperative wound infections **(27).**

Mechanisms of hyperglycemia-induced damage:

Many hypotheses about how hyperglycemia causes diabetic complications have generated a large amount of data as well as several clinical trials based on specific inhibitors of these mechanisms. **(27).**

The main hypothesis are:

- **the Aldose Reductase theory:**

Excessive amount of glucose is shunted to the polyol pathway, where AR reduces glucose into sorbitol at the expense of NADPH. Since NADPH is essential for generation of GSH (intracellular antioxidant) from GSSG, the depletion of NADPH by the AR pathway may impair intracellular antioxidant defense. Sorbitol is then converted to fructose by SDH with the production of NADH, potentially leading to increased ROS via NADH oxidase **(32)**.

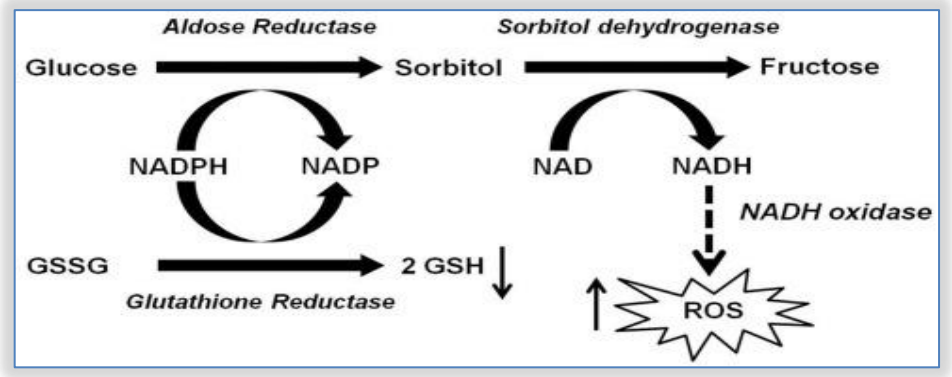

Figure 4 : Role of aldose reductase (AR) in hyperglycemia-induced oxidative stress **(32)**.

- **Advanced Glycation End Product (AGE) theory:**

Persistent hyperglycemic state in T2DM leads to the initiation and progression of non-enzymatic glycation reaction with proteins and lipids and nucleic acids. Glycation reaction leads to the generation of a heterogeneous group of chemical moieties known as advanced glycated end products (AGEs), which play a central role in the pathophysiology of diabetic complications. The binding of AGEs with its cellular receptor, RAGE, activates signaling pathways leading to enhanced oxidative stress and inflammation. The downstream consequences of the AGEs/RAGE axis involve compromised insulin signaling, perturbation of metabolic homeostasis, RAGE-induced pancreatic beta cell toxicity, and epigenetic modifications. The AGEs/RAGE signaling instigated modulation of gene transcription is associated with the progression of T2DM and pathogenesis of diabetic complications **(33)**

- **Activation of Protein Kinase C (PKC) isoform theory:**

a family of enzymes that are involved in controlling the function of other proteins. PKC has been associated with vascular alterations such as increases in permeability, contractility, extracellular matrix synthesis, cell growth and apoptosis, angiogenesis, leukocyte adhesion, and cytokine activation and inhibition. These perturbations in vascular cell homeostasis caused by different PKC isoforms (PKC-alpha, -beta1/2, and PKC-delta) are linked to the development of pathologies affecting large vessel (atherosclerosis, cardiomyopathy) and small vessel (retinopathy, nephropathy and neuropathy) complications **(34).**

- **Increased Hexosamine Pathway Flux theory:**

The metabolic effects of increased flux through HBP are thought to be mediated by increasing O-GlcNAcylation. Several investigators proposed that HBP functions as a cellular nutrient sensor and plays a role in the development of insulin resistance and the vascular complications of diabetes **(35)**.

- **the Reactive Oxygen Intermediate theory:**

chronic hyperglycemia is a cause of impairment of insulin biosynthesis and secretion. This process is called -cell glucose toxicity which is often observed under diabetic conditions. In the diabetic state, hyperglycemia per se and subsequent production of ROS decrease insulin gene expression and secretion and finally bring about apoptosis **(36)**

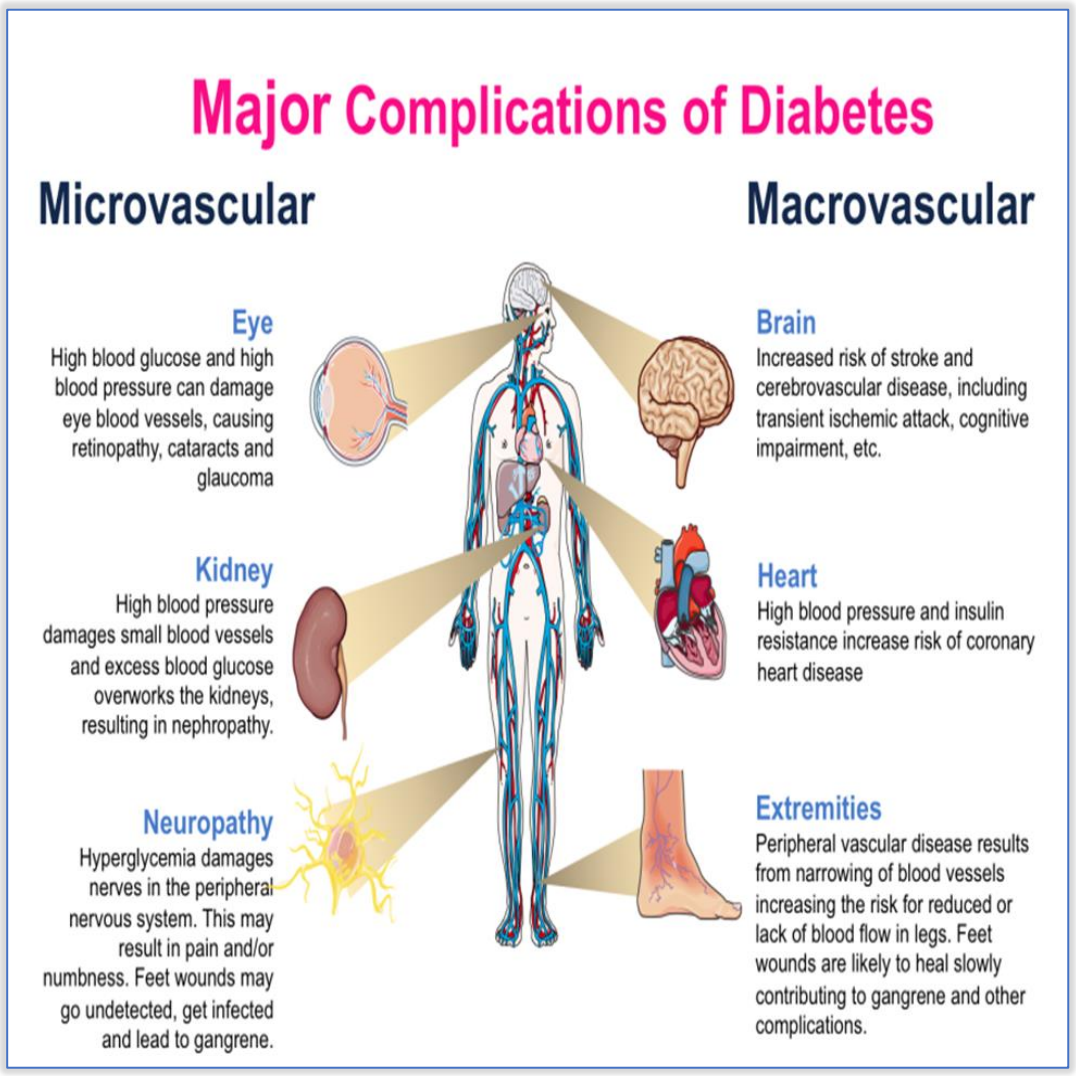

Figure 5: major complication of DM**(37)**

Intervention for prevention of T2DM:

Physical activity interventions

Nowadays, physical inactivity has been considered as one of the biggest public health problems worldwide . It is demonstrated that physical activity may contribute to 30-50% reduction in the development of T2DM . Physical activity interventions can improve glucose tolerance and reduce the risk of T2DM. walking, the most popular choice of physical activity, has been shown to reduce the relative risk of T2DM by 60% when walk for 150 min/week, compared to walking for <60 min/week **(38)** .

Healthy eating

Diabetes prevention studies have demonstrated that diet composition is another important factor to prevent the development of T2DM. Epidemiological studies have suggested that the risk of diabetes can be increased or decreased owing to dietary factors. The dietary factors which may increase the diabetes risk are consuming excessive amounts of refined grains, sugar-sweetened beverages, red and processed meat and alcohol, and those with the opposite effects are the intake of whole-grain cereal, vegetables, dairy, legumes, nuts, independently of body weight change **(14).**

Behavior change interventions

It has been shown that behavior change interventions can prevent or delay the development of T2DM for people with high risk . For instance, the Finnish Diabetes Prevention Study (DPS) and the Diabetes Prevention Program (DPP) demonstrated that changes in diet or physical activity could reduce the diabetes incidence by almost 60% in 4 years**(26) .**

Obesity management

Obesity is one of the most important risk factors for T2DM, whose basic cause is an imbalance between energy intake and expenditure . Adipose tissue, particularly of the tissue surrounding internal organs (e.g. visceral fat) can secrete various proinflammatory adipokines **(13)**, and the secretion of these cytokines will be changed if the adipose tissue mass increase, this will contribute to T2DM because of metabolic disturbances. Weight reduction may have effects on diabetes incidence, as seen in the DPP study, each kilogram of weight loss is correlated with a 16% reduction in the development of T2DM **(39)**. Weight reduction thus seems to be beneficial in the prevention of T2DM, at least in the short term **(40).**

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