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Type 2 Diabetes Mellitus in Adult; Pathogenesis and Therapy: A review

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Abstract

Type 2 diabetes mellitus (DM) is a long-term metabolic condition with a steadily rising prevalence worldwide. This trend has led to its classification as an epidemic in certain countries, with the number of affected individuals projected to double over the next decade. This increase is largely attributed to an aging population, further straining healthcare systems, particularly in underdeveloped nations. This review draws upon data from Medline, the Cochrane Database of Systematic Reviews, and reference lists of pertinent publications. The search focused on subject headings and keywords such as type 2 diabetes mellitus, prevalence, diagnosis, and treatment. Only English-language articles were considered. Screening and diagnosis continue to follow the guidelines established by the World Health Organization (WHO) and the American Diabetes Association (ADA), incorporating both clinical evaluations and laboratory tests. Although there is currently no cure for the disease, available treatments include lifestyle changes, obesity management, oral hypoglycemic drugs, and insulin

sensitizers. Metformin, a biguanide that reduces insulin resistance, remains the first-line therapy, especially for obese patients. Additional medications, such as non-sulfonylurea secretagogues, thiazolidinediones, alpha-glucosidase inhibitors, and insulin, have also proven effective. Recent advancements in the understanding of type 2 DM pathophysiology have resulted in the development of novel treatments. These include glucagon-like peptide-1 analogs, dipeptidyl peptidase-IV inhibitors, sodium-glucose cotransporter 2 inhibitors, and 11 β -hydroxysteroid dehydrogenase 1 inhibitors. Other innovations involve insulin-releasing glucokinase activators, pancreatic G-protein-coupled fatty-acid receptor agonists, glucagon-receptor antagonists, metabolic inhibitors targeting hepatic glucose production, and quick-release bromocriptine. Inhaled insulin, which was approved for use in 2006, has since been withdrawn from the market due to low consumer demand.

Keywords: Type-2 Diabetes Mellitus, Insulin Resistance, β -Cell, Liver, Adipocyte, Muscle, Cardiovascular Disease, Pathophysiology

1. Introduction

Diabetes mellitus (DM) is believed to be one of the oldest diseases recognized by humanity. Its earliest documentation can be traced back to an Egyptian manuscript dating approximately 3,000 years ago^[1]. The distinction between type 1 and type 2 diabetes mellitus (DM) was first clearly identified in 1936^[2]. Type 2 diabetes mellitus (DM), previously referred to as non-insulin-dependent diabetes mellitus, is the most prevalent form of the disease. It is characterized by hyperglycemia, insulin resistance, and a relative deficiency of insulin^[3]. Type 2 diabetes mellitus (DM) develops as a result of interactions among genetic, environmental, and behavioral risk factors^[4,5]. People living with type 2 DM are more vulnerable to various forms of both short- and long-term complications, which often lead to their premature death. This tendency of increased morbidity and mortality is seen in patients with type 2 DM because of the commonness of this type of DM, its insidious onset and late recognition, especially in resource-poor developing countries like Africa^[6].

2. Type 2 Diabetes Mellitus: Background and Epidemiology

According to the World Health Organization (WHO), diabetes mellitus is a long-term metabolic disorder characterized by high blood glucose levels, which, over time, can result in damage to the heart, blood vessels, eyes, kidneys, and nerves. More than 90% of diabetes mellitus cases are classified as type 2 diabetes mellitus (T2DM), a condition defined by insufficient insulin

secretion from pancreatic islet cells, insulin resistance (IR) in tissues, and an inadequate compensatory insulin secretion response^[7, 8]. As the disease progresses, insulin secretion becomes insufficient to sustain glucose homeostasis, leading to hyperglycemia. Most individuals with T2DM are characterized by obesity or an elevated body fat percentage, primarily concentrated in the abdominal area. In this state, adipose tissue contributes to insulin resistance through various inflammatory processes, such as increased release of free fatty acids (FFA) and dysregulation of adipokines. Key factors driving the T2DM epidemic include the global rise in obesity, sedentary lifestyles, high-calorie diets, and an aging population, which have collectively resulted in a fourfold increase in the incidence and prevalence of T2DM^[9, 10]. The organs implicated in the development of T2DM include the pancreas (β -cells and α -cells), liver, skeletal muscle, kidneys, brain, small intestine, and adipose tissue^[11]. Emerging evidence indicates that adipokine dysregulation, inflammation, abnormalities in gut microbiota, and immune dysfunction have become significant pathophysiological factors in T2DM^[12]. Epidemiological data reveal alarming trends, indicating a concerning outlook for T2DM. According to the International Diabetes Federation (IDF), diabetes was responsible for 4.2 million deaths in 2019, with 463 million adults aged 20 to 79 years affected—a figure projected to increase to 700 million by 2045. In 2019, diabetes accounted for at least 720 billion USD in healthcare expenditures. Furthermore, the true burden of T2DM may be underestimated, as 1 in 3 individuals with diabetes—approximately 232 million people—were undiagnosed. The highest prevalence of diabetes occurs among individuals aged 40 to 59 years. Incidence and prevalence rates vary geographically, with over 80% of cases occurring in low-to-middle-income countries, creating additional challenges for effective treatment. Patients with T2DM also face a 15% higher risk of all-cause mortality compared to non-diabetic individuals, with cardiovascular disease (CVD) being the leading cause of morbidity and mortality associated with the condition^[13]. A meta-analysis has demonstrated that diabetes is associated with a higher risk of coronary heart disease (hazard ratio [HR] 2.00; 95% CI 1.83–2.19), ischemic stroke (HR 2.27; 95% CI 1.95–2.65), and deaths related to other vascular diseases (HR 1.73; 95% CI 1.51–1.98)^[14]. The epidemiology of T2DM is influenced by both genetic and environmental factors. Genetic influences typically manifest when combined with environmental conditions such as sedentary lifestyles and high-calorie diets. Genome-wide association studies have identified common glycemic genetic variants associated with T2DM; however, these variants explain only about 10% of the total trait variance, suggesting that rare genetic variants may also play a crucial role^[15]. Individuals from different ethnic backgrounds may exhibit distinct phenotypes that heighten their susceptibility to clusters of cardiovascular disease (CVD) risk factors, such as hypertension, insulin resistance, and dyslipidemia^[16].

3. Pathophysiology

Type 2 diabetes mellitus (T2DM) is defined by insulin resistance, reduced insulin sensitivity, declining insulin production, and eventual failure of pancreatic beta cells^[17, 18]. As a result, less glucose is transported into the adipose,

muscle, and liver cells. Hyperglycemia causes an increase in the breakdown of fat. The Lately, the pathogenesis of type 2 diabetes has been linked to compromised alpha-cell activity^[19]. This malfunction prevents a meal from suppressing hepatic glucose and glucagon levels that increase during fasting. Hyperglycemia is the result of insufficient insulin and elevated insulin resistance. Important gastrointestinal mediators of insulin release and, in the case of GLP-1, glucagon suppression include the incretins. GLP-1 is a potentially useful therapeutic alternative because, despite reduced GIP function, its insulinotropic effects are maintained in individuals with type 2 diabetes^[19]. Two treatment strategies have been developed to address this issue: DPPIV inhibitors, which stop the breakdown of endogenous GLP1 and GIP, and GLP-1 analogues with longer half-lives^[19]. Studies on the role of mitochondrial dysfunction in the development of insulin resistance and the etiology of type 2 diabetes are still ongoing, but both classes of agents have demonstrated promise, with the potential to improve beta cell mass and functioning in addition to normalizing fasting and postprandial glucose levels^[20]. Most people with type 2 diabetes have central visceral adiposity and are obese. As a result, adipose tissue is essential to the pathophysiology of type 2 diabetes. Two recently developed theories are the ectopic fat storage syndrome (deposition of triglycerides in muscle, liver, and pancreatic cells) and the portal/visceral hypotension, which is the most widely accepted explanation for this connection and a major factor in increased nonesterified fatty acid concentrations. In the upcoming ten years, these two theories will serve as the foundation for research on the relationship between insulin resistance and beta cell malfunction in type 2 diabetes, as well as between our obesogenic environment and the risk of developing the disease.

4. Screening and Diagnosis

There are easily accessible tests for DM screening and diagnosis. A positive screen is similar to a diagnosis of pre-diabetes or diabetes mellitus (DM), and the test that is advised for screening is the same as the one used for diagnosis^[21]. Approximately 25% of individuals with type 2 diabetes already have microvascular problems at diagnosis, indicating that the disease has been present for longer than five years^[22]. It continues to be based on the World Health Organization's (WHO) National Diabetic Group Criteria of 2006 or the American Diabetic Association's (ADA) guidelines from 1997, which call for a single elevated glucose reading with symptoms (weight loss, polyuria, polydipsia, and polyphagia) or two other elevated values of either fasting plasma glucose (FPG) ≥ 7.0 mmol/L (126 mg/dL) or an oral glucose tolerance test (OGTT) with a plasma glucose level of ≥ 11.1 mmol/L (200 mg/dL) two hours after the oral dose^[21]. WHO prioritizes the OGTT for DM diagnosis, but the 1997 ADA guidelines center on the FPG^[21]. Fructosamine and glycated hemoglobin (HbA1c) are still helpful indicators of blood sugar regulation over time. Nevertheless, in addition to the suggested measures, actual physicians usually use other ones. The International Expert Committee (IEC) suggested in July 2009 that a HbA1c level of $\geq 6.5\%$ be included as an additional diagnostic criterion for DM. While identifying the range of HbA1c levels $\geq 6.0\%$ and $< 6.5\%$ to identify persons at high risk of developing DM, this committee recommended that the term pre-diabetes be

phased out^[23]. There is no clear HbA1c threshold at which normalcy stops and diabetes mellitus commences, much like with the glucose-based testing^[21]. The IEC decided to suggest a cut-off point for DM diagnosis that prioritizes specificity, stating that this struck a balance between the minimal clinical repercussions of postponing the diagnosis in a patient with a HbA1c level less than 6.5% and the stigma and expense of incorrectly classifying people as diabetic^[23].

5. Mechanisms Leading to T2DM and Pathophysiology

5.1 β Cell Physiology

Cellular integrity must be maintained, and the pathways and mechanisms involved in the physiology of the cell must be strictly controlled, in order to protect appropriate cell function^[24]. Insulin, which is formed as pre-proinsulin, is produced by β cells. Several proteins in the endoplasmic reticulum (ER) assist in the conformational change that pre-proinsulin goes through during the maturation process to produce proinsulin^[25]. Proinsulin then moves from the ER

to the Golgi apparatus (GA), where it enters immature secretory vesicles and is broken down into insulin and C-peptide^[26, 27]. After maturing, insulin is kept in granules until it is timed to release. The main cause of insulin release is a reaction to elevated glucose levels. It is important to remember that hormones, fatty acids, and amino acids are some additional substances that might cause the release of insulin^[28]. The glucose transporter 2 (GLUT2), a solute carrier protein that also serves as a glucose sensor for cells, is the primary mechanism by which cells absorb glucose as levels of circulating glucose rise. When glucose enters, the intracellular ATP/ADP ratio rises due to the activation of glucose catabolism, which causes the plasma membrane's ATP-dependent potassium channels to close. Ca^{2+} can enter the cell as a result of the membrane depolarizing and the voltage-dependent Ca^{2+} channels opening. Insulin exocytosis is the outcome of the priming and fusing of the secretory insulin-containing granules to the plasma membrane brought on by an increase in the intracellular Ca^{2+} concentration^[26, 28-30].

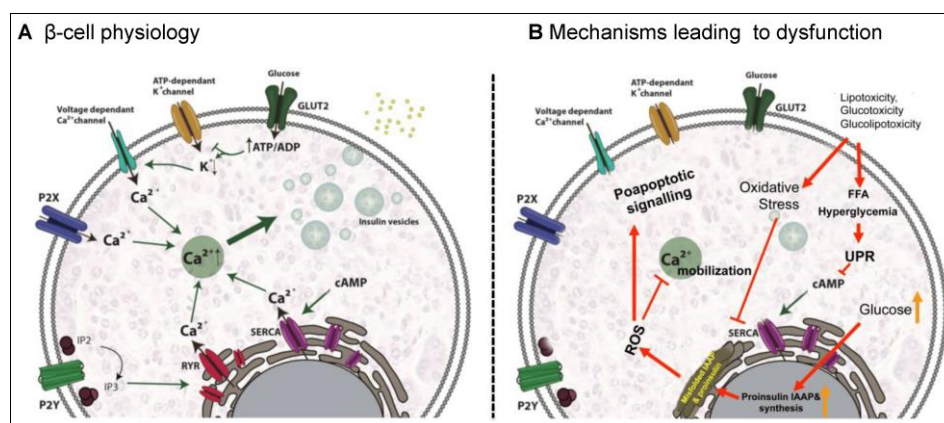


Fig 1: Mechanisms causing malfunction (B) and signaling pathways involved in insulin secretion in cells under normal conditions (A). (A) High glucose concentrations are the primary cause of insulin release, and the GLUT2 transporter is principally responsible for glucose internalization

Fig 1 shows the mechanisms causing malfunction (B) and the signaling pathways involved in insulin secretion in β -cells under physiological conditions (A). (A) High glucose concentrations are the primary cause of insulin release, and the GLUT2 transporter is principally responsible for glucose internalization. The ATP/ADP ratio rises as a result of glucose catabolism, and ATP-dependent potassium channels close, causing membrane depolarization and the activation of voltage-dependent Ca^{2+} channels. The latter facilitates Ca^{2+} influx, which in turn causes insulin exocytosis. Ca^{2+} mobilization and insulin secretion are facilitated by additional Ca^{2+} channels such as P2X, P2Y, SERCA, and RYR. (B) Oxidative stress is promoted by hyperglycemia and hyperlipidemia, which leads to the production of ROS, which triggers proapoptotic signals and prevents Ca^{2+} mobilization. Hyperglycemia and an excess of FFAs both cause ER stress and the activation of the apoptotic unfolded protein response (UPR) pathways. Prolonged elevated glucose levels promote the creation of proinsulin and IAAP, both of which produce ROS. IP2: inositol 1,3-bisphosphate; IP3: inositol 1,4,5-trisphosphate; RYR: ryanodine receptor channel; SERCA: sarcoplasmic reticulum Ca^{2+} -ATPase; FFA: free fatty acid; ROS: reactive oxygen species; GLUT2: glucose transporter 2; P2X: purinergic receptor X; P2Y: purinergic receptor Y."

6. Risk Factors

T2DM is caused by a complex interplay of genetic, metabolic, and environmental variables, which together make up its risk factors. Although a person's ethnicity and family history/genetic predisposition are non-modifiable risk factors for type 2 diabetes, robust genetic foundation, epidemiological research indicates that reducing the primary modifiable risk factors (obesity, inactivity, and poor food) can avoid many cases of type 2 diabetes^[31, 32].

6.1 Ethnicity and Family History/Genetic Predisposition

Ethnicity and geographic location have a significant impact on the incidence and prevalence of type 2 diabetes worldwide, with Native Americans, Japanese, and Hispanics having the highest risks^[33-35]. It has been demonstrated that Asians have greater incidence rates than White Americans^[36, 37], and white population in the UK^[38], where the highest risk is among the black population^[39]. Although the exact causes have not been identified, some contributing aspects have been hypothesized, including socioeconomic factors, direct genetic tendency, modern lifestyle variables that encourage obesity, and gene-environment interactions.

The chance of getting type 2 diabetes is significantly influenced by genetic predisposition. Numerous T2DM

genome-wide association studies conducted in the last ten years have demonstrated the complicated polygenic nature of T2DM, with the majority of these loci raising the risk of T2DM by primarily affecting insulin secretion, and a small percentage reduce insulin activity^[40, 41]. Four variants were identified by Dimas *et al.* based on their possible intermediary mechanisms in the pathophysiology of type 2 diabetes, exhibiting a distinct insulin resistance pattern; two lowering insulin secretion in conjunction with hyperglycemia while fasting; nine lowering insulin secretion in conjunction with normal fasting glycemia; and one modifying insulin processing^[42]. These findings suggest that T2DM has a highly polygenic genetic architecture, and more association research is required to pinpoint the majority of T2DM loci^[43]. Both observational studies show that the impact of a particular genetic variant can be influenced by environmental factors (and vice versa), suggesting that interactions between susceptibility loci and environmental factors may be the cause of the missing heritability of type 2 diabetes, as well as clinical trials^[44].

6.2 Obesity, Low Physical Activity and Unhealthy Diet

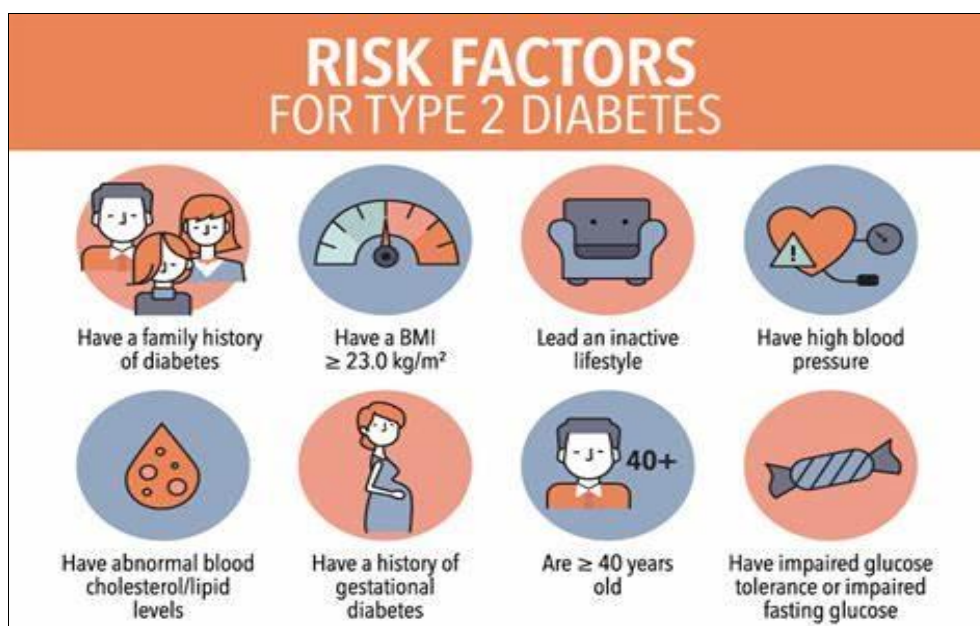
The biggest risk factor for type 2 diabetes is obesity, defined as a body mass index [BMI] of 30 kg/m²^[45, 46], and is linked to metabolic irregularities that cause IR^[47]. The age at which type 2 diabetes is diagnosed and BMI have an inverse linear relationship^[48]. The exact mechanisms by

which obesity induces T2DM and IR remain to be elucidated; however, numerous factors have shown a significant role in the development of this pathological process, which involves both cell-autonomous mechanisms and inter-organ communications^[49].

Another risk factor for type 2 diabetes is a sedentary lifestyle, as demonstrated by the Women's Health Study and the Kuipio Ischemic Heart Disease Risk Factor Study, which found that people who walked for two to three hours per week or for at least forty minutes had a 34% and 56% lower chance of getting type 2 diabetes^[50, 51]. Physical activity has three main advantages for delaying the onset of type 2 diabetes. First, as skeletal muscle cells contract, more blood flows into the muscle, which improves the muscle's ability to absorb glucose from plasma.

7. Conclusion

Novel treatments have been developed as a result of recent advances in our understanding of the biology of type 2 diabetes. These consist of dipeptidyl peptidase-IV inhibitors, sodium-glucose cotransporter 2 inhibitors, 11 β -hydroxysteroid dehydrogenase 1 inhibitors, and analogs of glucagon-like peptide-1. Additional advances include quick-release bromocriptine, glucagon-receptor antagonists, insulin-releasing glucokinase activators, pancreatic G-protein-coupled fatty acid receptor agonists, and metabolic inhibitors that target the synthesis of glucose in the liver.



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