Section: Biochemistry

Review Article

TYPE 2 DIABETES: A COMPLEX INTERPLAY OF GENES AND DISEASES WITH RECENT ADVANCES IN THE TREATMENT

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Abstract

Background: Type 2 diabetes is a diagnosis of exclusion and therefore demonstrates heterogeneity in terms of clinical presentation, course, and treatment response. Several attempts have been made to classify the disease using clinical data, but these classifications suffer from limitations. Alternatively, genetic data, which are fixed and based on mechanism, have shown promise in identifying groups of loci that may aid in deconstructing the heterogeneity of Type 2 diabetes. Genetics could be used into classification schemas to help us better understand and treat the illness. The existence of numerous risk factors contributing to diabetes, along with delayed diagnoses leading to severe micro- and macro-vascular complications, life-threatening consequences, insufficient existing treatments, and substantial financial burdens linked to therapy, underscore the urgency of creating innovative and effective therapeutic approaches and preventative measures for type 2 diabetes management. Additionally, our review offers insight into the present state of knowledge regarding type 2 diabetes epidemiology, encompassing the influence of genetic factors, lifestyle choices, and other elements in the rising prevalence of this condition. New therapeutic strategies, role of risk assessment in management of T2D and preventing T2DM through lifestyle intervention are also discussed.

INTRODUCTION

Type 2 diabetes (T2D) is a widespread and intricate metabolic disorder, presenting ongoing substantial public health challenges across the globe. It is characterized by chronic hyperglycemia resulting from resistance of cells for insulin and poor insulin secretion from pancreatic beta-cells. Type 2 diabetes holds the distinction of being the most prevalent form of diabetes, comprises the majority of global diabetes cases and is intimately linked with factors such as obesity, sedentary lifestyles, and other relevant lifestyle elements, as succinctly depicted in [Figure 1].[2,3]

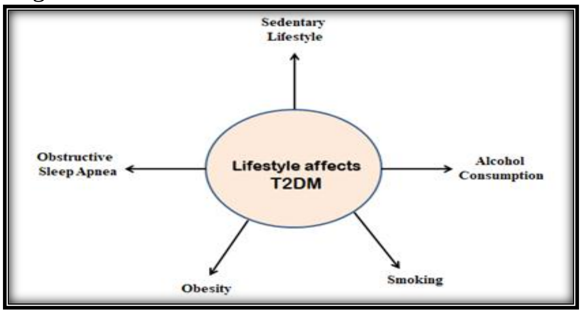

Figure 1: Lifestyle significantly affects Type 2 Diabetes Mellitus (T2DM)

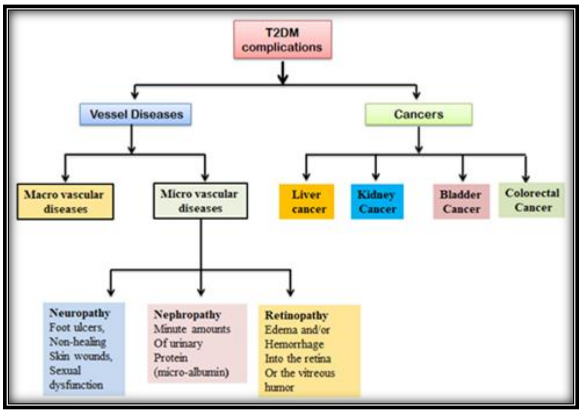

Figure 2: Complications arising from Type 2 Diabetes mellitus

Over the past few decades, there has been a growing recognition that T2D is not a singular disease but rather a highly heterogeneous condition with considerable variations in clinical presentation, disease progression, and treatment response among affected individuals. [Figure 2] described the various complications occurred due to T2D. This heterogeneity presents a substantial obstacle to achieving personalized and targeted therapeutic approaches, and highlights the need to delve deeper into the underlying factors contributing to the diverse manifestations of T2D.[4,5]

In the medical field, diagnosing the type of diabetes in a patient with high blood glucose levels involves investigating various causes, excluding other possibilities before settling on Type 2 diabetes (T2D). Autoantibodies may indicate Type 1 diabetes (T1D) or latent autoimmune diabetes in adults (LADA), while glucocorticoid use may suggest glucocorticoid-induced hyperglycemia. If no specific reason is found, the patient is classified as having T2D, which accounts for around 90% of diabetes cases.[6] T2D shows significant heterogeneity in clinical presentation and treatment response, likely influenced by genetic and environmental factors. Figure 3 shows the various factors responsible for pathogenesis of T2D. Efforts are underway to systematically classify diabetes using clinical and molecular data to improve understanding and management, particularly in preventing complications.[7]

Current clinical practice in diagnosing T2D relies primarily on exclusion criteria and phenotypic features. However, such classifications have their limitations, often failing to provide a comprehensive understanding of the diverse disease subtypes and their distinct pathophysiological mechanisms. As a result, there is a pressing demand for more refined and accurate subclassification systems that can better elucidate the underlying complexities of T2D.[8]

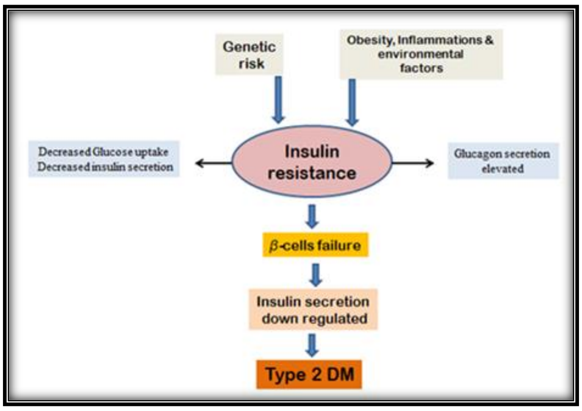

Figure 3: Pathogenesis of Type 2 Diabetes Mellitus

This article provides an overview of diabetes-subtyping schemas and their potential to shape our understanding and management of T2D, with a focus on genetics as a tool for deconstructing the heterogeneity of disease and identifying novel therapeutic strategies and preventive measures.

Epidemiology of Type 2 Diabetes: Burden of disease in India and worldwide

Type 2 diabetes is a significant health challenge in India and globally, with India being labeled as the "diabetes capital of the world." The increase in prevalence is attributed to factors such as urbanization, sedentary lifestyles, dietary changes, and genetics. Additionally, early-onset T2D and higher prevalence among younger individuals are emerging trends of concern in India. Understanding the epidemiological trends and risk factors of T2D is essential to implement targeted preventive strategies and healthcare interventions on a national and international level.[9]

The escalating burden of type 2 diabetes represents a significant apprehension within the realm of worldwide healthcare. Epidemiological data from the current Global Burden of Disease (GBD) dataset from the Institute of Health Metrics, Seattle, was used to examine the incidence, prevalence, and impact of diabetes mellitus. The global and regional trends of type 2 diabetes for all ages were assessed from 1990 to 2017, with the SPSS Time Series Modeler utilized to acquire forecast estimates. The data revealed that approximately 6.28% of the world's population was affected by type 2 diabetes, with over 462 million individuals in 2017 and a prevalence rate of 6059 cases per 100,000. Diabetes was accountable for over 1 million deaths per annum, establishing it as the ninth primary cause of mortality. Diabetes mellitus incidence is increasing rapidly worldwide, particularly in developed regions such as Western Europe, with a uniform gender distribution and an incidence rate peaking around 55 years of age. The global prevalence of type 2 diabetes is anticipated to increase to 7079 individuals per 100,000 by 2030, signifying a continued escalation worldwide. There are worrying trends of escalating prevalence in lower-income countries, emphasizing the pressing requirement for clinical and public health preventive measures.[10]

The incidence of diabetes in India has experienced a gradual increase since 1990, and this trend has been further exacerbated since the year 2000. The International Diabetes Federation reports that the prevalence of this condition has been on an upward trajectory in India during the past decade. Presently, the proportion of individuals with diabetes has risen from 7.1% in 2009 to 8.9% in 2019. As of now, there are an estimated 25.2 million adults with impaired glucose tolerance, and this number is projected to increase to 35.7 million by 2045. When it comes to the global diabetes epidemic, India ranks second only to China, with 77 million people affected by this condition. Among them, 12.1 million are aged over 65, with this figure expected to rise to 27.5 million by 2045. Furthermore, approximately 57% of adults with diabetes in India remain undiagnosed, which accounts for nearly 43.9 million individuals. The healthcare spending per person on diabetes is estimated to be 92 US dollars, and around 1 million deaths are directly attributed to this condition.[11]

Type 2 Diabetes: A Collection of Multiple Diseases:

Patients diagnosed with T2D are commonly associated with obesity and insulin resistance, but not all fit this profile. Diabetes heterogeneity has led to efforts in refining its classification. Maldonado et

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al. introduced the "AB" scheme in 2003 to categorize diabetic ketoacidosis patients, revealing diverse subgroups beyond typical T1D or T2D. The study involved 103 patients with different ethnic backgrounds admitted due to DKA, with 50% being A−B+, 22% A−B−, 17% A+B−, and 11% A+B+. Only 17% showed characteristics of T1D, and the majority did not fit the typical DKA profile of T2D or T1D. [9]

Schwartz et al. have introduced a beta-cell centric classification that emphasizes the presence of 11 distinct pathways leading to beta-cell dysfunction, enabling tailored treatment approaches for diabetes. This approach reflects the evolving understanding of diabetes beyond traditional T1D and T2D classifications, emphasizing the need for personalized approaches. Clinicians can better understand the causes underlying diabetes and create more efficient treatment plans by taking into account variables such as islet autoantibodies and beta-cell dysfunction.[12] The study by Hulman et al. revealed diverse clinical phenotypes in diabetes development. Analyzing data from 5861 individuals through oral glucose tolerance tests (OGTT) with a three time point at 30 minutes identified a subgroup, group 3, with normal glucose at two hours but elevated at 30 minutes. This subgroup had a fourfold increased diabetes risk and twofold higher all-cause mortality risk compared to group 1. Surprisingly, group 3 had similar insulin sensitivity to group 1 but reduced first-phase insulin response.[13] Further research is necessary to understand how subgroups, especially group 3, are linked to specific mechanistic pathways impacting diabetes risk and mortality. Investigating these pathways can provide valuable insights for targeted interventions and personalized treatments. The study by Li et al. analyzed data from 2551 individuals with T2D, identifying three distinct subgroups with unique disease risks and genetic associations, offering promise for understanding T2D complexity. However, some limitations need consideration.[14]

Ahlqvist et al. developed a new framework for characterizing adult-onset diabetes by utilizing six key clinical metrics to diagnose Scandinavian individuals. They utilized k-means and hierarchical clustering algorithms and successfully identified five subgroups of patients: severe autoimmune (T1D and LADA), severe insulin-deficient, severe insulin-resistant, mild obesity-related, and mild age-related forms. In a similar data-driven approach, Dennis et al. studied T2D by analyzing two large trial datasets of patients receiving different therapies and identified the same five clusters as Ahlqvist et al. However, Dennis et al. found that simpler continuous features, such as age at diagnosis and baseline-estimated glomerular filtration rate, were better predictors of glycemic progression, time to chronic kidney disease, and treatment response than the clustering approach. Their proposed model, which included sex, age at diagnosis, baseline BMI, and baseline hemoglobin A1c, performed better in predicting treatment response than the clustering approach.[15]

The success of precision medicine in the context of Type 2 Diabetes (T2D) relies on the use of particular phenotypic measurements for outcome prediction. Targeted clinical investigations utilizing these measures are practical and beneficial in developing treatments and understanding T2D's pathophysiology. While the study by Dennis et al. supports the advantages of this approach, the lack of replicability and unclear clinical relevance of the subgroups identified highlight the need for further research into underlying mechanisms and implications. Despite limitations, data analysis and machine learning offer potential for personalized management approaches for complex diseases like T2D.[16]

Multiple Genes in Type 2 Diabetes Subclassification:

For the development of personalized medicine, the discovery of disease subtypes or clinical indicators based on molecular processes offers enormous promise. When the disease is thoroughly characterized both clinically and with a well-researched etiological basis, it becomes possible to provide optimal and personalized management strategies. Type 2 diabetes (T2D) is recognized for its significant genetic component, with heritability estimates varying between 30% and 70%. These estimates encompass not only genetic risk factors but It also encompasses shared familial, prenatal, and postnatal environmental factors.[17]

T2D, like other complex diseases, is polygenic, influenced by multiple genes. Thousands of germline genetic loci are involved, with over 200 identified so far. Large-scale studies have increased our knowledge of T2D's genetic architecture, showing that common genetic variations contribute to disease risk. The challenge lies in connecting non-coding variants to specific regulatory elements, genes, and tissues. Despite this, advancements in genetic studies, access to large cohorts, and high-throughput genomic technologies offer promising opportunities to unlock the potential of genomics in diabetes research and enhance our understanding of the disease. The relevance of genetics in subclassifying type 2 diabetes (T2D) is uncertain. Germline genetics' role in T2D subclassification is speculative with limited impact on patient care. However, genetics has shown clinical utility in cancer treatment through targeted therapies based on somatic genetic sequencing of tumors.[18]

Considering the limited clinical use of germline genetics in complex disease subclassification, it's crucial to assess its relevance and potential benefits in T2D. Genetic factors significantly contribute to T2D risk, and integrating genetic data can refine diagnostics, tailor treatments, and identify high-risk individuals. Advancements in research and technology offer promise for more precise and personalized T2D management by combining genetic and phenotype-based approaches.

Monogenic diseases misdiagnosed as T2D highlight the importance of genetics in T2D subclassification. Genes implicated in monogenic diabetes, such as MODY, show clinical overlaps with T2D. The misclassification of MODY as T2D underscores the need for genetic information to detect monogenic diabetes and reduce the heterogeneity of T2D caused by misdiagnosis.[19]

Even within phenotypically defined disease subgroups, there can be significant genetic heterogeneity, as seen in phenocopies like MEN types 1 and 4. In diabetes, MODY is a prime example, where patients with similar clinical features may have monogenic diabetes resulting from different genes, such as GCK, HNF1A, and HNF4A. While clinicians can differentiate between genetic forms through phenotyping, genetic diagnosis provides objective evidence of distinct disease entities with shared phenotypes. Understanding such genetic heterogeneity can guide treatment decisions. Though our focus is on polygenic risk in T2D, there may be clinically relevant genetic heterogeneity within phenotypically similar subtypes, where genetics can offer a comprehensive diagnostic approach.[20]

Furthermore, genetics can provide valuable insights for guiding disease management. Unlike clinically defined subtypes, genetically defined subtypes of diseases offer the potential for targeted management strategies that focus on underlying mechanisms. It is important to acknowledge that single genetic perturbations associated with monogenic diseases usually have more significant downstream effects and influence disease risk to a greater extent compared to those associated with T2D, which typically have modest effect sizes. However, there may be individuals in whom the cumulative polygenic risk significantly impacts specific disease pathways, thereby making these pathways potential targets for tailored management approaches.[21]

In contrast to numerous clinical and laboratory characteristics, germline genetic markers remain stable throughout an individual's life and are not affected by treatments or disease progression. Consequently, a genetic classification test could be conducted at any stage during the course of the disease, including years after the initial diagnosis and the commencement of treatment, or conceivably even before the diagnosis itself. This facilitates the adoption of preventive strategies.[22]

"Multiple Genes' Role in Understanding T2D Pathways": What insights have we gained about the pathophysiology of T2D from extensive genetic association studies? These studies have significantly advanced our understanding through two main approaches: first, analyzing specific T2D genetic regions harboring genes that have already been associated with diabetes pathophysiology, and second, investigating specific loci through detailed follow-up mapping and functional studies, such as SLC30A8, SLC16A11, and TM6SF2.[23]

The TM6SF2 association with T2D exemplifies how genetics has led to the discovery of a new disease mechanism. Initially, the CILP2 locus, containing TM6SF2, was linked to T2D in a 2012 GWAS meta-analysis. Table 1 briefly described the susceptibility loci that are linked to type 2 diabetes mellitus (T2DM). Further analysis using an exome chip identified a specific variant, p.Glu167Lys, significantly linked to T2D. This variant was also associated with NAFLD. Functional experiments on mice and human cell lines supported TM6SF2's role in liver fat metabolism and triglyceride secretion. These findings reveal a novel disease pathway from the liver tissue, increasing the risk of both T2D and NAFLD, highlighting genetics' remarkable ability to uncover disease mechanisms.[24]

Recent studies have used a new approach to explore T2D loci. By leveraging multiple variant-trait associations, clusters of related genetic variants are formed to deduce disease pathways. However, challenges arise due to numerous highly correlated non-coding variants within loci, making it difficult to establish connections. An encouraging solution to address this gap is the use of multi-trait cluster analysis, directly connecting variants to pathways based on their pattern of trait associations.[25] The "soft" clustering approach, allowing variants to belong to multiple clusters, yields more interpretable outcomes than the "hard" clustering approach, making it better suited for modeling complex disease biology and understanding T2D mechanisms.[26] Udler et al. employed a soft clustering approach called Bayesian nonnegative matrix factorization (bNMF) to group 94 T2D variants and 47 metabolic traits into five distinct genetic loci clusters. Each cluster exhibited specific tissue-specific enhancer and promoter enrichment based on epigenomic data from 28 cell types.[26] Two clusters were associated with reduced beta-cell function, with one linked to high proinsulin levels (potential defective insulin processing) and the other with low proinsulin levels (suggesting defective insulin synthesis). The other three clusters represented mechanisms of insulin resistance: obesity-mediated, "lipodystrophy-like" fat distribution, and disrupted liver lipid metabolism. The loci implicated in each cluster showed differential associations with other metabolic diseases, with certain clusters being linked to increased stroke risk or blood pressure. These findings highlight the potential of genetically informed pathways to represent distinct disease mechanisms and provide valuable insights into T2D's complex nature.[4,27]

Mahajan et al. utilized the C-means soft clustering method to analyze GWAS data for 94 T2D association signals, partially overlapping with Udler et al.'s signals. Along with 10 T2D-related traits, this analysis revealed six variant clusters, five of which aligned with the clusters found by Udler et al. This consistency between two independent clustering approaches supports the robustness and reliability of

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the genetically driven disease pathways. Drawing inspiration from cancer biology, Hanahan and Weinberg's "Hallmarks of Cancer" provided a conceptual model to understand the fundamental deregulated pathways in cancer development.[18] Similarly, we can propose the "Hallmarks of Diabetes" to identify crucial pathways, guiding disease classification and management. In cancer, disruptions in these functional pathways trigger tumor growth, leading to distinct disease etiologies and treatment considerations. By identifying key functional pathways in diabetes, we can simplify complexity, improve understanding, and facilitate targeted therapies' development and clinical use.[28]

While cancer and diabetes have distinct disease biology, this approach emphasizes diabetes-specific germline variation. Still, cancer demonstrates how integrating pathway deregulation with genomic knowledge can transform disease treatment. As we discover the hallmarks of diabetes, we can explore if individuals develop the disease through one or multiple pathways, offering potential treatment targets. If most individuals develop diabetes via multiple deregulated pathways, a combination therapy targeting these pathways, like a "poly-pill," could be advantageous.[29]

As our understanding of disease mechanisms deepens, our perspective on metabolic diseases is changing. Type 2 Diabetes (T2D) and other conditions like obesity and hypertension are defined by specific thresholds against the continuum of hyperglycemia, BMI, and blood pressure. The pathways leading to increased T2D risk also seem to influence other metabolic diseases, suggesting shared disease processes or "endophenotypes". As we uncover more about genetic variation in metabolic diseases, clustering and other approaches will help us better comprehend these fundamental endophenotypes, such as dysregulated insulin processing or unfavorable fat distribution. Understanding the molecular basis of shared risk among metabolic diseases could improve disease screening for unaffected individuals and enhance preventive measures and screenings for individuals with T2D to reduce complications.[30]

Recent Advances in the Treatment and Prevention of T2D

Treatment through common non-insulin antidiabetic drugs Biguanides, such as metformin, are crucial antidiabetic drugs utilized as primary treatment for diabetes mellitus, as they effectively reduce blood glucose, increase insulin sensitivity, and improve cardiovascular outcomes while lowering mortality rates in T2DM patients. However, elderly diabetics should use caution when taking metformin due to potential side effects, and it is contraindicated in patients with chronic or acute renal insufficiency.[31] Sulphonylureas are often used as second-line treatment for type 2 diabetes in patients who are not severely obese. These drugs work directly on the islet β cells, stimulating insulin secretion. However, they are associated with a higher risk of hypoglycemia, particularly in older patients with impaired renal function, hepatic dysfunction, or inadequate oral intake, and they may cause weight gain.[32] Thiazolidinediones (TZDs) are insulin sensitizers that improve insulin sensitivity in skeletal muscle and the liver by acting as peroxisome proliferator-activated receptor γ (PPAR-γ) ligands. They offer a more sustained effect on regulating hyperglycemia and lower risk of hypoglycemia when used alone compared to sulfonylureas and metformin, and have proven effective in combination therapy, particularly with insulin. However, TZDs have drawbacks such as an increased risk of bladder cancer, weight gain, and edema, as well as the potential for adverse effects in older patients with congestive heart failure. Careful consideration of these factors is necessary when prescribing TZDs for T2DM management.[33] α-Glucosidase inhibitors (AGIs) such as acarbose, voglibose, and miglitol are effective for managing postprandial hyperglycemia by reducing carbohydrate absorption. While voglibose has shown improvements in glucose tolerance and acarbose has been associated with a reduced risk of cardiovascular diseases, AGIs can cause gastrointestinal side effects such as abdominal bloating, diarrhea, and flatulence. Therefore, healthcare providers must consider the potential adverse effects of AGIs, particularly in older patients and those with renal impairment, and provide individualized treatment plans to optimize their use for T2DM management.[34] Incretin-based therapies have been developed to regulate blood sugar levels by stimulating insulin secretion and suppressing glucagon secretion in a glucose-dependent manner. These therapies are effective in managing type 2 diabetes mellitus as they improve glycemic control without increasing the risk of hypoglycemia, and promote weight loss. In addition, incretin-based therapy may also have positive effects on inflammation, sleep quality, cardiovascular health, and liver function.[35] The effectiveness of GLP-1 receptor agonists, such as exenatide and liraglutide, in reducing HbA1c levels makes them valuable tools for managing diabetes. GLP-1 receptor agonists play a crucial role in regulating glucose metabolism through various mechanisms, making them effective in improving glycemic control and reducing the risk of hyperglycemia-related complications. GLP-1 receptor agonists have shown comparable efficacy and safety profiles across different age groups, making them a suitable treatment choice for older adults with diabetes.[36] [Table 2] summarized the Alternative antidiuretic medications used in the treatment of patients with type 2 diabetes mellitus (T2DM).

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Table 1: Genome-wide association studies (GWAS) have identified susceptibility loci associated with type 2 diabetes mellitus (T2DM)

Gene	Gene Region	SNPs	Population	P-Value
	11p15.4	rs2237897	Japanese	6.8×10-13
	11p15.4	rs2237895	Chinese	9.7×10-10
	11p15.4	rs231362	European	2.8×10-13
KCNQ1	11p15.4	rs2237892	Japanese	1.7×10^{-42}
	11p15.1	rs5219	European	6.7×10^{-11}
KCNJ11	11p15.1	rs5215	UK	5.0×10^{-11}
TCF7L2	10q25.2	rs7903146	European	2.0×10^{-31}
MTNR1B	11q14.3	rs1387153	European	7.8×10^{-15}
IGF2BP2	3q27.2	rs4402960	European	8.9×10^{-16}
	3q27.2	rs6769511	European	9.0×10^{-16}
PPARG2	3p25.2	rs1801282	European	1.7×10^{-6}
	3p25.2	rs17036101	European	7.5×10^{-6}
IRS1	2q36.3	rs7578326	European	5.4×10-20
HHEX	10q23.33	rs1111875	European	5.7×10^{-10}
	10q23.33	rs5015480	European	1.0×10-15
CDKN2A/B	9p21.3	rs10811661	European	7.8×10^{-15}
	9p21.3	rs2383208	Japanese	1.6×10^{-7}
	9p21.3	rs564398	UK	1.3×10^{-6}

Table 2: Alternative antidiuretic medications used in the treatment of patients with type 2 diabetes mellitus (T2DM) are as follows:

Biguanides	Metformin	AMP-kinase	Decrease blood glucose Increase insulin sensitivity Decrease cardiovascular risk Decrease hypoglycemia risk	GI side effects Lactic acidosis Vitamin B12 and folate deficiency
Sulfonylureas	Glimepiride/ Glyburide/ Gliclazide/ Glipizide	K+ channels ATP-sensitive,	Increase insulin secretion↑	Hypoglycemia and weight gain
TZDs	Troglitazone/ Pioglitazone/ Roziglitazone	PPAR-γ	Increase insulin sensitivity↑ Decrease hypoglycemia risk Increase glycemic control	High risk of bladder cancer, weight gain and edema
AGIs	Acarbose/ Voglibose/ Miglitol	α-glucosidase	Decrease carbohydrate absorption	Side effects of GI
GLP-1 receptor agonists	Liraglutide/ Exenatide	GLP1 receptors	Increase insulin secretion glucagon secretion↓ satiety↑ hypoglycemia risk↓	Side effects of GI, acute pancreatitis, renal dysfunction and thyroid C-cell tumors in rodents

Use of Insulin and its derivative for treatment: Insulin revolutionized T2DM treatment by improving glycemic control and addressing metabolic abnormalities. It enhances insulin sensitivity and β-cell function, delays diabetic complications, and suppresses ketosis. Insulin is available in four injectable forms, with long-acting variants posing the lowest risk of hypoglycemia. Insulin analogues have different pharmacokinetic profiles, and rapid-acting and long-acting analogues are available. Long-acting analogues can reduce the risk of hypoglycaemic events. Insulin therapy is generally required when lifestyle changes and oral antidiabetic agents fail to control glycemia. Combination therapy with insulin and oral antidiabetic agents has been shown to be effective.

New therapeutic development in diabetic treatment: While oral antidiabetic drugs and insulin are presently employed in the treatment of Type 2 Diabetes (T2DM) and have demonstrated promising results, challenges persist, including insufficient effectiveness and adverse effects. Therefore, there is a need to explore innovative therapeutic approaches. Sodium glucose co-transporter type 2 (SGLT2) inhibitors reduce blood glucose levels by preventing glucose reabsorption and increasing urinary glucose elimination. They effectively reduce HbA1c, FPG, systolic blood pressure, and bodyweight. Dapagliflozin is an effective SGLT2 inhibitor for T2DM patients. However, treatment may result in genital infections and breast and bladder cancer. Long-term studies are needed to examine possible negative effects.[37] DPP-4 inhibitors, such as vildagliptin, sitagliptin, saxagliptin, and linagliptin, are effective in protecting pancreatic β cells and inhibiting the progression of T2DM by blocking the degradation of GLP-1 and GIP. These inhibitors are

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well tolerated due to their cardiovascular protection and anti-arteriosclerotic action, with minimal gastrointestinal side effects and weight neutrality. Clinical studies have assessed their pharmacokinetics/pharmacodynamics, safety, efficacy, and tolerability, with vildagliptin and sitagliptin showing particular long-term advantages in the preservation of α- and β-cell functions and reduction in fasting lipolysis.[38] Lixisenatide, a GLP-1 receptor agonist, was granted marketing approval by the European Medicines Agency in 2013. Its activation of the GLP-1 receptor results in increased insulin secretion, decreased glucagon secretion, and satiety promotion through reduced gastrointestinal motility. Lixisenatide monotherapy or in combination with insulin and oral antidiabetic drugs has effectively lowered HbA1c, FPG, and PPG, while also reducing bodyweight, with primary combined therapy with basal insulin and ongoing clinical development as a combination product with insulin glargine.[39] GPR40 agonists are a type of drug that stimulate the G protein-coupled receptor 40, which is highly expressed in pancreatic β-cells. When stimulated with free fatty acids, GPR40 leads to insulin secretion through a β-cell-specific signaling pathway, and a number of chemical compounds have been found to act as GPR40 agonists, including TAK-875 and three novel agonists recently reported by Tanaka and colleagues. Among these, AS2034178 has been shown to reduce microvascular complications and has the most promising potential for treating type 2 diabetes mellitus.[40] Nitric oxide (NO) is a significant molecule synthesized from L-arginine by various NOS enzymes. NO3- and NO2- have therapeutic potential, but high plasma NO3- levels may have harmful effects. Natural sources of NO3-/NO2- from vegetables may be preferable, but further research is needed to identify suitable candidates for NO3-/NO2- therapy.[41] T2DM patients often experience immune dysfunctions and chronic metabolic inflammation. Stem cell therapy aims to address immune dysfunctions by co-culturing lymphocytes with cord blood-derived multi-potent stem cells. Early-phase studies have shown promising results, indicating the safety and therapeutic efficacy of this therapy in T2DM.Immune system alterations have been observed in T2DM, affecting various body tissues and circulating leukocytes. Salicylates and interleukin-1 antagonists are representative drugs with immunomodulatory effects in T2DM treatment, effectively lowering blood glucose levels and reducing associated complications.[42] Antioxidant therapy presents a promising approach for treating T2DM patients, effectively reducing the risk of diabetes and its related complications. Various antioxidants have been explored for combating oxidative stress in T2DM. With their potential to counter oxidative stress, antioxidant therapies hold significant potential for enhancing T2DM management and improving patient outcomes.[43]

Role of Risk assessment in management of T2D: Early detection of type 2 diabetes is crucial, given that 50% of people with diabetes are undiagnosed, and 20-30% experience complications before diagnosis. Risk assessment tools based on self-assessment, biochemical measures, or genetic markers are more practical and valuable than traditional blood glucose screening tests, allowing for timely interventions and potentially delaying the onset of T2DM.[44] Noninvasive risk assessment tools for predicting diabetes onset require various information, including age, sex, height, waist circumference, BMI, ethnicity, history of hypertension, and medication use, along with lifestyle factors like physical activity and dietary habits. The utilization of noninvasive screening tools has been shown to be cost-effective as a first-stage screening method compared to blood tests, with good sensitivity and specificity in identifying impaired glucose regulation or incident cases of T2DM, thereby aiding in early detection and intervention to ultimately reduce the burden of diabetes and its complications.[45] Biochemical testing is essential for identifying individuals who are at risk of developing type 2 diabetes. These tests typically involve several steps, beginning with simple questionnaires or noninvasive measures and culminating in the measurement of biochemical markers in pre-screened individuals. Many studies have evaluated prediction models for metabolic syndromes, which typically include measurements of blood lipids, plasma glucose, blood pressure, and waist circumference. Novel biochemical markers, such as C-reactive protein and liver enzymes, have also been studied for their prognostic potential.[46] Various genetic variants have been examined to predict T2DM, but their effectiveness is limited when compared to noninvasive characteristics. The accuracy of prediction depends on the number of genes, allele frequency, and genotype-associated risks. Identifying additional variants remains a challenge, and utilizing genetic information for patient benefit requires consideration of how to provide meaningful and actionable information to encourage healthier lifestyles and medical interventions.[47,48]

Preventing T2DM through Lifestyle Intervention

Physical inactivity is a major worldwide health problem, but physical activity interventions can reduce the risk of Type 2 Diabetes Mellitus (T2DM) by up to 50%. Walking is a popular choice of physical activity that can significantly reduce the relative risk of T2DM. Encouraging a daily step count can also be an effective self-regulatory strategy. For people with joint problems, alternative physical activities, such as cycling or swimming, should be considered. Diet composition is also an important factor in preventing the development of T2DM. Consuming excessive amounts of refined grains, sugar-sweetened beverages, red and

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processed meat, and alcohol can increase the risk, while whole-grain cereals, vegetables, dairy, legumes, and nuts can decrease it. Various prevention studies have examined the effects of reducing fat and increasing fiber density in the diet. A Mediterranean diet that includes vegetables, fruits, legumes, extra virgin olive oil, nuts, fish, whole grains, and red wine have also been shown to decrease the incidence of diabetes. It is recommended to limit the intake of red meat and processed foods and opt for unrefined grain products with high natural fiber content. DPS and DPP showed diet and exercise changes can reduce diabetes incidence by 60%. Vermunt group used various techniques, but continuity is a barrier to lifestyle change. Stimulus control can help resist temptation. Monitoring psychological causes and habitual behavior can identify future high-risk situations. Obesity is a major T2DM risk factor. Lifestyle-improving factors include increased fiber intake and reduced energy-dense foods. Weight reduction is beneficial in T2DM prevention. Modest and sustained lifestyle changes can reverse weight gain. Efficient prevention and control of T2DM requires further investigation.

CONCLUSION

Significant strides have been made in exploring diverse approaches to categorize and comprehend type 2 diabetes (T2D). The subgroups are expected to undergo additional characterization, which will provide insights into the underlying mechanisms for each group. Pathway-specific genetic risk scores have the potential to guide management and further narrow the T2D segment, although challenges remain in applying these methods to diverse populations and developing online calculators for clinical use. Further, global burden of T2DM and related complications remains heavy, with no fully effective measures in place to combat the disease. While genetic and environmental factors contribute to the onset of diabetes, several other factors are also at play. While antidiabetic agents can be beneficial, they can also have negative side effects, making the search for a more ideal therapy a top priority. Stem cell educator therapy has shown promise in the development of new therapeutic strategies for T2DM, with a focus on investigating the disease's mechanisms, effective intervention trials and prevention measures, earlier diagnosis, and novel drugs with fewer adverse effects.

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REFERENCES

1. Choudhury, A. A., Devi Rajeswari, V. Gestational diabetes mellitus - A metabolic and reproductive disorder. Biomedicine & Pharmacotherapy. 2021; 143: 112183. doi:https://doi.org/10.1016/j.biopha.2021.112183
2. Association, A. D. 2. Classification and diagnosis of diabetes: standards of medical care in diabetes—2018. Diabetes care. 2018; 41(Supplement_1): S13-S27.
3. Diagnosis and classification of diabetes mellitus. Diabetes care. 2009; 32 Suppl 1(Suppl 1): S62-67. doi:10.2337/dc09-S062
4. Galicia-Garcia, U., Benito-Vicente, A., Jebari, S., Larrea-Sebal, A., Siddiqi, H., Uribe, K. B., et al., Pathophysiology of Type 2 Diabetes Mellitus. 2020; 21(17). doi:10.3390/ijms21176275
5. Ahlqvist, E., Prasad, R. B., Groop, L. Subtypes of Type 2 Diabetes Determined From Clinical Parameters. Diabetes. 2020; 69(10): 2086-2093. doi:10.2337/dbi20-0001
6. Khawandanah, J. Double or hybrid diabetes: A systematic review on disease prevalence, characteristics and risk factors. Nutrition & Diabetes. 2019; 9(1): 33. doi:10.1038/s41387-019-0101-1
7. Chung, W. K., Erion, K., Florez, J. C. Precision Medicine in Diabetes: A Consensus Report From the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). 2020; 43(7): 1617-1635. doi:10.2337/dci20-0022
8. Williams, D. M., Jones, H., Stephens, J. W. Personalized Type 2 Diabetes Management: An Update on Recent Advances and Recommendations. 2022; 15: 281-295. doi:10.2147/dmso.s331654
9. Jha, R. P., Shri, N. Trends in the diabetes incidence and mortality in India from 1990 to 2019: a joinpoint and age-period-cohort analysis. 2021; 20(2): 1725-1740. doi:10.1007/s40200-021-00834-y
10. Khan, M. A. B., Hashim, M. J., King, J. K., Govender, R. D., Mustafa, H., Al Kaabi, J. Epidemiology of Type 2 Diabetes - Global Burden of Disease and Forecasted Trends. J Epidemiol Glob Health. 2020; 10(1): 107-111. doi:10.2991/jegh.k.191028.001
11. Pradeepa, R., Mohan, V. Epidemiology of type 2 diabetes in India. Indian J Ophthalmol. 2021; 69(11): 2932-2938. doi:10.4103/ijo.IJO_1627_21
12. Schwartz, S. S., Epstein, S., Corkey, B. E., Grant, S. F., Gavin, J. R., 3rd, Aguilar, R. B. The Time Is Right for a New Classification System for Diabetes: Rationale and Implications of the β-Cell-Centric Classification Schema. Diabetes care. 2016; 39(2): 179-186. doi:10.2337/dc15-1585
13. Kuo, F. Y., Cheng, K. C., Li, Y., Cheng, J. T. Oral glucose tolerance test in diabetes, the old method revisited. World J Diabetes. 2021; 12(6): 786-793. doi:10.4239/wjd.v12.i6.786
14. Bancks, M. P., Chen, H. Type 2 Diabetes Subgroups, Risk for Complications, and Differential Effects Due to an Intensive Lifestyle Intervention. 2021; 44(5): 1203-1210. doi:10.2337/dc20-2372
15. Ahlqvist, E., Storm, P., Käräjämäki, A., Martinell, M., Dorkhan, M., Carlsson, A., et al., Novel subgroups of adult-onset diabetes and their association with outcomes: a data-driven cluster analysis of six variables. Lancet Diabetes Endocrinol. 2018; 6(5): 361-369. doi:10.1016/s2213-8587(18)30051-2
16. Dennis, J. M. Precision Medicine in Type 2 Diabetes: Using Individualized Prediction Models to Optimize Selection of Treatment. Diabetes. 2020; 69(10): 2075-2085. doi:10.2337/dbi20-0002
17. Strianese, O., Rizzo, F. Precision and Personalized Medicine: How Genomic Approach Improves the Management of Cardiovascular and Neurodegenerative Disease. 2020; 11(7). doi:10.3390/genes11070747
18. Udler, M. S. Type 2 Diabetes: Multiple Genes, Multiple Diseases. Curr Diab Rep. 2019; 19(8): 55. doi:10.1007/s11892-019-1169-7
19. Merino, J., Florez, J. C. Precision medicine in diabetes: an opportunity for clinical translation. Ann N Y Acad Sci. 2018; 1411(1): 140-152. doi:10.1111/nyas.13588

20. Alkorta-Aranburu, G., Carmody, D., Cheng, Y. W., Nelakuditi, V., Ma, L., Dickens, J. T., et al., Phenotypic heterogeneity in monogenic diabetes: the clinical and diagnostic utility of a gene panel-based next-generation sequencing approach. Mol Genet Metab. 2014; 113(4): 315-320. doi:10.1016/j.ymgme.2014.09.007
21. Claussnitzer, M., Cho, J. H., Collins, R., Cox, N. J., Dermitzakis, E. T., Hurles, M. E., et al., A brief history of human disease genetics. Nature. 2020; 577(7789): 179-189. doi:10.1038/s41586-019-1879-7
22. Tainsky, M. A. Genomic and proteomic biomarkers for cancer: a multitude of opportunities. Biochim Biophys Acta. 2009; 1796(2): 176-193. doi:10.1016/j.bbcan.2009.04.004
23. DeForest, N., Majithia, A. R. Genetics of Type 2 Diabetes: Implications from Large-Scale Studies. Curr Diab Rep. 2022; 22(5): 227-235. doi:10.1007/s11892-022-01462-3
24. Kim, D. S., Jackson, A. U., Li, Y. K., Stringham, H. M., Kuusisto, J., Kangas, A. J., et al., Novel association of TM6SF2 rs58542926 genotype with increased serum tyrosine levels and decreased apoB-100 particles in Finns. J Lipid Res. 2017; 58(7): 1471-1481. doi:10.1194/jlr.P076034
25. Goodarzi, M. O., Rotter, J. I. Genetics Insights in the Relationship Between Type 2 Diabetes and Coronary Heart Disease. Circ Res. 2020; 126(11): 1526-1548. doi:10.1161/circresaha.119.316065
26. Udler, M. S., Kim, J., von Grotthuss, M., Bonàs-Guarch, S., Cole, J. B. Type 2 diabetes genetic loci informed by multi-trait associations point to disease mechanisms and subtypes: A soft clustering analysis. 2018; 15(9): e1002654. doi:10.1371/journal.pmed.1002654
27. Kettunen, J. L. T., Tuomi, T. Human Physiology of Genetic Defects Causing Beta-cell Dysfunction. Journal of Molecular Biology. 2020; 432(5): 1579-1598. doi:https://doi.org/10.1016/j.jmb.2019.12.038
28. Durrani, I. A., Bhatti, A. The prognostic outcome of 'type 2 diabetes mellitus and breast cancer' association pivots on hypoxia-hyperglycemia axis. 2021; 21(1): 351. doi:10.1186/s12935-021-02040-5
29. Caulfield, J. I., Aizenbud, L., Perdigoto, A. L., Meffre, E., Jilaveanu, L., Michalek, D. A., et al., Germline genetic variants are associated with development of insulin-dependent diabetes in cancer patients treated with immune checkpoint inhibitors. 2023; 11(3). doi:10.1136/jitc-2022-006570
30. Ginsberg, H. N., MacCallum, P. R. The obesity, metabolic syndrome, and type 2 diabetes mellitus pandemic: Part I. Increased cardiovascular disease risk and the importance of atherogenic dyslipidemia in persons with the metabolic syndrome and type 2 diabetes mellitus. J Cardiometab Syndr. 2009; 4(2): 113-119. doi:10.1111/j.1559-4572.2008.00044.x
31. Nasri, H., Rafieian-Kopaei, M. Metformin: Current knowledge. J Res Med Sci. 2014; 19(7): 658-664.
32. Sola, D., Rossi, L., Schianca, G. P., Maffioli, P., Bigliocca, M., Mella, R., et al., Sulfonylureas and their use in clinical practice. Arch Med Sci. 2015; 11(4): 840-848. doi:10.5114/aoms.2015.53304
33. Quinn, C. E., Hamilton, P. K., Lockhart, C. J., McVeigh, G. E. Thiazolidinediones: effects on insulin resistance and the cardiovascular system. Br J Pharmacol. 2008; 153(4): 636-645. doi:10.1038/sj.bjp.0707452
34. van de Laar, F. A. Alpha-glucosidase inhibitors in the early treatment of type 2 diabetes. Vasc Health Risk Manag. 2008; 4(6): 1189-1195. doi:10.2147/vhrm.s3119
35. Nauck, M. A., Vilsbøll, T., Gallwitz, B., Garber, A., Madsbad, S. Incretin-based therapies: viewpoints on the way to consensus. Diabetes Care. 2009; 32 Suppl 2(Suppl 2): S223-231. doi:10.2337/dc09-S315
36. Unger, J. R., Parkin, C. G. Glucagon-like peptide-1 (GLP-1) receptor agonists: Differentiating the new medications. Diabetes Ther. 2011; 2(1): 29-39. doi:10.1007/s13300-010-0013-5
37. Bays, H. Sodium Glucose Co-transporter Type 2 (SGLT2) Inhibitors: Targeting the Kidney to Improve Glycemic Control in Diabetes Mellitus. Diabetes Ther. 2013; 4(2): 195-220. doi:10.1007/s13300-013-0042-y
38. Kang, S. M., Park, J. H. Pleiotropic Benefits of DPP-4 Inhibitors Beyond Glycemic Control. Clin Med Insights Endocrinol Diabetes. 2021; 14: 11795514211051698. doi:10.1177/11795514211051698
39. Bolli, G. B., Owens, D. R. Lixisenatide, a novel GLP-1 receptor agonist: efficacy, safety and clinical implications for type 2 diabetes mellitus. Diabetes Obes Metab. 2014; 16(7): 588-601. doi:10.1111/dom.12253
40. Negoro, N., Sasaki, S., Mikami, S., Ito, M., Suzuki, M., Tsujihata, Y., et al., Discovery of TAK-875: A Potent, Selective, and Orally Bioavailable GPR40 Agonist. ACS Med Chem Lett. 2010; 1(6): 290-294. doi:10.1021/ml1000855
41. Gantner, B. N., LaFond, K. M., Bonini, M. G. Nitric oxide in cellular adaptation and disease. Redox Biol. 2020; 34: 101550. doi:10.1016/j.redox.2020.101550
42. Zhao, Y., Jiang, Z., Zhao, T., Ye, M., Hu, C., Zhou, H., et al., Targeting insulin resistance in type 2 diabetes via immune modulation of cord blood-derived multipotent stem cells (CB-SCs) in stem cell educator therapy: phase I/II clinical trial. BMC Med. 2013; 11: 160. doi:10.1186/1741-7015-11-160
43. Shrivastav, D., Dabla, P. K., Sharma, J., Viswas, A., Mir, R. Insights on antioxidant therapeutic strategies in type 2 diabetes mellitus: A narrative review of randomized control trials. World J Diabetes. 2023; 14(6): 919-929. doi:10.4239/wjd.v14.i6.919
44. Buijsse, B., Simmons, R. K., Griffin, S. J., Schulze, M. B. Risk assessment tools for identifying individuals at risk of developing type 2 diabetes. Epidemiol Rev. 2011; 33(1): 46-62. doi:10.1093/epirev/mxq019
45. Dong, W., Tse, T. Y. E. Non-laboratory-based risk assessment model for case detection of diabetes mellitus and pre-diabetes in primary care. 2022; 13(8): 1374-1386. doi:10.1111/jdi.13790
46. Wu, Y., Ding, Y., Tanaka, Y., Zhang, W. Risk factors contributing to type 2 diabetes and recent advances in the treatment and prevention. Int J Med Sci. 2014; 11(11): 1185-1200. doi:10.7150/ijms.10001
47. Venkatachalapathy, P., Padhilahouse, S. Pharmacogenomics and Personalized Medicine in Type 2 Diabetes Mellitus: Potential Implications for Clinical Practice. 2021; 14: 1441-1455. doi:10.2147/pgpm.s329787
48. Herder, C., Kowall, B., Tabak, A. G., Rathmann, W. The potential of novel biomarkers to improve risk prediction of type 2 diabetes. Diabetologia. 2014; 57(1): 16-29. doi:10.1007/s00125-013-3061-3