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Diabetes Mellitus in the 21st century: Challenges, Breakthroughs, and Unmet Needs

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Abstract

With a startling global increase in prevalence, diabetes mellitus has become one of the most significant health issues of the twenty-first century. According to current estimates, more than 530 million adults have diabetes; if current trends continue, that number is expected to rise to over 780 million by 2045. Type 1 diabetes and gestational diabetes also make a substantial contribution to the worldwide burden of diabetes, although type 2 diabetes is still the most common type and is mostly caused by lifestyle factors like obesity, poor diet, and sedentary behavior. Diabetes is a leading cause of disability and premature mortality, contributing to blindness,

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amputations, cardiovascular disease, and kidney failure in addition to hyperglycemia. New pharmacological treatments (GLP-1 receptor agonists, dual incretin therapies, and SGLT2 inhibitors), technological advancements (continuous glucose monitoring, hybrid closed-loop systems), and developing regenerative medicine techniques (stem cell therapy, gene editing) have all changed the face of diabetes care. However, particularly in low- and middle-income nations, there are still significant gaps in patient-centered care, early detection, affordability, and access to insulin and contemporary treatments. In order to achieve better management and, eventually, a cure, future directions require a comprehensive strategy that incorporates translational research, global equity initiatives, preventive public health measures, and precision medicine.

Keywords: Gestational diabetes, Diabetes mellitus, SGLT2 inhibitors, GLP-1 receptor agonists, Pharmacological advancements, Continuous glucose monitoring, Regenerative medicine.

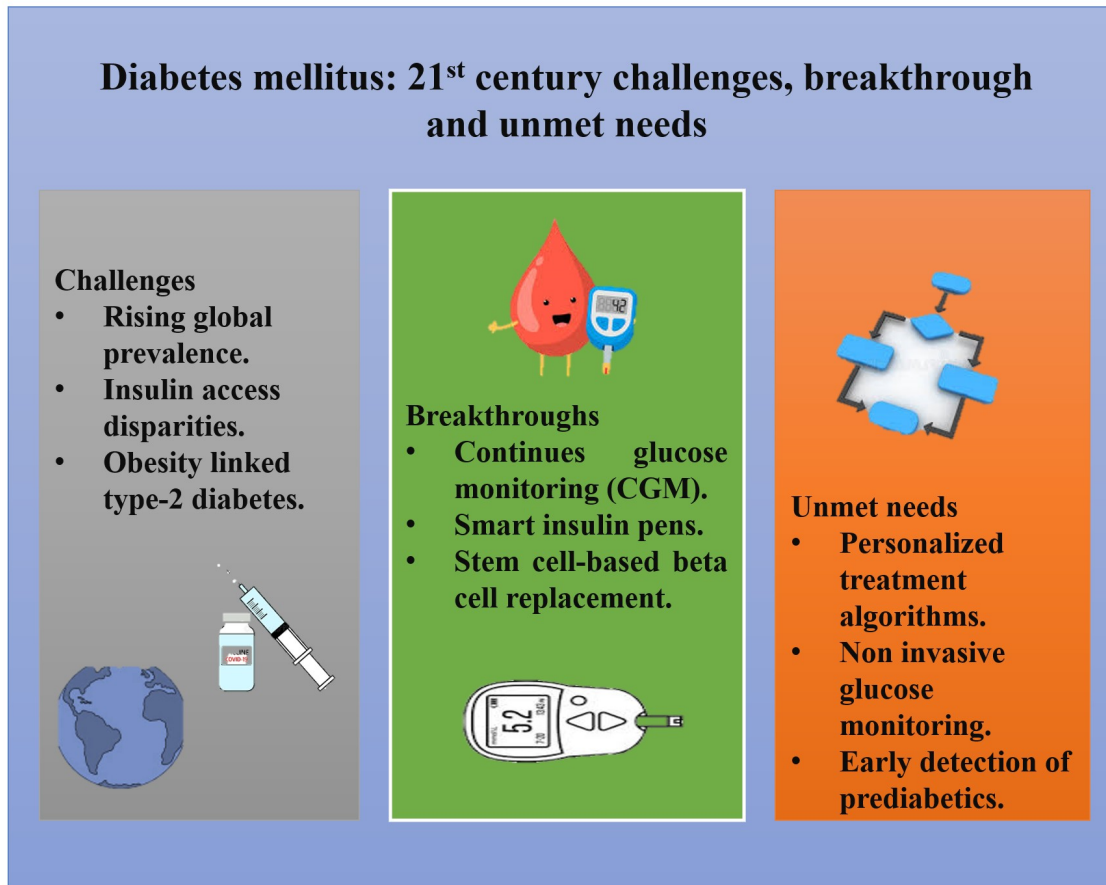


Figure 1: The Abstract diagram summarizes rising global prevalence, insulin access disparities, and obesity-linked type 2 diabetes. It also illustrates advances in glucose monitoring and insulin delivery, alongside the need for personalized and early care strategies.

1. Introduction

Diabetes mellitus (DM) is among the diseases that have been characterized as defining the 21st century and the burden of the disease is increasing at an unbelievable rate at any part of the globe [1]. The International Diabetes Federation (IDF) states that over 530 million adults had diabetes in 2021 and the number is expected to go beyond 780 million in 2045 without any changes in current trends [2]. Most cases are type 2 diabetes which is mainly contributed by lifestyle factors including sedentary lifestyle, improper dieting practices, obesity and the rapid urbanization [3].

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Nevertheless, type 1 diabetes, which is less prevalent, is still an issue, especially in younger populations. In contrast to previous decades, when diabetes was regarded as a symptom of wealth, nowadays over three-quarters of patients with diabetes reside in low and middle-income countries (LMICs) [4]. The underlying cause of this epidemiological change is the rate of economic development, unhealthy food system globalization and poor healthcare infrastructures in such areas [5]. The reality weight of diabetes is more than just hyperglycemia but rather in the weight of the complication's cardiovascular disease, kidney failure, blindness, and lower-limb amputations, which put diabetes as one of the top causes of disability, diminished quality of life, and premature mortality globally. The significance of this social health issue is supported by epidemiological data. An iconic combined report in *The Lancet* showed that the international occurrence of diabetes in adults has increased greater than twofold since 1980, increasing to 4.7% in 1980 to almost 10% during the past years [6]. This growth is however disproportionate with high-income countries having a heavy burden whilst regions like South Asia, Middle East as well as sub-Saharan Africa are witnessing the highest growth [7]. Some of the factors include ageing of the population, the increased prevalence of obesity, and the growing trend of sedentary living and particularly in urban areas where people are likely to consume fast-food and engage in fewer physical activities [8].

As an alarming development, diabetes is currently life. The other epidemiological issue is the prevalence of the undiagnosed diabetes; almost 50 percent of the impacted people do not know they have it, especially in the LMICs where screening and diagnostic services are scarce being diagnosed at earlier ages and this not only puts individuals at risk of prolonged periods of disease but also increases the risks of complications and healthcare spending throughout. Diabetes has been identified by the World Health Organization (WHO) as a direct health threat to global health targets due to its contribution to early death caused by non-communicable diseases (NCDs) [9]. Notably, the early treatment of diabetes is a medical and economic necessity: it has been demonstrated that the preventive measures, which include the promotion of healthy lifestyles, the introduction of early-detecting programs, and the reinforcement of the community-based care, could greatly lower the occurrence and severity of type 2 diabetes [10]. Furthermore,

the cost of diabetes in the economy is more than healthcare expenses to missed productivity, manpower loss, and developmental issues. Thus, a comprehensive approach to diabetes, involving policies, education, prevention, and equal access to treatment, is the key to reducing the effect of this disease and enhancing the quality of life of millions of people in the world [11].

2. Pathophysiology and Classification of Diabetes Mellitus

Diabetes mellitus encompasses a spectrum of disorders characterized by chronic hyperglycemia, resulting from defects in insulin secretion, insulin action, or both [12]. Understanding the underlying mechanisms is critical not only for accurate diagnosis but also for guiding treatment and predicting complications [13]. Traditionally, diabetes has been classified into type 1 diabetes (T1DM), type 2 diabetes (T2DM), and gestational diabetes mellitus (GDM), (**Figure 2**) but recent advances highlight additional subtypes and phenotypes that blur conventional boundaries [14].

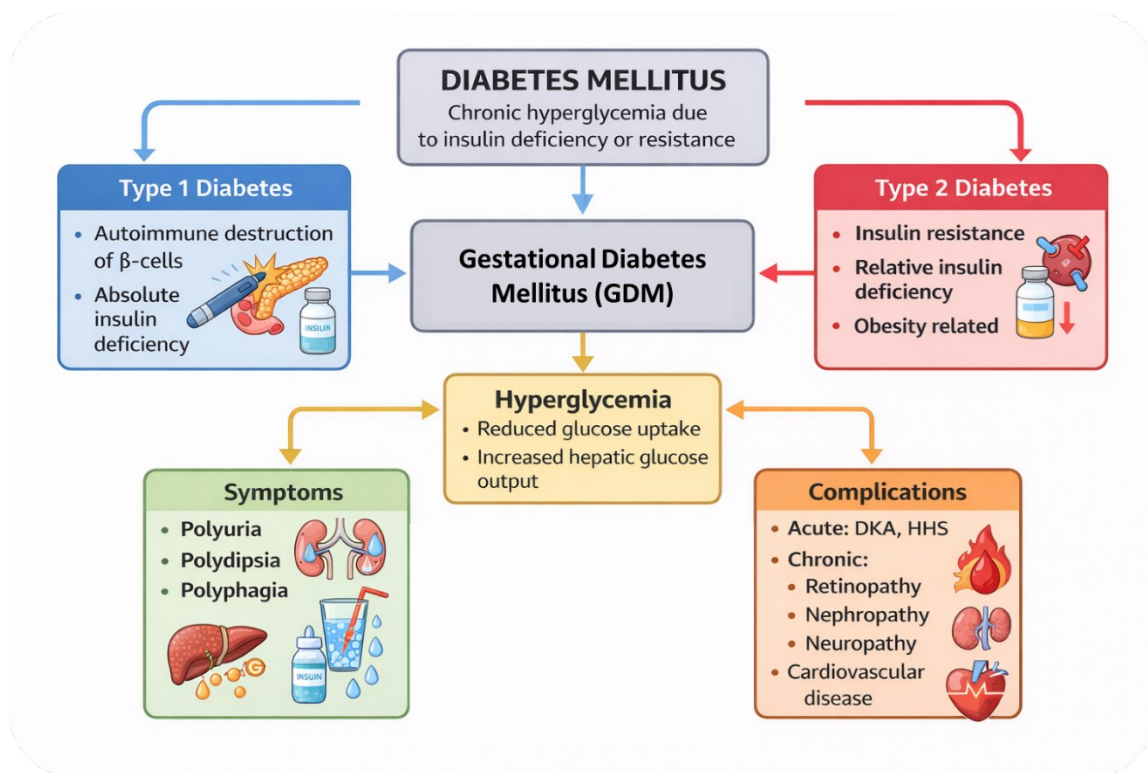


Figure 2: *Diagram illustrating the pathophysiology of Diabetes Mellitus and its major types. Type 1, Type 2, and gestational diabetes result from insulin deficiency or resistance. These defects lead to hyperglycemia with classical symptoms such as polyuria and polydipsia. Prolonged hyperglycemia causes acute and chronic complications affecting multiple organs.*

2.1 Type 1 Diabetes

Diabetes type 1 is mostly an autoimmune disease where the immune system develops some selective destruction of the insulin producing β -cells in the pancreatic islets [15]. The most common disease prediction and diagnostic biomarkers include islet cell antigens, including glutamic acid decarboxylase (GAD65), insulinoma-associated antigen-2 (IA-2), and zinc transporter 8 (ZnT8) in the production of autoantibodies [16]. Genetics: HLA class II separately variants in the human leukocyte antigen (HLA) region are also associated with almost half of the genetic risk [17]. The susceptibility is further modified by non-HLA loci containing genes (INS, PTPN22, and CTLA4). Nevertheless, genetic risk factors cannot be considered as the sole reason behind increased incidence, which means that environmental factors play a significant role [18]. A number of environmental factors have been identified in the cause or worsening of β -cell autoimmunity [19]. Active research is conducted on viral infections (e.g., enteroviruses), the diet of early life, changes in microbiome, and vitamin D deficiency. It is important to note that the growing proportion of T1DM among populations with low genetic predisposition in the past indicates the dynamic interaction of genes and environmental factors [20].

2.2 Type 2 Diabetes

In diabetic patients, 2 diabetes is an insulin resistance (IR) in the peripheral tissues (muscle, liver and adipose tissue) [21]. The cells do not react to insulin properly in IR leading to the inability of these cells to take up glucose, high levels of glucose production in the liver, and lipid abnormality [22]. Although insulin resistance triggers the pathophysiology of T2DM, the onset of overt diabetes is caused by the inability of β -cells to counterbalance the deficit of insulin secretion (Zhang et al., 2004) [23]. Glucotoxicity, lipotoxicity and mitochondrial stress and low grade inflammation

may result in functional deterioration of b-cells. Genetic mutations in the genes controlling insulin secretion (e.g. TCF7L2, KCNJ11, SLC30A8) are also considered to be in the b-cell predisposition [24]. The most evident risk factor of T2DM is obesity, in particular, central adiposity, which is caused by the consumption of high-calorie foods, sedentary living, and urbanization [25]. Aging also makes one more vulnerable, as does exposure to endocrine-disrupting chemicals, psychosocial stress and low quality of sleep. Significantly, T2DM is a condition that is disproportionately prevalent among the population facing a rapid socioeconomic transition, such as South Asia, where people become diabetic at lower body mass indices compared to Western members of the population [26].

2.3 Gestational Diabetes Mellitus (GDM): Gestational diabetes refers to glucose intolerance first recognized during pregnancy. It arises when hormonal changes induce insulin resistance that exceeds maternal β -cell compensatory capacity [27]. Key risk factors include maternal obesity, advanced maternal age, and family history of diabetes [28]. GDM poses dual risks: short-term complications such as preeclampsia, macrosomia, and neonatal hypoglycemia, and long-term risks including maternal progression to T2DM and increased risk of obesity and diabetes in offspring. Screening strategies vary globally, but universal glucose testing in the second trimester is widely recommended [29].

2.4 Emerging Subtypes and Phenotypes

While the tripartite classification of diabetes remains clinically useful, it oversimplifies a highly heterogeneous disease spectrum. Recent efforts have identified distinct phenotypic clusters that may guide personalized care [30]. Latent Autoimmune Diabetes in Adults (LADA): A slowly progressive form of autoimmune diabetes that shares features of both T1DM and T2DM [31]. Patients are often misclassified as T2DM initially but eventually require insulin therapy, Maturity-Onset Diabetes of the Young (MODY): A monogenic form of diabetes caused by mutations in genes regulating β -cell function (e.g., HNF1A, GCK) [32]. Unlike T1DM and T2DM, MODY is inherited in an autosomal dominant fashion and often responds to sulfonylureas rather than insulin, Ketosis-Prone Diabetes: Observed mainly in African and Asian populations,

characterized by acute presentation with diabetic ketoacidosis but without permanent β -cell failure, Severe Phenotype Clustering in T2D Recent Scandinavian studies have proposed stratification of T2DM into clusters based on age, BMI, insulin resistance, and β -cell function [33]. These include subgroups such as severe insulin-deficient diabetes (SIDD), severe insulin-resistant diabetes (SIRD), and mild obesity-related diabetes, each associated with different complication risks [34].

3. Current Challenges in Diabetes Management

Despite advances in understanding and treating diabetes mellitus, significant barriers persist in effective prevention, diagnosis, and management [35]. The complexity of diabetes lies not only in its biological heterogeneity but also in the socioeconomic, cultural, and infrastructural challenges that influence patient outcomes [36]. In the 21st century, diabetes has become both a clinical and a systemic issue, requiring multifaceted strategies that extend beyond pharmacological interventions [37].

3.1 Rising Global Prevalence

3.1.1 Lifestyle Changes and Urbanization

The rapid rise in diabetes prevalence is closely linked to global lifestyle shifts. Urbanization has promoted sedentary behaviors, processed food consumption, and high-calorie diets, leading to widespread obesity and metabolic dysfunction [38]. Traditional diets rich in whole grains, fruits, and vegetables are increasingly replaced with energy-dense, nutrient-poor alternatives. Combined with reduced physical activity due to mechanization and digitalization, these factors have created environments conducive to diabetes development [39].

3.1.2 Childhood and Adolescent Diabetes

Another alarming trend is the increasing diagnosis of diabetes in younger populations. Type 1 diabetes continues to rise among children, but more concerning is the emergence of type 2

diabetes in adolescents, historically considered an adult-onset condition [40]. Early-onset T2DM is associated with rapid disease progression, poor glycemic control, and heightened risk of complications at a young age, placing an unprecedented burden on healthcare systems. Childhood obesity, genetic predisposition, and unhealthy lifestyle patterns are central drivers of this trend [41].

3.1.3 Socioeconomic and Ethnic Disparities

prevalence and outcomes are not similar among populations. The South Asians, Hispanics, Native Americans, and Pacific Islanders, as ethnic groups, have a disproportionately high risk and may be threatened by lower BMI levels [42]. Socioeconomic status also has an impact on the outcomes of the disease-low-income groups are exposed to risk factors more, and they have less access to preventive and treatment means [43].

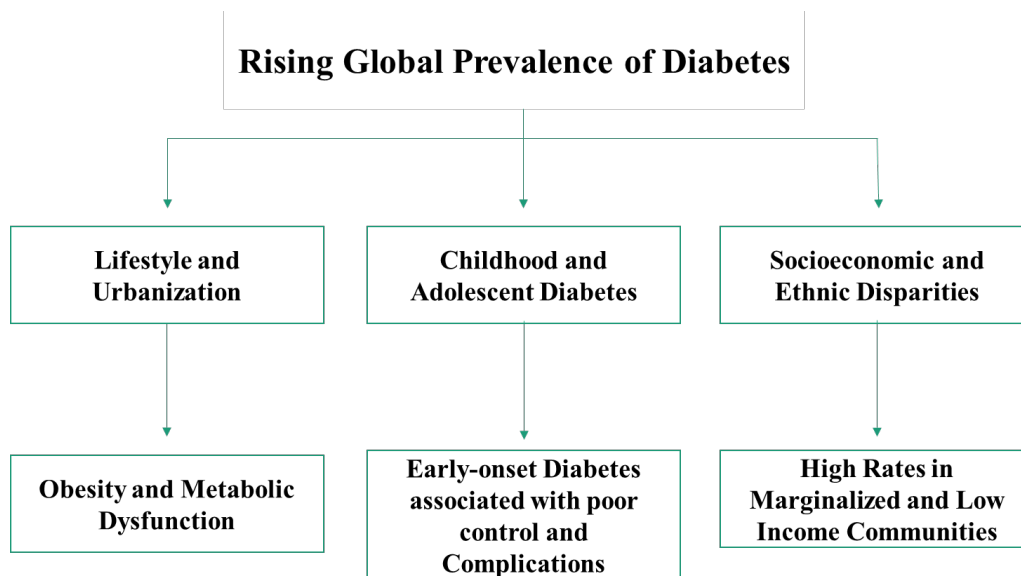


Figure 3: *Rising global prevalence of diabetes highlighting key contributing factors. Lifestyle changes, urbanization, and childhood-onset diabetes increase metabolic risk and early complications. Socioeconomic and ethnic disparities lead to higher diabetes burden in marginalized and low-income populations.*

3.2 Diagnostic and Monitoring Limitations

Diabetes often remains undiagnosed until complications develop, particularly in low-resource settings. Estimates suggest that up to 50% of individuals with diabetes worldwide are unaware of their condition [44]. The asymptomatic nature of early hyperglycemia and limited awareness contribute to delayed diagnosis, which in turn leads to preventable morbidity and mortality [45]. The use of advanced diagnostic tools such as glycated hemoglobin (HbA1c) and continuous glucose monitoring (CGM) is unevenly distributed across the globe [46]. While HbA1c testing is the gold standard for long-term glycemic assessment, its availability and affordability remain limited in many LMICs. Similarly, CGM devices, though transformative for real-time glucose monitoring, are prohibitively expensive and concentrated in high-income countries [47]. Another barrier lies in the lack of standardized diagnostic thresholds across regions. Different organizations, including the World Health Organization (WHO) and the American Diabetes Association (ADA), employ slightly different cutoffs for fasting glucose, HbA1c, and oral glucose tolerance tests [48]. These variations complicate global surveillance efforts and may hinder comparability of epidemiological data, affecting policymaking and intervention strategies [49].

3.3 Complications and Comorbidities

3.3.1. Microvascular Complications: Chronic hyperglycemia damages small blood vessels, leading to classic microvascular complications such as retinopathy, nephropathy, and neuropathy. These complications contribute significantly to disability and reduced quality of life [50]. Diabetic retinopathy remains a leading cause of blindness in working-age adults, while diabetic nephropathy is a major driver of end-stage renal disease requiring dialysis or transplantation. Peripheral neuropathy not only impairs quality of life but also predisposes to foot ulcers and amputations, representing a major cause of morbidity worldwide [51].

3.3.2. Macrovascular Complications: Macrovascular disease, including cardiovascular disease (CVD), stroke, and peripheral arterial disease (PAD), is the leading cause of death among people with diabetes [52].

Patients with diabetes face a two- to four-fold increased risk of cardiovascular events compared to non-diabetic populations. Importantly, many individuals already have established vascular disease by the time of diabetes diagnosis, underscoring the need for earlier intervention and aggressive risk factor management [53].

3.3.3. Coexistence with Obesity, Metabolic Syndrome, and NASH: The overlap between diabetes, obesity, and metabolic syndrome complicates management. Non-alcoholic fatty liver disease (NAFLD) and its progressive form, non-alcoholic steatohepatitis (NASH), are increasingly recognized as comorbidities of T2DM [54]. These conditions not only exacerbate insulin resistance but also increase the risk of cirrhosis and hepatocellular carcinoma. The clustering of metabolic disorders creates a syndemic that requires integrated management approaches rather than siloed treatment [55].

3.4 Access and Affordability Issues

Insulin, discovered over a century ago, remains inaccessible to millions of patients due to high costs, limited supply chains, and monopolized market dynamics [56]. The World Health Organization estimates that one in two people who require insulin globally cannot reliably access it. Pricing disparities are particularly stark in LMICs, where out-of-pocket expenses can consume a substantial portion of household income. This inequity results in preventable complications and premature deaths [57]. Even when insulin and medications are available, healthcare infrastructure may not support optimal diabetes management [58]. Many regions lack adequately trained healthcare professionals, structured diabetes education programs, and reliable supply chains for medications and diagnostic tools. Rural and remote communities are especially disadvantaged, often relying on primary care providers with limited specialized training [59]. The divide between high- and low-income countries extends beyond medication access. In developed nations, patients may benefit from advanced technologies such as CGM, insulin pumps, and integrated digital health platforms [60]. In contrast, patients in resource-limited settings often struggle to access even basic glucose meters and test strips. This global inequity

perpetuates disparities in disease outcomes and contributes to the widening gap in life expectancy and quality of life between regions (Table 1) [61].

Table 1: Global Access and Affordability Challenges in Diabetes Care

Sr. No.	Issue	Key Challenges	Impact on Patients	References
1.	Insulin Availability and Pricing	<ul style="list-style-type: none"> • High market prices and monopolized supply chains • Inconsistent availability, especially in LMICs • Out-of-pocket costs consuming household income 	<ul style="list-style-type: none"> • 1 in 2 patients globally cannot reliably access insulin (WHO) • Increased risk of preventable complications and premature deaths 	[62]
2.	Healthcare Infrastructure Gaps	<ul style="list-style-type: none"> • Limited trained healthcare professionals • Lack of structured diabetes education programs • Weak supply chains for medicines and diagnostic tools 	<ul style="list-style-type: none"> • Suboptimal diabetes management • Rural/remote populations especially disadvantaged • Poor adherence to treatment and monitoring 	[63]
3.	Inequality Between Developed and Developing	<ul style="list-style-type: none"> • Advanced technologies (CGM, insulin pumps, digital health) concentrated in high-income countries 	<ul style="list-style-type: none"> • Widening disparities in outcomes and life expectancy • Reduced quality of life in resource-limited 	[64]

	Nations	• Limited access to even basic glucose meters and test strips in LMICs	regions	
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4. Breakthroughs in Diabetes Research and Management

The past two decades have witnessed remarkable progress in diabetes research and care. These advances span across diagnostics, pharmacology, medical technology, lifestyle interventions, and regenerative medicine [65]. Collectively, they reflect a shift from one-size-fits-all strategies toward precision medicine approaches that tailor interventions to the needs of individual patients. The following subsections highlight some of the most significant breakthroughs shaping the future of diabetes management in the 21st century [66].

4.1 Advances in Diagnostics: Artificial intelligence (AI) and machine learning (ML) algorithms are being integrated into diabetes risk prediction and early detection [67]. These systems analyze large datasets including electronic health records, laboratory values, genetic information, and even retinal images to identify individuals at high risk before clinical symptoms emerge. AI-driven predictive models have shown promise in stratifying populations, enabling early interventions and reducing the risk of complications [68]. For example, AI-enhanced retinal imaging has demonstrated utility in screening for diabetic retinopathy, improving diagnostic efficiency in resource-limited settings. Beyond traditional measures like fasting glucose and HbA1c, researchers are exploring novel biomarkers for early disease detection and progression monitoring [69]. Circulating microRNAs, inflammatory cytokines, and metabolomic signatures are under investigation as predictors of β -cell decline and insulin resistance. In addition, genetic testing is increasingly used to identify monogenic diabetes forms such as MODY, guiding specific therapy choices. These advances support a move toward more personalized diagnostic pathways [70].

4.2 Pharmacological Innovations

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) represent a major advance in diabetes pharmacotherapy [71]. These agents not only improve glycemic control but also promote weight loss and confer cardiovascular protection. More recently, dual incretin therapies such as tirzepatide, which targets both GLP-1 and glucose-dependent insulinotropic polypeptide (GIP) receptors, have demonstrated superior efficacy in lowering blood glucose and body weight compared to existing drugs [72]. These breakthroughs are redefining treatment goals by addressing both metabolic control and cardiometabolic risk, Sodium-glucose cotransporter-2 (SGLT2) inhibitors, originally developed as glucose-lowering drugs, have shown unexpected benefits in reducing cardiovascular events and slowing chronic kidney disease progression [73]. Drugs such as empagliflozin and dapagliflozin are now considered standard therapy not only for diabetes but also for heart failure and chronic kidney disease, regardless of diabetic status. This paradigm shift highlights the pleiotropic benefits of targeting renal glucose reabsorption, In T1DM, immunotherapeutic approaches are being explored to preserve residual β -cell function [74]. Monoclonal antibodies targeting immune pathways, such as teplizumab (anti-CD3 antibody), have shown the ability to delay progression to clinical diabetes in high-risk individuals [75]. These therapies represent a significant step toward disease-modifying treatment, although challenges in long-term efficacy and safety remain, Pharmacogenomics is beginning to influence drug selection in diabetes care [76]. Variations in genes such as TCF7L2 influence response to sulfonylureas, while polymorphisms in SLC22A1 impact metformin efficacy. Incorporating genetic profiles into treatment algorithms may optimize drug choice, minimize side effects, and improve adherence, paving the way for individualized therapy (**Table 2**) [77].

Table 2: Emerging Pharmacological Innovations in Diabetes Management

Sr. No.	Innovation	Key Features	Clinical Benefits	Limitations/Challenges	References
1.	GLP-1 Receptor Agonists and	• GLP-1 RAs improve glycemic control, weight loss, and	• Enhanced glucose lowering • Significant	• High cost • Injectable administration	[78]

	Dual Incretin Therapies	<p>cardiovascular outcomes</p> <ul style="list-style-type: none"> • Dual incretin (GLP-1 + GIP) therapies (e.g., tirzepatide) show superior efficacy 	<p>weight reduction</p> <ul style="list-style-type: none"> • Cardiovascular protection 	<ul style="list-style-type: none"> • Gastrointestinal side effects 	
2.	SGLT2 Inhibitors	<ul style="list-style-type: none"> • Block renal glucose reabsorption • Agents: empagliflozin, dapagliflozin 	<ul style="list-style-type: none"> • Glycemic control • Cardiorenal benefits (reduce CV events, slow CKD) • Effective in HF and CKD regardless of diabetes 	<ul style="list-style-type: none"> • Risk of genital infections • Not suitable for severe renal impairment 	[79]
3.	Immunotherapy for Type 1 Diabetes	<ul style="list-style-type: none"> • Monoclonal antibodies (e.g., teplizumab, anti-CD3) • Aim to preserve residual β-cell function 	<ul style="list-style-type: none"> • Delay onset of clinical T1DM in high-risk individuals • Potential disease-modifying effect 	<ul style="list-style-type: none"> • Limited long-term efficacy data • Safety concerns (immunosuppression) • High treatment cost 	[80]
4.	Personalized Medicine (Pharmacogenomics)	<ul style="list-style-type: none"> • Genetic variants guide drug response • TCF7L2: sulfonylurea response 	<ul style="list-style-type: none"> • Optimized drug selection • Minimized side effects 	<ul style="list-style-type: none"> • Requires genetic testing infrastructure • Limited routine 	[81]

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		• SLC22A1: metformin efficacy	• Improved adherence	clinical application currently	
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4.3 Technological Breakthroughs

CGM systems have revolutionized diabetes management by providing real-time glucose data and trends. These devices empower patients to make informed decisions about insulin dosing, diet, and exercise while reducing hypoglycemia risk [82]. Integration of CGM with digital platforms allows remote monitoring and personalized feedback, improving engagement and outcomes. Advancements in insulin delivery include modern pumps and hybrid closed-loop (HCL) systems, often referred to as “artificial pancreas” technologies [83]. These systems combine CGM with automated insulin delivery algorithms, reducing the burden of constant manual adjustment. Recent iterations have demonstrated improved time-in-range and reduced hypoglycemia, representing a major quality-of-life improvement for people with T1DM. Digital health solutions, including smartphone applications, wearable devices, and telemedicine platforms, are increasingly integrated into diabetes care [84]. These tools facilitate self-monitoring, lifestyle tracking, medication reminders, and virtual consultations. The COVID-19 pandemic accelerated adoption of telehealth, making digital platforms indispensable for continuity of care, particularly in remote or underserved areas [85].

4.4 Lifestyle and Preventive Strategies

Dietary management remains a cornerstone of diabetes prevention and control. Advances in nutritional science emphasize precision nutrition, where dietary recommendations are tailored to individual metabolic profiles, genetic predispositions, and microbiome composition [86]. Low-carbohydrate, Mediterranean, and plant-based diets have shown benefits in glycemic control and cardiovascular risk reduction. Personalized dietary interventions,

informed by continuous monitoring and AI tools, are expected to further enhance effectiveness. Regular physical activity improves insulin sensitivity and aids in weight management [87]. Recent innovations include digital fitness platforms and wearable devices that track activity, provide feedback, and motivate adherence. Virtual coaching and AI-driven exercise programs are being explored as scalable interventions for diabetes prevention and management. Community-based interventions and national campaigns targeting obesity and diabetes prevention have gained traction [88]. Initiatives focusing on healthy school meals, taxation of sugar-sweetened beverages, and urban planning to encourage physical activity are increasingly recognized as effective population-level strategies. These preventive measures highlight the role of policy in shaping healthier environments [89].

4.5 Regenerative Medicine and Future Therapies

Stem cell research has opened new possibilities for restoring insulin production. Differentiation of pluripotent stem cells into insulin-producing β -like cells holds potential for curative therapies [90]. Early clinical trials have demonstrated partial restoration of C-peptide levels in patients with T1DM, signaling progress toward functional β -cell replacement. CRISPR-Cas9 technology offers opportunities to modify genes implicated in diabetes susceptibility and progression. Potential applications include correcting genetic mutations in MODY, enhancing β -cell survival, and modulating immune responses in T1DM [91]. Although still in experimental stages, gene editing represents one of the most exciting frontiers in diabetes research. Islet transplantation has long been investigated as a curative option for T1DM, but widespread adoption has been limited by immune rejection and donor shortages. Advances in encapsulation technologies aim to protect transplanted islets from immune attack while maintaining glucose responsiveness [92]. Progress in bioengineering, including development of immunoprotective biomaterials, is reinvigorating this field. Despite major advances in research, pharmacology, and technology, diabetes mellitus remains a global health crisis with substantial gaps in prevention, diagnosis, and management [93]. These unmet needs highlight the persistent disconnect between scientific progress and real-

world outcomes, particularly in low-resource settings. Addressing these gaps is essential to reduce the global burden of diabetes and improve quality of life for affected individuals [94].

5. Unmet needs in diabetes prevention

5.1 Early Detection and Prevention

A critical unmet need is the ability to detect diabetes at its earliest stages or, ideally, prevent its onset [95]. Many individuals remain undiagnosed until complications arise, reflecting both the silent nature of early hyperglycemia and limitations in current screening programs. Biomarkers, genetic testing, and AI-driven predictive models show promise, but their integration into routine care is limited [96]. In type 2 diabetes, preventive interventions such as weight reduction, dietary modification, and physical activity have proven efficacy. However, scaling these strategies to at-risk populations, particularly children and adolescents, remains a challenge [97]. Youth-onset type 2 diabetes progresses rapidly and increases lifetime morbidity, underscoring the need for early preventive policies targeting younger populations [98].

5.2 Patient-Centered Care

While technology and pharmacology have advanced, patient-centered approaches lag behind. Effective diabetes management requires sustained adherence to medications, lifestyle changes, and regular monitoring, yet many patients face barriers such as treatment fatigue, limited health literacy, and psychosocial stressors [99]. Diabetes distress and mental health **issues** are frequently overlooked in clinical practice. Depression, anxiety, and burnout are common among people living with diabetes, and these conditions negatively impact self-care behaviors and glycemic outcomes [100]. Integration of psychological support into routine diabetes care is therefore a major unmet need. Furthermore, healthcare delivery often emphasizes

short-term glycemic targets rather than long-term quality of life. Patient empowerment, shared decision-making, and culturally sensitive education are essential for improving engagement and adherence [101].

5.3 Affordability and Accessibility

Perhaps the most pressing unmet need is equitable access to essential therapies and technologies. Insulin, despite being discovered over a century ago, remains unaffordable or unavailable to millions of patients, especially in low- and middle-income countries [102]. The high cost of newer therapies such as GLP-1 receptor agonists and SGLT2 inhibitors further exacerbates inequality, leaving the most vulnerable populations behind. Access challenges extend beyond medications [103]. Diagnostic tests, CGM devices, insulin pumps, and digital health platforms are concentrated in wealthier nations, creating a stark divide in outcomes between developed and developing countries. Bridging this gap requires global collaboration, price regulation, and innovative delivery models to ensure that advances in diabetes care benefit all populations [104].

5.4 Research Gaps

Despite growing knowledge, several areas of diabetes research remain underexplored. Heterogeneity in Type 2 Diabetes: T2DM encompasses multiple subtypes with distinct pathogenic mechanisms. A deeper understanding of these phenotypes is needed to enable precision medicine approaches [105]. Long-Term Safety of New Therapies: While GLP-1 RAs, SGLT2 inhibitors, and immunotherapies show promising short- and medium-term outcomes, their long-term safety and effectiveness in diverse populations remain uncertain. Integration of Genomics into Clinical Practice: Although pharmacogenomics holds potential for tailoring drug therapy, its routine clinical application is limited by cost, infrastructure, and lack of standardized guidelines [106]. Global Implementation Science: Research has disproportionately focused on high-income countries, leaving knowledge gaps on how to implement effective interventions in resource-limited settings. Addressing these gaps is essential to ensure that innovations translate into meaningful outcomes worldwide [107].

6. Future Directions

The future of diabetes research and care in the twenty-first century depends on the successful translation of the scientific breakthrough into the solutions that will be accessible and equitable. Despite the increased rate of innovations, the practical implications of the innovations are dependent on the system level reforms based on affordability, preventive measures, and international reach. Precision medicine is set to be driven by artificial intelligence and large-scale data analytics through integration of electronic health records, genomic data, and real time monitoring so as to inform therapy choices, predict complications, and help take proactive measures especially in prediabetes. The international policies and the global collaborative structures as well as the increased access to the diagnostics, insulin derivations, and modern therapeutic options are the prerequisites to an equitable advancement of various geographically dispersed areas. Low-resource settings cannot have done without the expansion of telemedicine, empowerment of community health workers, and introduction of innovative financing mechanisms. Prevention should stay the focus, with the goals being obesity, inappropriate diet, and physical activity, which can be met by means of intervention in the public health policy, health initiatives in childhood, and online health technologies. Although modern therapeutic approaches are focused on the management of diseases, new modalities, including stem cell therapy, gene-editing technologies, immunotherapeutic agents, and islet transplantation, are promising to restore endogenous insulin secretion and advance towards functional cures.

Conclusion

The incidence of diabetes mellitus in the world is increasing at an astounding pace thus posing a daunting health issue in the twenty first century. The general burden of the disease still increases, although significant progress has been made in explaining its pathophysiology and in preparing some innovative therapeutic solutions. New pharmacotherapies such as sodium -glucose cotransporter-2, dual incretin, and glucagon-like peptide-1 receptor agonists have shown benefits in glycemic control, cardiovascular, and renal safeguarding. Nevertheless,

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they are costly and are not available to a large proportion of the population especially in low-resource environments. The same applies to all modern care modalities like insulin pumps and continuous glucose monitoring that have transformed care management in the wealthiest areas but are out of reach to a good number of the population. Even a vital treatment, as old as a hundred years and still used, like insulin, is not available or unaffordable to almost half the people who need it, a fact that illustrates an ongoing lack of contact between science and reality. The only way to bridge this gap is through the existence of solid policy frameworks, well-trained healthcare systems, reduced disparities in the world, and sustained biomedical innovation. Incorporation of pharmacogenomics, regenerative medicine, and precision medicine and preventative strategies will determine the future of diabetes care. It is important to provide equitable access in order to transform the scientific progress into practical global health outcomes.

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