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# Revolutionary Innovations in Diabetes Research: From Biomarkers to Genomic Medicine

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## Abstract

Diabetes mellitus is a chronic metabolic disease characterized by hyperglycemia resulting from inadequate insulin signaling. Current management relies on biomarkers such as hemoglobin A1c (HbA1c) to guide therapy, but emerging tools offer opportunities to transform care through more personalized approaches. Molecular biomarkers, including microRNAs, metabolites, and proteins, may enable better prediction of disease course and risk of complications in individuals. Genomic medicine leverages knowledge of genetic architecture to guide tailored prevention and treatment based on an individual's genomic profile. Stem cell research differentiates functional insulin-secreting cells for transplantation into patients as an alternative to exogenous insulin. Gene silencing techniques such as RNA interference can restore defective insulin production and secretion pathways by inhibiting dysregulated gene expression. Artificial intelligence applications automate glucose monitoring, insulin delivery, diagnostic screening for complications, and digital health coaching. Despite barriers to translation, these technologies have disruptive potential for predictive, preventive, precise, and participatory care paradigms in diabetes management. Continued research on molecular biomarkers, pharmacogenomics, stem cell therapies, gene editing, and artificial intelligence (AI) aims to improve patient outcomes through more personalized approaches tailored to the specific biological vulnerabilities underlying each individual's diabetes.

**Keywords**: Diabetes mellitus; Molecular biomarkers; Genomic medicine; pharmaceutical advances; gene therapy, Artificial intelligence

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## Introduction

Diabetes mellitus is a metabolic disorder characterized by chronic hyperglycemia resulting from defects in insulin secretion, action, or both. Diabetes has both monogenic and polygenic forms. Autoimmune destruction of pancreatic beta cells causes type 1 diabetes mellitus (T1D). Genetic risks such as HLA haplotypes and environmental triggers also contribute to the disease. Type 2 diabetes largely stems from obesity-related insulin resistance and progressive beta cell failure. Over 400 genetic loci identified via genome-wide studies confer susceptibility and interact with lifestyle factors (1).

In addition, mutations in genes such as GCK and HNF1A cause maturity-onset diabetes in the young. Gestational diabetes resulting from insulin deficiency related to pregnancy-induced insulin resistance. Gluco-toxicity and lipo-toxicity further worsen insulin signaling defects via mechanisms such as endoplasmic reticulum stress. Hyperglycemia induces tissue damage through oxidative stress and advanced glycation end-products (2). The global prevalence of diabetes has risen dramatically, affecting over 420 million adults, with projections of 700 million by 2045. The prevalence varies by region, with higher rates observed in North America, the Middle East, and Australia. Up to 95% of cases are type 2 diabetes, whereas type 1 diabetes affects approximately 1 in 300 people. The incidence of diabetes is increasing worldwide, likely driven by aging populations, urbanization, obesity, and sedentary lifestyles. Gestational diabetes affects approximately 1 in 7 births globally but reverses postpartum for most women (3).

Chronic hyperglycemia leads to microvascular damage affecting the eyes, nerves, and kidneys, as well as macrovascular atherosclerotic disease, causing heart attacks, strokes, and peripheral arterial disease. Diabetic retinopathy is the leading cause of blindness. Nephropathy results in renal failure. Peripheral neuropathy causes foot ulcers and limb amputations. Autonomic neuropathy involves gastrointestinal, genitourinary, and cardiovascular manifestations. Accelerated atherosclerosis increases the risk of myocardial infarction, cerebrovascular disease, and peripheral vascular disease (4).

Treatment involves lifestyle modifications, oral medications, and insulin therapy. Lifestyle changes such as diet, exercise, and weight loss are first-line. Oral agents include metformin, sulfonylureas, DPP4 inhibitors, and SGLT2 inhibitors. Insulin administration is required for type 1 and advanced type 2 DM. However, new ways of treating DM are emerging. Molecular biomarkers, genomics, stem cell therapy, and artificial intelligence enable more personalized and precise care. This review focused on advanced management of diabetes mellitus using emerging tools such as molecular biomarkers, genomics, stem cell therapy, and artificial intelligence to enable more personalized, precise care.

## Molecular biomarkers

Proper management of diabetes is critical for controlling blood sugar levels and preventing complications such as cardiovascular disease, neuropathy, nephropathy, and retinopathy (5). While biomarkers such as hemoglobin A1c (HbA1c), fasting blood glucose, and oral glucose tolerance tests are commonly used to diagnose, monitor, and guide the treatment of diabetes, molecular biomarkers are emerging as powerful new tools that can provide deeper insights into an individual's disease state (6).

Molecular biomarkers are biological molecules found in bodily fluids that indicate normal or abnormal biological processes. These can include metabolites, proteins, RNAs, or other molecules that reflect particular disease pathways. In diabetes research, molecular biomarkers can provide personalized information about an individual's diabetes progression, development of complications, and response to treatment. By





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measuring biomarkers, clinicians may be able to better predict diabetic complications, tailor therapies, and improve patient outcomes through precision medicine approaches. Molecular biomarkers also can enable earlier diagnosis of diabetes (7).

Several categories of molecular biomarkers are being investigated for diabetes monitoring and management. These include microRNAs (miRNAs), metabolites, inflammatory markers, and markers of vascular dysfunction, among others. MicroRNAs (miRNAs) in particular have shown promise as regulators of insulin production and secretion (8). However, substantial research is required to validate and standardize molecular biomarkers into clinically actionable tests.

## 1. Current biomarkers used for diabetes management

Hemoglobin A1c (HbA1c) has become one of the most important biomarkers used in the management of diabetes HbA1c provides insight into a patient's average blood glucose levels over the preceding 2-3 months. It is formed by the non-enzymatic glycosylation of hemoglobin in erythrocytes, reflecting the ambient glucose concentrations in the bloodstream.

By serving as a surrogate measure of chronic hyperglycemia, HbA1c allows physicians to monitor long-term glycemic control in their patients with diabetes. Furthermore, clinical recommendations use HbA1c levels to guide treatment plans and adjustments to optimize blood sugar control. Lower HbA1c levels are associated with reduced risk of developing diabetic complications (9). Therefore, regular HbA1c testing is critical for tracking treatment efficacy and adjusting medications to improve glycemic control in patients with diabetes.

Along with HbA1c, fasting blood glucose and the oral glucose tolerance test are essential for diagnosing and categorizing patients with diabetes or prediabetes. Fasting blood glucose is measured after at least 8 h of no caloric intake and indicates blood sugar levels at baseline. Meanwhile, the oral glucose tolerance test involves measuring blood glucose levels before and 2 h after consuming standard 75 g glucose drink, assessing the body's ability to normalize blood sugar. Both can identify impaired fasting glucose and impaired glucose tolerance, which are prediabetes states. In addition, meeting certain thresholds of fasting blood glucose or 2-h glucose during an oral glucose tolerance test are diagnostic criteria for diabetes according to the American Diabetes Association (10). Therefore, these tests are indispensable for screening and definitive diagnosis of abnormal glucose homeostasis.

The C-peptide is another important biomarker measured in diabetes care. Unlike insulin, C-peptide is not degraded as rapidly and therefore reflects endogenous insulin production. In patients with type 1 diabetes, C-peptide levels are very low or undetectable because of the destruction of insulin-producing beta cells. However, in type 2 diabetes, C-peptide levels can be normal or even elevated as insulin resistance increases the demand for functional beta cells.

Therefore, the assessment of C-peptide levels helps distinguish between type 1 and type 2 diabetes. It can also be used to monitor beta cell function decline over time in type 2 diabetes mellitus. Additionally, because exogenously administered insulin does not contain C-peptide, testing for it helps determine how much insulin production is endogenous versus administered (11).

## 2. Emerging molecular biomarkers for diabetes research

MicroRNAs (miRNAs) have recently emerged as novel molecular biomarkers for diabetes with the potential to transform disease monitoring and management. miRNA-204 has been proven to be specific to T1DM because it has not been detected at abnormal values in T2DM (type 2 diabetes mellitus). Moreover, lncRNAs such as LINC01410 are emerging as potential biomarkers and therapeutic targets in diabetic nephropathy.



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Further research on dysregulated lncRNAs may provide new insights into the molecular mechanisms and personalized medicine approaches for this complication (12). miRNAs are short noncoding RNA molecules that play a key role in regulating gene expression at the post-transcriptional level. They bind to complementary sequences in mRNA transcripts, leading to the inhibition of protein synthesis.

Several miRNAs have been implicated in pancreatic beta cell activities such as insulin biosynthesis, secretion, and apoptosis. Changes in the expression of specific miRNAs are associated with impaired insulin production and secretion in patients with diabetes. For example, miR-375 is highly enriched in pancreatic islets and directly targets genes involved in exocytosis pathways (13).

Overexpression of miR-375 suppresses glucose-stimulated insulin secretion. Multiple other miRNAs regulate pathways involved in beta cell proliferation and insulin synthesis. Therefore, circulating miRNA profiles could serve as sensitive biomarkers to detect declining beta cell function and personalize treatment well before the onset of overt diabetes. With further validation, miRNA-based biomarkers have exciting potential for earlier diagnosis, prognostication, and therapeutic decisions (14).

Intermediary products generated during metabolic processes, known as metabolites, have also emerged as promising molecular biomarkers of diabetes. Metabolomics analysis allows global assessment of small-molecule metabolite levels in biological samples. Altered metabolite patterns have been associated with insulin resistance, impaired insulin secretion, and diabetic complications.

For example, branched-chain and aromatic amino acids were found at higher levels in patients with diabetes and correlated with insulin resistance. Branched-chain and aromatic amino acids, as well as glycolytic intermediates such as methylglyoxal, have shown potential as predictive biomarkers for diabetes progression and complications. Lipid species such as ceramides and lysophosphatidylcholines are also dysregulated in diabetes and are associated with insulin resistance and cardiovascular outcomes. Elevated metabolites related to gluconeogenesis and lipids are also associated with diabetes progression. Some metabolites may even predict the later development of diabetes (15).

Proteins represent another abundant category of molecular biomarkers under investigation for diabetes monitoring and management. Many studies have identified associations between various protein levels and diabetes progression. For example, elevated levels of inflammatory markers such as interleukin-6 (IL-6), tumor necrosis factor alpha (TNF-α), and C-reactive protein (CRP) correlate with insulin resistance and pancreatic beta cell dysfunction. These pro-inflammatory proteins likely contribute to the pathogenesis of diabetes. Other protein biomarkers reflective of vascular dysfunction, such as endothelial lipase and P-selectin, are associated with the development of diabetes complications (16).

Testing for these protein biomarkers could detect early signs of diabetic nephropathy, retinopathy, neuropathy, and cardiovascular damage before symptom onset. This would allow earlier intervention with reno-protective and neuro-protective therapies. Although further validation is required, proteins hold promise as molecular biomarkers to guide personalized medicine and improve outcomes in patients with diabetes. Standardization of protein-based assays will help translate the most useful biomarkers from the research setting into clinical practice (17).

## 3. Advantages of molecular biomarkers

Molecular biomarkers for diabetes provide distinct advantages over traditional clinical biomarkers by offering more personalized data to optimize patient care and outcomes. One major advantage is the ability to tailor therapy using a precision medicine approach. By profiling biomarkers such as microRNAs,





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metabolites, and proteins, clinicians can gain insights into the specific pathological processes active in an individual patient. This allows treatment to be adapted on the basis of the molecular underpinnings of disease progression in that individual.

For example, certain microRNA signatures could indicate decreased therapeutic response to particular oral hypoglycemic medications. MiR-103/107 and let-7 miRNAs decrease response to metformin and sulfonylureas, respectively, in diabetes treatment. MiR-21, miR-29a/b, and miR-146a confer insulin resistance and alter the efficacy of insulin therapy. MiR-494, miR-126, and miR-33 affect lipid metabolism genes, affecting statin response. This would prompt consideration of alternate treatment regimens that are more likely to succeed.

Molecular biomarkers enable a personalized approach to care rather than a one-size-fits-all strategy. Earlier diagnosis and screening for diabetes is another advantage conferred by molecular biomarkers. Traditional screening relies on glucose tests that only detect diabetes once clinical thresholds are crossed. However, molecular biomarkers can serve as early indicators of the biological processes that lead to impaired insulin secretion and glucose homeostasis. For instance, abnormal levels of branched-chain amino acids and lipid metabolites can be detected well before the onset of overt diabetes. This creates opportunities for earlier intervention to prevent the progression to diabetes. In addition, molecular biomarkers could facilitate targeted screening in high-risk subgroups to diagnose diabetes in its earliest stages before complications develop (18).

Molecular biomarkers also provide unique insights into an individual's risk of diabetic complications and progression. This is a key advantage because currently available clinical biomarkers mainly track overall blood glucose control rather than the risk of specific complications. Biomarkers related to vascular dysfunction and inflammation could predict the development of cardiovascular, renal, and neurovascular complications. Patients could then receive intensified monitoring and therapy to mitigate the risk of complications based on their biomarker profiles. Finally, molecular biomarkers allow closer monitoring of an individual's response to therapies such as insulin, metformin, and other antidiabetic medications.

This helps to quickly identify when treatment regimens are failing to achieve goals, prompting medication adjustments. Specific biomarkers could even identify the likelihood of responding to particular drugs. Low miR-424 levels predict poor response to DPP4 inhibitors in patients with T2DM Increased miR-126 and miR-155 expression is associated with better glycemic response to thiazolidinedione. Consequently, molecular biomarkers facilitate more timely and evidence-based therapeutic decisions to provide optimal diabetes care (19).

## 4. Challenges/limitations in developing molecular biomarkers

Although molecular biomarkers have exciting potential, there are substantial challenges and barriers to be addressed before their clinical implementation. One major challenge is that the discovery and validation of novel biomarkers requires extensive research on large cohorts. Identifying and confirming the links between biomarkers and health outcomes is a long process. Molecular biomarkers must not only show associations with disease but also add value to existing clinical measures. Validation in diverse populations is also critical. Thousands of biomarker candidates may be assessed before being applied to viable clinical tests. Sufficient funding and resources are essential to support the rigorous research required (20).

Another current limitation is that few molecular biomarker tests for diabetes are standardized and readily available for clinical use. While research may uncover promising biomarkers, transitioning these into standardized assays and platforms for clinical laboratories represents a significant barrier.



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Lack of consistency in sample handling, processing protocols, reference ranges and reporting format limits test reliability. Considerable work is required to refine and optimize laboratory-developed tests, analytic techniques, and quality control procedures to operationalize molecular biomarkers. Adoption and reimbursement issues further hinder the integration of novel molecular biomarkers into clinical practice. Clinical uptake requires evidence of cost-effectiveness and benefit over conventional tests.

However, the costs of evaluating and validating new biomarkers are extensive. Without adequate insurance coverage and incentives, health care providers may resist ordering newer, specialized tests. Lack of reimbursement also represents a barrier to commercial development. Overcoming these financial and logistical barriers is critical for the clinical translation of molecular biomarkers (21).

## Genomic interventions

Genomic medicine represents an emerging field focused on the use of information about a person's genome to guide health decisions and personalized care. This involves characterizing an individual's unique inherited DNA sequence variations to predict disease susceptibility, improve diagnostic precision, tailor treatment approaches, and drive novel drug development. Rapid advances in DNA sequencing technology and expanded knowledge of genetic contributors to disease are catalyzing a shift toward genomic medicine. For complex heterogeneous disorders such as diabetes, insights into the underlying genomic architecture are unveiling new targeted intervention opportunities (22).

Diabetes mellitus encompasses metabolic disorders of glucose homeostasis in both monogenic and polygenic forms. While type 1 diabetes results from autoimmune destruction of insulin-producing beta cells and type 2 diabetes is largely driven by obesity-induced insulin resistance, genetic risk factors are thought to contribute significantly. Genome-wide association studies (GWAS) have uncovered >400 genetic loci associated with type 2 diabetes susceptibility. In addition, researchers have identified over 60 rare variants in genes implicated in neonatal and maturity-onset diabetes of the young. Knowledge of the genetic underpinnings of diabetes subtypes enables more accurate diagnosis, especially for atypical monogenic cases mistaken for type 1 or 2. Furthermore, characterizing an individual's genomic risk profile may allow early identification of high-risk individuals who would benefit most from targeted prevention efforts (23).

Beyond elucidating genetic risk, genomic medicine is paving the way for novel interventions such as pharmacogenomics, gene editing, and epigenetic therapy that target the molecular pathogenic mechanisms of diabetes. The personalization of treatment guided by an individual's genomic information promises to improve outcomes by maximizing efficacy and minimizing adverse effects. Although barriers to implementation exist, genomic medicine offers unprecedented opportunities for precision in predicting, preventing, classifying, and treating this chronic disease. Unlocking the genomic basis of diabetes will catalyze more proactive, effective, and customized management tailored to the specific biological vulnerabilities of each patient (24).

### 1. Understanding the genetic architecture of diabetes through genome-wide studies

#### *1.1. Genome-wide association studies*

GWAS has been instrumental in elucidating genes and genetic loci that confer susceptibility to type 2 diabetes (T2D). By genotyping hundreds of thousands to millions of single-nucleotide polymorphisms (SNPs) across the genome in large cohorts, GWAS have enabled the discovery of common genetic variants associated with modest effects on T2D risk (25). Over the past decade, expanded sample sizes and collaborative GWAS meta-analyses have facilitated the identification of more than 400 genetic loci linked to T2D, including variants in or near key genes





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regulating pancreatic beta cell function, such as TCF7L2, SLC30A8, and KCNJ11.

The identified SNPs collectively explain ~10-15% of T2D heritability, providing biological insights into disease pathogenesis (26). Many associated variants appear to affect insulin secretion rather than insulin sensitivity, highlighting the primary role of progressive beta cell failure in T2D development. Furthermore, GWAS-derived risk loci may have clinical utility for predicting future T2D, especially when incorporated into polygenic risk scores. Thus, GWAS has successfully revealed common variants contributing to the complex genetic architecture of T2D (27).

### *1.2. Sequencing studies reveal rarer variants with larger effects*

While GWAS have uncovered common T2D-associated variants, next-generation sequencing enables the characterization of rarer coding variants, which likely confer larger magnitude effects on disease risk. Targeted sequencing of candidate genes has uncovered heterozygous mutations implicated in maturity-onset diabetes of the young (MODY), including those in the transcription factor genes HNF1A, HNF4A, and HNF1B (28). Such variants demonstrate the contribution of beta cell dysfunction to young-onset diabetes, distinguishing MODY cases from typical type 1 or 2 diabetes to guide management. In addition, whole exome and whole genome sequencing of individuals with extreme phenotypes can facilitate the discovery of implicated rare alleles. Analyses estimate that protein-coding variants with frequencies <5% contribute about half of the genetic risk to T2D, underscoring the importance of evaluating rare variations. Furthermore, aggregating rare variants across the exome into polygenic risk scores may help predict T2DM susceptibility. Therefore, sequencing studies are critical for defining the full spectrum of rare to common alleles that influence T2D risk (29).

## 2. Leveraging genetic insights to guide prevention and treatment

### *2.1. Genetic risk scores*

One promising application of genomic research is leveraging genetic risk scores to identify high-risk individuals who could benefit most from targeted diabetes prevention interventions. By combining information from multiple common genetic variants identified through (GWAS), genetic risk scores provide an estimate of an individual's inherited T2D susceptibility.

Algorithms that weight GWAS SNPs based on effect sizes and incorporate large sets of disease-associated variants can achieve high predictive ability that may exceed conventional clinical risk factors such as body mass index (BMI), glucose levels, and family history. Genetic risk scores could be used in early-life to identify young asymptomatic individuals with elevated lifetime T2D risk based on their genomic profiles.

This would enable targeted prevention such as lifestyle modification or metformin treatment in the subset of people most likely to progress to T2D given their genetic burden. Early risk-stratified prevention informed by genetics may have advantages over universal T2D screening, allowing a more efficient allocation of resources only to those most genetically vulnerable. Realizing the potential of genomic risk prediction will require further improvement of predictive accuracy, development of appropriate testing and counseling infrastructure, and generation of evidence that acting on genetic risk drives clinically meaningful prevention (30).

### *2.2. pharmacogenomics to optimize diabetes medications*

Pharmacogenomics represents another emerging genomic application with the potential to enable a more precise, personalized medication selection for patients with diabetes. This field leverages knowledge of genetic variability influencing drug response to optimize efficacy and safety profiles. Numerous studies have uncovered





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associations between gene variants and responses to commonly prescribed T2D drugs such as metformin and sulfonylureas. For example, variants in organic cation transporters affect gastrointestinal absorption and renal excretion of metformin, which are linked to differential efficacy and tolerability. Variants altering CYP2C9 activity influence the metabolism of sulfonylureas, with reduced function alleles demonstrating a higher risk of hypoglycemia.

Testing for key variants before treatment selection could provide clinically actionable data to guide the choice and dosing of diabetes medications for individual patients. This personalized approach promises to increase effectiveness, minimize adverse events, and enhance medication adherence compared with trial-and-error prescribing. However, translating pharmacogenomics discoveries into clinical implementation faces barriers such as clinical validation, developing guidance for test interpretation, and addressing cost-effectiveness concerns (31).

### *2.3. Gene editing and silencing techniques for targeting diabetes risk genes*

Novel genomic tools, such as CRISPR/Cas9 gene editing and gene silencing using antisense oligonucleotides or RNA interference (RNAi), are poised to enable direct modification of disease-causing genes to mitigate diabetes risk. Gene editing via CRISPR/Cas9 induces targeted DNA double-strand breaks, allowing the removal of harmful mutations or insertion of protective variants. For diabetes, CRISPR-based therapies are being developed to disrupt genes such as PCSK9 and ANGPTL4, whose inhibition may improve glucose and lipid metabolism. Meanwhile, gene silencing leverage antisense oligoes or short interfering RNAs to bind target mRNAs and selectively inhibits the translation of proteins that drive disease (32).

Small interfering RNAs targeting key gluconeogenic enzymes such as FBPase have shown promise in preclinical diabetes models. In addition, silencing apolipoprotein C3 (ApoC3) translation with an antisense oligo significantly reduced triglycerides in clinical trials. These next-generation genomic approaches may provide superior specificity over traditional pharmaceuticals. However, challenges such as off-target effects, efficient in vivo delivery, and durability of response will need to be addressed (33).

## 3. Limitations and ongoing research on translating genomic medicine to diabetes care

### *3.1. Barriers to clinical implementation*

While genomic applications hold great promise in enhancing diabetes prevention, diagnosis, and treatment, substantial barriers must be overcome to translate these tools into clinical care. One major challenge is the lack of definitive evidence demonstrating the clinical utility and cost-effectiveness of most genomic interventions.

Large prospective studies and implementation trials are required to confirm that acting on genetic information improves patient outcomes sufficiently to justify costs. Provider education on genomic principles and the appropriate use of genetic counseling services also remains limited. Clinicians require training on how to interpret and communicate complex risk estimates and guidance on evidence-based applications of pharmacogenomics testing. Additionally, ethical concerns around the return of genetic results, privacy, and discrimination need to be addressed through expanded genetic literacy and protection policies. Overcoming to these barriers are the key of the responsible and equitable implementation of genomic medicine (34).

### *3.2. Ongoing research to expand genomic applications*

Continued research across diverse populations and diabetes subtypes is critical to further characterize the genomic architecture and refine genomic predictive tools, therapies, and clinical guidance. Most genomic studies have focused on common variants in European




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ancestries, necessitating research in broader populations and minority ethnic groups to enable the equitable realization of genomic medicine. Expanding the investigation into monogenic forms of diabetes will also accelerate the diagnosis and management of these patients. Furthermore, multidimensional omics integration that combines genomics, epigenomes, transcriptomics, proteomics, and metabolomics with deep phenotyping will provide comprehensive molecular insights into diabetes heterogeneity. This system-level analysis promises to unravel interactive effects across biological layers that drive personalized risk and pathology (35).

## Emerging pharmaceutical therapies

### 1. Cell-based therapies using stem cells

#### *1.1. Generation of insulin-producing beta cells from stem cells*

Cell therapy using stem cells aims to replace damaged or destroyed insulin-producing beta cells in patients with diabetes as an alternative to insulin administration. Pluripotent stem cells such as embryonic stem cells (ESCs) and induced pluripotent stem cells (iPSCs) can differentiate in vitro into functional pancreatic beta cells capable of secreting insulin in response to glucose stimulation (36). Directed differentiation methods recapitulating pancreatic development allow the generation of beta-like cells from both human ESCs and iPSCs derived from easily accessible tissues such as skin. In addition, direct reprograming of other differentiated cells such as hepatocytes into insulin-secreting cells is being explored using transcription factors central to beta cell identity and function. However, the efficiency and consistency in deriving fully mature, glucose-responsive beta cells remains a key challenge. Ongoing protocol optimization to improve beta cell maturation will help make stem cell-derived beta cells a feasible cell replacement therapy (37).

#### *1.2. Transplantation of stem cell-derived beta cells*

A major goal of stem cell-based diabetes therapy is the transplantation of functional beta cells to restore natural insulin secretion in patients. Transplantation of ESC or iPSC-derived beta cell progenitors or mature beta cells could normalize blood glucose level in the long term, thereby reducing complications. Autologous transplantation using a patient's own iPSC-derived beta cells is especially promising for avoiding rejection, but requires optimization. In addition, for patients with autoimmune diabetes, suppression of ongoing autoimmunity is critical for graft survival and prevention of recurrent beta cell destruction.

A major current limitation is poor engraftment and survival of transplanted cells within host tissues due to factors such as hypoxia, inflammation, and anoikis. Advances in tissue engineering approaches, such as 3D scaffold encapsulation and vascularization strategies, may promote durable engraftment and function (38). The process of differentiating pancreatic β cells from human pluripotent stem cells occurs stepwise. First, pancreatic islets are derived from the definitive endoderm, a developmental stage that arises during gastrulation and forms the primitive gut tube. During this process, pancreatic buds composed of pancreatic progenitor cells emerge from both the dorsal and ventral sides of the posterior foregut. Subsequently, the pancreatic epithelium expands and undergoes differentiation, leading to the formation of endocrine progenitor cells. Finally, these endocrine progenitor cells develop into β cells. To replicate the natural progression of pancreatic development, researchers use human pluripotent stem cells (PSCs) and guide their differentiation in a stepwise manner, ultimately generating β cells as shown in Figure (1) (39).

### 2. Gene silencing in diabetes therapy

#### *2.1. RNA interference to block genes that impair insulin release*

Gene silencing using RNA interference (RNAi) is emerging as a promising approach





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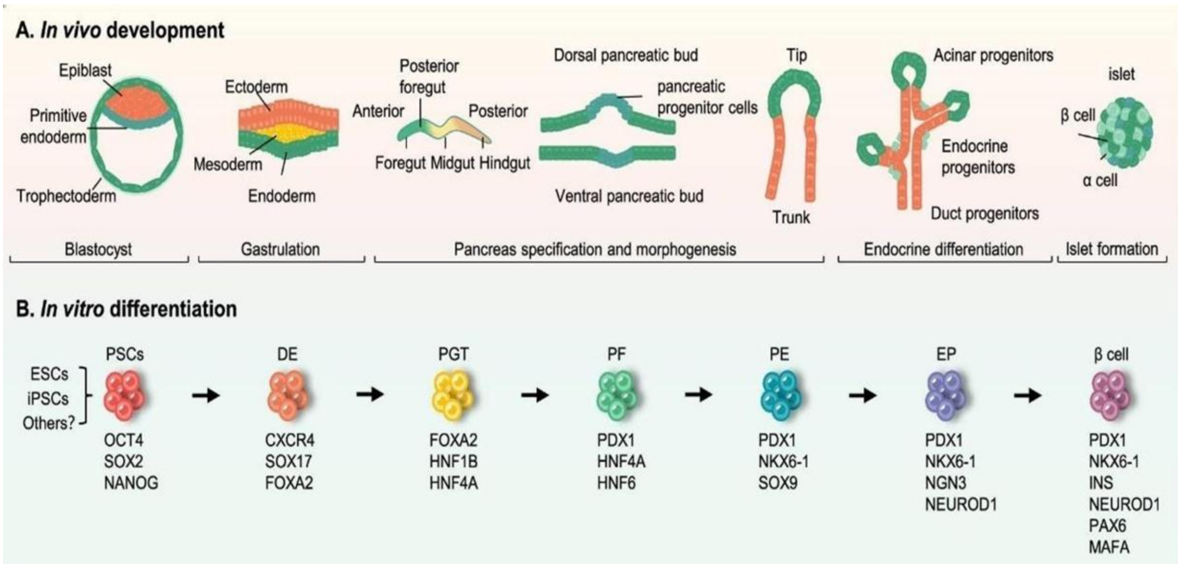


**Figure 1. Stepwise differentiation of pancreatic β cells from human pluripotent stem cells**

to restore defective insulin secretion in diabetes by inhibiting genes that impair beta cell function. Small interfering RNAs (siRNAs) or short hairpin RNAs (shRNAs) can be designed to specifically bind and promote the degradation of mRNAs encoding proteins that dysregulate insulin production and release. Viral vector delivery of shRNAs enables stable knockdown of target genes in beta cells (40).

Alternatively, complexing siRNAs with nanoparticles protects them from degradation and facilitates cellular uptake. In preclinical diabetic rodent models, RNAi silencing of genes involved in beta cell dysfunction and apoptosis, such as caspase-3, Txnil, and Pdxl, improved glucose-stimulated insulin secretion. siRNAs against inflammatory cytokines like TNF-α, IL-1β, and MCP-1 suppress inflammation and insulin resistance in diabetes models. siRNAs silencing gluconeogenic genes such as PEPCK and G6Pase reduce hepatic glucose production in diabetic rodents. Furthermore, RNAi targeting of the glucagon receptor increased beta cell mass and proliferation. However, off-target effects, inflammatory activation, and efficient in vivo delivery remain challenges (41).

### *2.2. Correcting defective insulin production and secretion pathways*

By downregulation genes that impair insulin release, RNA interference therapy restores the normal expression and function of insulin production and secretion pathways in pancreatic beta cells. Diabetes pathogenesis involves dysregulated expression of genes that control key steps such as insulin biosynthesis, packaging into secretory granules, granule trafficking, exocytosis, and beta cell survival and replication. RNAi using siRNAs or virally delivered shRNAs allows selective inhibition of genes that drive dysfunction at these critical nodes, potentially reactivating functional secretion.

For example, silencing TXNIP, which is overexpressed in diabetes, improved insulin release and reduced apoptosis by relieving inhibition of the antioxidant thioredoxin system. Knockdown of the glucagon receptor enhanced insulin secretion by inhibiting excess alpha cell to beta cell paracrine signaling. Additionally, directly replacing mutated genes such as PDX1 via RNAi-based gene therapy approaches could rectify impaired insulin gene transcription (42).





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## 3. Novel routes of insulin administration

### *3.1. Smart insulin patches*

In efforts to move beyond cumbersome insulin injections, smart insulin patch technologies are being developed for convenient, sustained transdermal insulin delivery. These patches contain an array of microneedles, often made of glucose-responsive materials, which provide controlled diffusion of insulin across the skin in response to interstitial glucose levels.

This allows dynamic, closed-loop delivery that mirrors natural pancreatic function. Patches may also incorporate glucose sensors and wireless connectivity, enabling programmable, on-demand dosing using mobile apps. By continuously delivering insulin based on prevailing blood glucose levels, smart patches aim to better mimic physiological patterns, improving glycemic control while avoiding multiple daily injections. However, adequate insulin absorption, lag times for glucose-mediated release, and variability among patients pose challenges. If smart patch technologies can provide clinically effective glycemic control with enhanced adherence and convenience compared with injections, they could significantly advance diabetes management (43).

### *3.2. Oral Insulin Alternatives*

Oral administration is the most patient-friendly route for insulin delivery. However, insulin digestion in the GI tract has hindered the development of oral formulations. Novel approaches, such as nanoparticle or polymer encapsulation, now aim to protect insulin from degradation and facilitate absorption into the circulation. Co-administration of enzyme inhibitors that temporarily block proteolysis in the gut has also shown promise in early trials. Orally delivered insulin analogs engineered for gut stability are also being explored. While still early in development, oral insulin alternatives that are well-tolerated and successfully elevate systemic insulin levels could dramatically improve the quality of life and outcomes for patients with diabetes compared with injectable insulin (44).

### *3.3. Inhaled insulin options*

Inhalable insulin is another emerging alternative to injections, delivering rapid-acting insulin directly into the lungs for faster absorption into the blood. Early inhaled insulin products used powdered insulin formulations; however, challenges with dosing precision, lung function effects, and low patient adherence resulted in discontinuation. However, new ultra-rapid formulations using thinner liquid aerosols have demonstrated improved pharmacokinetics and ease of use. Although inhalers require higher doses than injections, non-invasive delivery may promote patient acceptance and compliance. Ensuring consistent dosing, adequate absorption, and long-term safety of chronic use will be critical for successfully introducing inhaled insulin systems into clinical practice (45).

# Artificial Intelligence for diabetes

## 1. Glucose monitoring and insulin delivery

### *1.1. Closed-loop insulin pumps*

Closed-loop insulin pump systems, also known as artificial pancreatic devices, automate glucose monitoring and insulin delivery to relieve the daily burden of diabetes management. These systems combine continuous glucose monitors that measure interstitial glucose levels with sophisticated control algorithms that determine insulin dosing in an automated, self-regulating process. The algorithms, powered by advances in artificial intelligence and machine learning, model the complex relationship between insulin and glucose over time for a specific individual.

This allows the system to predict future glucose patterns and make automatic adjustments to insulin infusion rates, thereby approximating non-diabetic physiology. AI-driven artificial pancreatic systems have achieved promising results in clinical trials, but challenges remain around managing exercise and meal behaviors (46).





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*1.2. Glucose forecasting and predictive analytics*

In addition to closed-loop pumping, machine learning shows promise for glucose forecasting and predictive analytics to support diabetes self-management. Advanced algorithms can process continuous glucose data, insulin dosing, diet, and physical activity to identify glycemic patterns and variability. Models can then forecast future glucose levels and the risk of hypo/hyperglycemia, providing personalized decision support for preventive actions such as dosing changes.

Some mobile apps integrate glucose forecasting with education and lifestyle recommendations. By applying AI predictive analytics to identify individual's unique fluctuations, data-driven glucose forecasting augments diabetes self-care. However, robust validation across diverse individuals and conditions is required (47).

## 2. Screening and diagnosis

*2.1. Retinal image analysis for diabetic eye disease*

Artificial intelligence applied to retinal imaging enables automated screening and diagnosis of diabetes-related eye complications. Deep learning algorithms can analyze retinal fundus photographs and optical coherence tomography scans for lesions indicative of diabetic retinopathy or macular edema. Some FDA-approved AI systems, such as IDx-DR, perform on par or better than experts in identifying referable diabetic retinopathy. Automated grading of disease severity could facilitate screening and monitoring, overcoming limited specialist access and screening adherence. However, the diversity of imaging equipment and populations could impact performance. Overall, AI retinal image analysis demonstrates the potential to expand the access and efficiency of eye disease evaluation in people with diabetes (48).

*2.2. Electrocardiogram analysis to detect cardiac autonomic neuropathy*

Cardiac autonomic neuropathy is a common complication of diabetes, but it lacks sensitive diagnostic tools beyond specialized autonomic testing. Applying AI to distinguish neuropathy patients from electrocardiogram (ECG) patterns could enable earlier and more convenient detection. Machine learning can extract ECG features affected by reduced heart rate variability and parasympathetic tone in neuropathy such as QRS (QRS complex) intervals and QT (QT interval) dynamics. AI models analyzing standard 12-lead ECG outperformed cardiologists in classifying patients by neuropathy status in preliminary research. By augmenting clinician review or enabling self-monitoring via wearable sensors, AI-enabled ECG analysis could become an accessible screening tool for this often underdiagnosed diabetes complication (49).

## 3. Lifestyle and behavior modification

*3.1. Personalized nutrition recommendations*

Nutrition therapy is critical in diabetes, but identifying optimal eating patterns tailored to the individual represents a major challenge. AI chariots and coaching apps provide personalized nutrition recommendations by analyzing glucose data along with information on diet, exercise, biometrics, and health history. Machine learning models can detect associations between food, glucose response, and behavior in an individual to generate personalized plans and nudges supporting adherence. While human providers remain integral, AI augmentation could help uncover dietary approaches that best fit individual's unique needs and lifestyle. However, larger datasets encompassing diverse individuals are still required to refine recommendations (50).

*3.2. Digital coaching and motivation*

Lifestyle modification is demanding in chronic disease, requiring tailored strategies to motivate and support self-management behaviors. AI chatbots and avatar coaches allow interactive, responsive digital coaching integrated with educational content and reminders. Natural language processing enables conversational experiences that





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support behavior changes such as healthy eating or exercise.

Machine learning can also tailor communication style, feedback, and recommendations to an individual’s stage of change, culture, and preferences to optimize engagement. While lacking human empathy, such AI coaching solutions have evidenced modest benefits for improving diet and physical activity when thoughtfully designed. They have the potential to increase access, convenience, and personalization of diabetes self-management support (51).

## Conclusion

Emerging tools such as molecular biomarkers, genomics, cell therapy, and artificial intelligence have transformational potential in diabetes care. Molecular biomarkers enable personalized insights into disease progression and treatment response. Genomic medicine allows tailored prediction, prevention, diagnosis, and therapy based on an individual’s genetic makeup. Stem cell-derived beta cell transplantation restores insulin secretion. Gene silencing techniques directly target the molecular drivers of diabetes. AI empowers automated glucose control, screening, and digital health coaching. Despite limitations, these technologies promise more predictive, preventive, precise, and participatory approaches to diabetes management.

## Recommendations

Further research is needed to validate emerging biomarkers such as miRNAs in large, diverse cohorts and to develop standardized assays to enable clinical implementation. The clinical utility of genomic risk scores and pharmacogenomics testing should be demonstrated through prospective trials before widespread adoption. Optimization of stem cell differentiation protocols and transplant techniques is critical for the progress toward cell-based diabetes therapies. Gene silencing methods require more preclinical research to improve delivery while monitoring off-target effects. For AI applications, ongoing validation across diverse settings and populations is essential to support integration into clinical care.

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## Conflict of Interest

The authors hereby declare that they have no competing interests.

## Authors' contributions

All authors have accepted responsibility for the entire content of this manuscript and agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved and approved the version to be published.

## References

1. Buschard K. The etiology and pathogenesis of type 1 diabetes–A personal, non-systematic review of possible causes, and interventions. Frontiers in Endocrinology. 2022;13:876470.
2. Ke C, Narayan KV, Chan JC, Jha P, Shah BR. Pathophysiology, phenotypes and management of type 2 diabetes mellitus in Indian and Chinese populations. Nature Reviews Endocrinology. 2022;18(7):413-32.
3. Wang J, Zhang L, Bai Y, Wang X, Wang W, Li J, et al. The influence of shorter red blood cell lifespan on the rate of HbA1c target achieved in type 2 diabetes patients with a HbA1c detection





[ DOI: 10.18502/ijdo.v15i4.14556 ]

value lower than 7%. Journal of Diabetes. 2023;15(1):7-14.
4. Wang Y, Xu W, Mak IL, Chin WY, Yu EY, Lam CL, et al. Trends of clinical parameters and incidences of diabetes mellitus complications among patients with type 2 diabetes mellitus in Hong Kong, 2010–2019: a retrospective cohort study. Eclinicalmedicine. 2023;60:101999.
5. Overgaard KS, Andersen TR, Mohamed RA, Heinsen LJ, Binderup HG, Möller S, et al. Can prediabetes diagnosed using HemoglobinA1c or oral glucose tolerance test predict presence and severity of coronary artery disease in symptomatic patients?. Diabetes & Vascular Disease Research. 2023;20(3):14791641231179870.
6. Cetin EG, Demir N, Kalkan K, Ozturkmen YA, Nazif P, Yucelen SY, et al. The Compatibility of Hemoglobin A1c with Oral Glucose Tolerance Test and Fasting Plasma Glucose. Ş iş li Etfal Hastanesi Tip Bülteni. 2020;54(3):351-6.
7. Sufianov A, Kostin A, Begliarzade S, Kudriashov V, Ilyasova T, Liang Y, et al. Exosomal non coding RNAs as a novel target for diabetes mellitus and its complications. Non-coding RNA Research. 2023,8(2),192–204.
8. Karami M, Mousavi SH, Rafiee M, Heidari R, Shahrokhi SZ. Biochemical and molecular biomarkers: unraveling their role in gestational diabetes mellitus. Diabetology & Metabolic Syndrome. 2023;15(1):1-1.
9. Lupu L, Taha L, Farkash R, Bayya F, Karmi M, Steinmetz Y, et al. Hemoglobin A1C as a prognostic factor and the pre-diabetic paradox in patients admitted to a tertiary care medical center intensive cardiac care unit: The Jerusalem platelets thrombosis and intervention in cardiology (JUPITER-6) study group. Cardiovascular Diabetology. 2022;21(1):86.
10. Jamieson EL, Dimeski G, Flatman R, Hickman PE, Jones GR, Marley JV, et al. Oral glucose tolerance test to diagnose gestational diabetes mellitus: impact of variations in specimen handling. Clinical Biochemistry. 2023;115:33-48.
11. Maddaloni E, Bolli GB, Frier BM, Little RR, Leslie RD, Pozzilli P, et al. C‐peptide determination in the diagnosis of type of diabetes and its management: A clinical perspective. Diabetes, Obesity and Metabolism. 2022;24(10):1912-26.
12. Asadollahi S, Hadizadeh M, Namiranian N, Kalantar SM, Firoozabadi AD, Injinari N. Misexpression of LINC01410, FOSL1, and MAFB in peripheral blood mononuclear cells associated with diabetic nephropathy. Gene. 2023;862:147265.
13. Taylor HJ, Hung YH, Narisu N, Erdos MR, Kanke M, Yan T, et al. Human pancreatic islet microRNAs implicated in diabetes and related traits by large-scale genetic analysis. Proceedings of the National Academy of Sciences. 2023;120(7):e2206797120.
14. Keller DM, Perez IG. Dual regulation of miR-375 and CREM genes in pancreatic beta cells. Islets. 2022;14(1):139-48.
15. Li LJ, Wang X, Chong YS, Chan JK, Tan KH, Eriksson JG, et al. Exploring preconception signatures of metabolites in mothers with gestational diabetes mellitus using a non-targeted approach. BMC medicine. 2023;21(1):99.
16. Bashir H, Majid S, Khan MS, Bhat MH, Hamid R, Ashraf R, et al. Inter-relationship of Pro-and Anti-inflammatory Biomarkers with the development of Type 2 Diabetes Mellitus. Heliyon. 2022;8(11), e11329.
17. Denimal D, Monier S, Bouillet B, Vergès B, Duvillard L. High-Density Lipoprotein Alterations in Type 2 Diabetes and Obesity. Metabolites. 2023;13(2):253.
18. Lu W, Hu C. Molecular biomarkers for gestational diabetes mellitus and postpartum diabetes. Chinese Medical Journal. 2022;135(16):1940-51.
19. Khan RS, Malik H. Diagnostic Biomarkers for Gestational Diabetes Mellitus Using Spectroscopy Techniques: A Systematic Review. Diseases. 2023;11(1):16.
20. Rodrigues Oliveira SM, Rebocho A, Ahmadpour E, Nissapatorn V, de Lourdes Pereira M. Type 1 diabetes mellitus: A review on advances and challenges in creating insulin producing devices. Micromachines. 2023;14(1):151.
21. Xu X, Wang X, Jiang H. Current Status and Prospect of Diabetes Diagnosis and Treatment Based on Biosensing Technology. Chemosensors. 2023;11(7):391.
22. Laakso M, Fernandes Silva L. Genetics of type 2 diabetes: past, present, and future. Nutrients. 2022;14(15):3201.
23. Srinivasan S, Todd J. The genetics of type 2 diabetes in youth: Where we are and the road ahead. The Journal of pediatrics. 2022;247:17-21.
24. Vollenbrock CE, Roshandel D, van der Klauw MM, Wolffenbuttel BH, Paterson AD. Genome-wide association study identifies novel loci associated with skin autofluorescence in individuals without diabetes. BMC genomics. 2022;23(1):1-8.
25. Hettiarachchi G, Komar AA. GWAS to Identify SNPs Associated with Common Diseases and Individual Risk: Genome Wide Association Studies (GWAS) to Identify SNPs Associated with Common Diseases and Individual Risk. InSingle Nucleotide Polymorphisms: Human Variation and a Coming Revolution in Biology and Medicine 2022(pp. 51-76). Cham: Springer International Publishing.
26. Shastry BS. SNPs in disease gene mapping, medicinal drug development and evolution. Journal of human genetics. 2007;52(11):871-80.





[ DOI: 10.18502/ijdo.v15i4.14556 ]

27. Azarova I, Polonikov A, Klyosova E. Molecular genetics of abnormal redox homeostasis in type 2 diabetes mellitus. International Journal of Molecular Sciences. 2023;24(5):4738.
28. Francis Y, Tiercelin C, Alexandre-Heyman L, Larger E, Dubois-Laforgue D. HNF1B-MODY masquerading as type 1 diabetes: A pitfall in the etiological diagnosis of diabetes. Journal of the Endocrine Society. 2022;6(8):bvac087.
29. Amaral S, Palha A, Bogalho P, Silva-Nunes J. Maturity-onset diabetes of the young secondary to HNF1B variants (HNF1B-MODY): a series of 10 patients from a single diabetes center. Diabetology & Metabolic Syndrome. 2023;15(1):21.
30. Shitomi-Jones LM, Akam L, Hunter D, Singh P, Mastana S. Genetic risk scores for the determination of type 2 diabetes mellitus (T2DM) in North India. International Journal of Environmental Research and Public Health. 2023;20(4):3729.
31. Jan A, Saeed M, Mothana RA, Muhammad T, Rahman N, Alanzi AR, et al. Association of CYP2C9* 2 Allele with Sulphonylurea-Induced Hypoglycaemia in Type 2 Diabetes Mellitus Patients: A Pharmacogenetic Study in Pakistani Pashtun Population. Biomedicines. 2023;11(8):228.
32. Osto E, Bonacina F, Pirillo A, Norata GD. Neutral effect of SGLT2 inhibitors on lipoprotein metabolism: From clinical evidence to molecular mechanisms. Pharmacological Research. 2023;188:106667.
33. Cervantes J, Kanter JE. Monocyte and macrophage foam cells in diabetes-accelerated atherosclerosis. Frontiers in Cardiovascular Medicine. 2023;10:1213177.
34. Florez JC, Pearson ER. A roadmap to achieve pharmacological precision medicine in diabetes. Diabetologia. 2022;65(11):1830-8.
35. Michalek DA, Onengut-Gumuscu S, Repaske DR, Rich SS. Precision Medicine in Type 1 Diabetes. Journal of the Indian Institute of Science. 2023;103:335-51.
36. Silva IB, Kimura CH, Colantoni VP, Sogayar MC. Stem cells differentiation into insulin-producing cells (IPCs): recent advances and current challenges. Stem cell research & therapy. 2022;13(1):309.
37. Hsieh MC, Wang WT, Lin CY, Kuo YR, Lee SS, Hou MF, et al. Stem cell-based therapeutic strategies in diabetic wound healing. Biomedicines. 2022;10(9):2085.
38. Du S, Li Y, Geng Z, Zhang Q, Buhler LH, Gonelle-Gispert C, et al. Engineering Islets From Stem Cells: The Optimal Solution for the Treatment of Diabetes?. Frontiers in Immunology. 2022;13:869514.
39. Jin W, Jiang W. Stepwise differentiation of functional pancreatic β cells from human pluripotent stem cells. Cell Regeneration. 2022 ;11(1):24.
40. Rahmadanthi FR, Maksum IP. Transfer RNA Mutation Associated with Type 2 Diabetes Mellitus. Biology. 2023;12(6):871.
41. Urizar AI, Prause M, Ingerslev LR, Wortham M, Sui Y, Sander M, et al. Beta cell dysfunction induced by bone morphogenetic protein (BMP)-2 is associated with histone modifications and decreased NeuroD1 chromatin binding. Cell death & disease. 2023;14(7):399.
42. Sun H, Sun R, Hua Y, Lu Q, Shao X. An update on the role of thioredoxin-interacting protein in diabetic kidney disease: A mini review. Frontiers in Medicine. 2023;10:1153805.
43. Zahid M, Dowlatshahi S, Kansara AH, Sadhu AR. The Evolution of Diabetes Technology–Options Towards Personalized Care. Endocrine Practice. 2023;29(8):653-62.
44. Natesan V, Kim SJ. The Trend of Organic Based Nanoparticles in the Treatment of Diabetes and Its Perspectives. Biomolecules & Therapeutics. 2023;31(1):16.
45. Karmakar S, Bhowmik M, Laha B, Manna S. Recent advancements on novel approaches of insulin delivery. Medicine in Novel Technology and Devices. 2023;19:100253.
46. Elian V, Popovici V, Ozon EA, Musuc AM, Fiț a AC, Rusu E, et al. Current Technologies for Managing Type 1 Diabetes Mellitus and Their Impact on Quality of Life—A Narrative Review. Life. 2023;13(8):1663.
47. Zafar A, Lewis DM, Shahid A. Long-Term Glucose Forecasting for Open-Source Automated Insulin Delivery Systems: A Machine Learning Study with Real-World Variability Analysis.Healthcare 2023, *11* (6):779.
48. Lim JI, Regillo CD, Sadda SR, Ipp E, Bhaskaranand M, Ramachandra C, et al. Artificial intelligence detection of diabetic retinopathy: subgroup comparison of the EyeArt system with ophthalmologists' dilated examinations. Ophthalmology Science. 2023;3(1):100228.
49. Chaki J, Ganesh ST, Cidham SK, Theertan SA. Machine learning and artificial intelligence based Diabetes Mellitus detection and self-management: A systematic review. Journal of King Saud University-Computer and Information Sciences. 2022;34(6):3204-25.
50. Sharma S, Pajai S, Prasad R, Wanjari MB, Munjewar PK, Sharma R, et al. A Critical Review of ChatGPT as a Potential Substitute for Diabetes Educators. Cureus. 2023;15(5):e38380.
51. Aggarwal A, Tam CC, Wu D, Li X, Qiao S. Artificial Intelligence–Based Chatbots for Promoting Health Behavioral Changes: Systematic Review. Journal of Medical Internet Research. 2023;25:e40789.





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