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**Review Article**

# Innovative Approaches to Diabetes Mellitus Treatment: A Review

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## ABSTRACT

Diabetes mellitus is a fast-expanding worldwide health issue that calls for the investigation of innovative treatment approaches. This review examines innovative approaches to antidiabetic treatment, encompassing both natural and synthetic agents. We analyze recent advancements in biotechnological innovations. The review also delves into biotechnological innovations, including gene therapy, stem cell therapy, and personalized medicine, which offer promising avenues for diabetes management. Furthermore, the review provides a useful resource for researchers, clinicians, and policymakers attempting to navigate the changing landscape of diabetes therapy. We discuss new drug delivery systems, like nanotechnology and smart drug delivery, that improve the efficacy and precision of antidiabetic therapies. We also present comparative analyses of traditional and modern treatments to provide a thorough understanding of their mechanisms and clinical outcomes. The findings highlight the significance of ongoing study and development in the field of antidiabetic treatments, aiming to improve patient outcomes and quality of life.

## INTRODUCTION

Diabetes mellitus is a long-term metabolic disease characterized by consistently elevated blood sugar levels. It is caused by either inadequate insulin synthesis or the body's incapacity to utilize insulin efficiently. [1] This disorder can take many different forms, such as Type 1 diabetes, which is an autoimmune condition in which the immune system targets the pancreatic beta cells that produce insulin. The most common type of diabetes is type 2, which is distinguished by inadequate insulin production and insulin resistance. Pregnancy causes gestational diabetes, which usually goes away after delivery but raises the chance of Type 2 diabetes in the future. Other specific types of diabetes can arise from genetic conditions, surgeries, medications, or other illnesses. [2,3] Globally, the incidence of diabetes mellitus has been rising. The International Diabetes Federation (IDF) estimates that 537 million persons aged 20 to 79 had diabetes in 2021,

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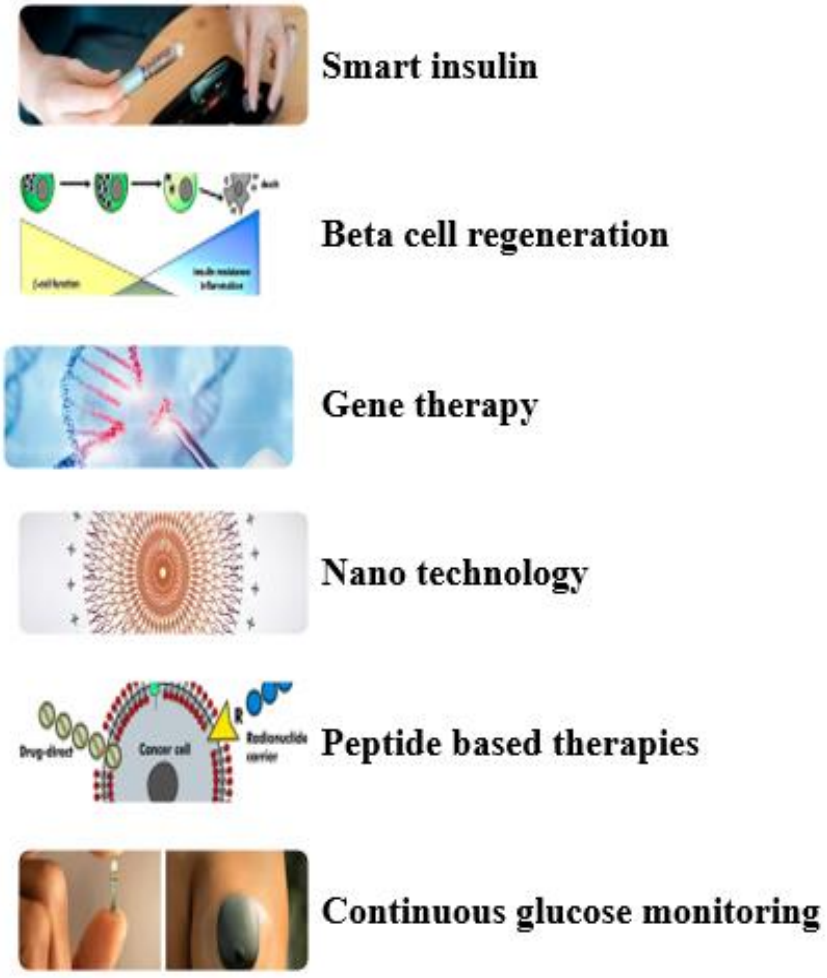
and by 2030, that figure is expected to increase to 643 million. Compared to high-income countries, the prevalence of diabetes is increasing more quickly in low- and middle-income countries. Compared to 7% in 1990, 14% of persons aged 18 and over had diabetes in 2022. [4] Recent, microvascular and macrovascular problems are two types of diabetes mellitus complications. Microvascular problems, such as diabetic retinopathy, affect tiny blood vessels. which is damage to the retinal blood vessels and can lead to blindness. Diabetic nephropathy, another microvascular complication, affects the kidneys and can result in chronic kidney disease or kidney failure. Damage to the nerves that results in tingling, pain, or loss of feeling, particularly in the limbs, is a hallmark of diabetic neuropathy. Large blood vessels are involved in macrovascular problems, which include peripheral artery disease, strokes, heart attacks, and other cardiovascular conditions caused by atherosclerosis. Additionally, people with diabetes are more susceptible to infections, particularly bacterial and fungal infections affecting the skin and mouth. [5,6]

**Biotechnological innovations:**

Biotechnological innovations have significantly advanced diabetes management in recent years. Here are some notable developments:




**Smart Insulin:**

Glucose-responsive insulin (GRI), another name for smart insulin, is a sophisticated type of insulin

that reacts automatically to variations in blood glucose levels. Here's how it works:

**Real-Time Glucose Responsiveness**: In order to replicate the body's natural insulin control, smart insulin automatically measures blood glucose levels and modifies its release accordingly. This removes a major drawback of conventional insulin therapy: the requirement for frequent monitoring by hand and changes.

**Convenience and Reduced Burden**: Unlike traditional insulin requiring multiple daily injections, smart insulin offers potential alternatives such as weekly injections or advanced delivery systems (e.g., patches, pens). This reduces the physical and mental burden on patients.

**Advanced Delivery Systems**: Smart insulin delivery methods include technologies like *smart insulin pens* and *closed-loop systems*. These integrate continuous glucose monitoring (CGM) devices with AI-powered algorithms to optimize insulin dosing in real time, ensuring tighter glycemic control.

**Prevention of Hypoglycemia**: Traditional insulin therapy often leads to hypoglycemia due to over-administration or delayed adjustments. Smart insulin's self-regulating mechanism prevents this by inhibiting insulin release when blood glucose levels are low.

**Improved Glycemic Control**: Studies show that smart insulin systems significantly improve metrics like *time in range (TIR)* and reduce HbA1c levels, enhancing overall diabetes management outcomes.

**Integration with Digital Ecosystems**: Smart insulin pens and systems use Bluetooth connectivity, smartphone apps, and machine learning algorithms for personalized dosing recommendations and real-time data analysis. This digital transformation fosters a connected care ecosystem for patients and providers. Currently, NNC2215 is still in the experimental stage and has not yet been approved for widespread use. Researchers have conducted promising studies on animals, such as rats and pigs, showing that it effectively lowers blood glucose levels1. However, it will need to undergo further clinical trials in humans to ensure its safety and efficacy before it can be made available to the public. The most recent study presents NNC2215, a modified insulin molecule with an integrated "on-and-off switch" that enables it to react to changes in blood glucose levels automatically. [7].

**Figure 1: Smart Insulin**

The innovative insulin, NNC2215, is designed with two key components: a ring-shaped structure and a glucoside molecule that mimics glucose in form. These parts work together to regulate insulin activation based on blood sugar levels. When blood sugar is low, the glucoside binds to the ring, ensuring the insulin remains inactive to avoid further drops in blood sugar. However, as blood glucose rises, glucose molecules replace the glucoside, causing the insulin to alter its shape and activate. This process helps restore blood sugar to safer levels.

In testing, NNC2215 demonstrated similar effectiveness to human insulin in lowering blood glucose in animal studies involving rats and pigs. [8]

| Characteristics | Traditional Insulin | Smart Insulin |
|---|---|---|
| Monitoring | Requires frequent blood glucose monitoring | Automatically detects blood glucose levels |
| Administration | Multiple injections per day | Potential for fewer injections or alternative delivery methods (pills, patches) |
| Adjustment | Manual adjustment based on monitoring | Automatically adjusts insulin release |

**Beta-Cell Regeneration:**

The process of repairing or renewing the pancreatic beta cells that produce insulin is known as beta-cell regeneration. For those who have insulin resistance, especially those with type 1, this is very crucial, where the immune system destroys these cells, leading to a lifelong dependence on insulin therapy. [9]

**Researchers are exploring various methods to stimulate beta-cell regeneration, including:**

**Pharmacological Approaches:** Using drugs to stimulate the growth and function of existing beta cells. For example, some studies have shown that certain FDA-approved drugs used for cancer treatment can help regenerate pancreatic cells. [10]

**Stem cell therapy:** is the process of using stem cells to produce new beta cells that patients can receive as transplants.

**Gene therapy:** altering genes to encourage beta cell survival and regeneration. [11] Restoring the body's natural capacity to make insulin is the aim of beta-cell regeneration, which will lessen or completely eliminate the requirement for exogenous insulin delivery.

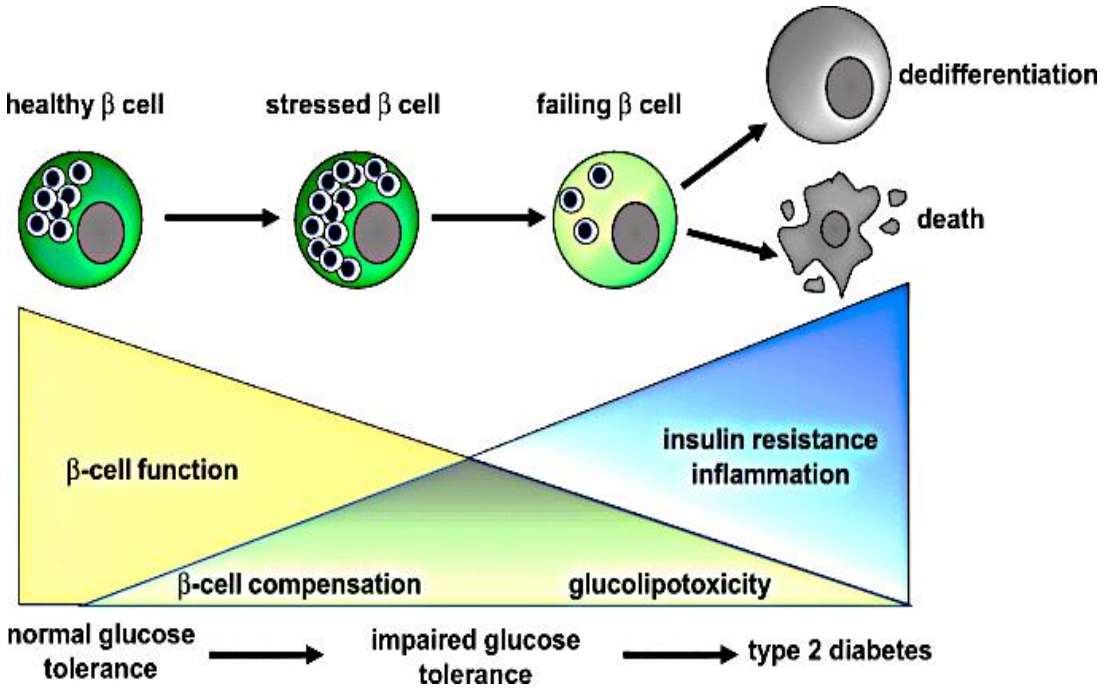



**Figure 2: Beta-Cell Regeneration**

Currently, there are no widely available beta-cell regeneration therapies approved for clinical use. However, researchers are making significant progress in this field1. One promising approach involves the use of a drug called harmine, which has shown potential in regenerating beta cells in preclinical studies. Human beta cell mass has been observed to be considerably increased by harmine, a DYRK1A (Dual-Specificity Tyrosine Phosphorylation-Regulated Kinase 1A) inhibitor, particularly when used in conjunction with GLP-1 receptor agonists such as exenatide (Byetta) and semaglutide (Ozempic). These results give promise for future therapies that can help the body manufacture insulin again naturally. [12]

**Gene Therapy:**

It is a method of treating or preventing disease by changing the genetic content of cells. It seeks to replace the faulty, disease-causing gene with a healthy, functioning one. They can function in a number of ways, including introducing a new or altered gene into the body to aid in the treatment of an illness, eliminating an illness-causing gene that is not working correctly, and substituting a functioning variant of the gene for a disease-causing gene. The main goals of genetic therapy for diabetes with type 1 are to stop β cell death and restore the production of insulin by the islet cells or their replacements. On the other hand, the treatment of genes for type 2 diabetes focuses on a number of pathways to increase cellular energy expenditure, decrease insulin resistance, and improve glucose tolerance. Strategies for gene therapy can be categorized in various ways. One approach distinguishes between in vivo therapy, in which genetic alterations take place directly within the patient, and ex vivo therapy, in which genes are altered beyond the body before being transferred into the patient. [13] The delivery technique determines another classification.

**Figure 3: Gene Therapy**

Viral Vectors- These include lentivirus and adeno-associated virus, which are utilized to transfer genes that promote angiogenesis and control insulin synthesis. Viral vectors are efficient at delivering genetic material into target cells, but they must be carefully designed to avoid immune responses and potential toxicity. Non-Viral Vectors- These methods include liposomal particles and lecithin nano-liposomal particles, which can deliver CRISPR-Cas9 complexes. Non-viral vectors are less likely to trigger immune responses and can be safer than viral vectors. CRISPR-Cas9 Technology- This gene-editing tool is used to target specific genes involved in diabetes, such as those related to insulin production and glucose metabolism. CRISPR-Cas9 can be delivered using both viral and non-viral vectors. Nanocarriers- These are used to deliver genetic material efficiently and safely to target cells. Nanocarriers can protect the genetic material from degradation and help it reach the target cells effectively. [14] Genes and their expressions have been the focus of numerous investigations. For example, type 1 diabetes and immunological dysregulation can result from mutations and deficits in FOXP3. By increasing the quantity and functionality of Tregs, a subset of CD4+ and regulatory T-cells, gene therapy techniques that raise FOXP3 can protect beta cells and foster immunological tolerance. Early type 1 diabetes prevention with FOXP3 mutation correction makes it an essential future gene therapy technique. [15] Hepatocytes and beta cells use glucokinase (GCK) as a sensor for glucose to help preserve glucose homeostasis. In reaction to blood sugar levels, GCK starts glycolysis and controls insulin release by converting glucose to glucose-6-phosphate. Maturity-onset diabetes of the young (MODY) can result from mutations in this gene. [16] An anti-inflammatory cytokine that is crucial for immunological modulation, IL-10 inhibits inflammatory reactions and guards against autoimmunity attacks that cause type 1 diabetes beta cell destruction. Deterioration of beta cells and chronic inflammation are caused by decreased or changed IL-10 levels. Viral vectors can transmit the IL-10 gene to particular organs by gene transfer, improving local anti-inflammatory actions and reducing the symptoms of diabetes. [17] PDX1 is a transcription factor involved in pancreatic development and beta cell function, crucial for insulin production. Deficient PDX1 expression impairs beta-cell function and insulin production, leading to type 1 and type 2 diabetes. Gene therapy can introduce functional PDX1 genes into beta cells to restore insulin production. PDX1 is also used to differentiate stem cells into insulin-producing beta cells. Correcting PDX1 mutations using CRISPR-Cas9 can activate or enhance gene expression, restoring insulin production. NK6 Homeobox1 is a transcription factor that maintains beta cell identity and insulin secretion, promoting beta cell proliferation and survival in the pancreas, thereby improving their function and insulin production [18]. Fishman et al. demonstrated that gene-modified T cells might be redirected against pathogenic CD8 T cells via mRNA generating chimeric MHC-I receptors. This was accomplished by adding TCR to chimeric MHC molecules. The study explained how mRNA electroporation was used to transfer peptide/β2m/CD3-ζ genes to a reporter T cell line.

After MHC-I cross-linking, the endogenous MHC-I chains together with peptide/β2m/CD3-ζ products sent powerful activation signals. Additionally, primary CD8 T cells transfected with InsB15-23/β2m/CD3-ζ mRNA prevented diabetes in NOD animals and significantly reduced insulitis. Consequently, one possible method of treating T1DM is to use gene therapy to target TCR. [19]

**Nanotechnology:**

**Nanotechnology-aided drug delivery in diabetes:**

**PLGA Nanoparticles:** These particles are a blend of Lactic acid and glycolic acid polymers and are used to encapsulate insulin. They enable controlled release through the gradual degradation of the polymer. PLGA nanoparticles revolutionize diabetes management by providing a controlled insulin release, preserving steady blood glucose levels and reducing the need for frequent injections. [20] These nanoparticles can be engineered for targeted delivery to specific cells, like pancreatic cells, enhancing insulin efficiency and minimizing side effects. [21] Researchers are also exploring their use for oral insulin delivery, potentially improving patient compliance by eliminating injections. Additionally, PLGA nanoparticles protect insulin from degradation in the gastrointestinal tract, enhancing stability and reducing immune reactions and other side effects. Overall, these innovative approaches make diabetes treatment more effective and convenient for patients. [22]

**Crosslinked Nanogels:** Made from specific copolymers, these nanogels respond to temperature changes, allowing for the temperature-sensitive release of insulin. Crosslinked nanogels are revolutionizing diabetes treatment by providing glucose-responsive insulin delivery, releasing insulin precisely when blood glucose levels are high. [23] These nanogels offer enhanced stability and biocompatibility, protecting insulin from degradation and reducing immune reactions. Insulin efficiency can be increased and adverse effects can be reduced by engineering them for targeted delivery to particular cells, such as pancreatic cells. Furthermore, by delivering several therapeutic compounds at once, crosslinked nanogels facilitate combination therapies, improving the efficacy of treatment as a whole. They drastically improve patients compliance and quality of life by lowering the frequency of injections by providing regulated and sustained insulin release. [23,24]

**Liposomal Formulations:** Phospholipids like DOPC form bilayer structures that provide a stable environment for insulin, ensuring sustained release. Phospholipids like DOPC (dioleoylphosphatidylcholine) form bilayer structures that are essential in liposomal formulations for diabetes treatment. Antidiabetic medications are encapsulated in vesicles made of these bilayer structures, which improves the stability and bioavailability of the medication. These liposomal formulations decrease adverse effects and increase the effectiveness of drug delivery by specifically targeting particular tissues or cells, such as pancreatic cells. Furthermore, the regulated release of medications from these liposomes contributes to stable blood sugar levels, which lessens the need for regular dosage and enhances patient compliance. [25]

**Pamam Dendrimers:** These have a branching architecture that encapsulates insulin and controls its release through interactions between the dendrimer surface and insulin. PAMAM (Polyamidoamine) dendrimers are revolutionizing diabetes treatment by enabling targeted drug delivery to specific cells, such as pancreatic cells,

thereby improving drug efficiency and reducing side effects. They offer controlled and sustained release of antidiabetic drugs, maintaining stable levels of blood glucose and reducing the frequency of dosing. These dendrimers also enhance drug stability and bioavailability, protecting them from degradation. Additionally, Combination therapies are supported by PAMAM dendrimers, which deliver several therapeutic molecules at once to increase therapy efficacy. Overall, they minimize systemic side effects by targeting drugs directly to the affected areas, significantly advancing diabetes management. [26]

**Gold Nanoparticles:** Coated with thiolated PEG, these nanoparticles offer a multi-functional environment for insulin encapsulation and targeted release. Gold nanoparticles coated with thiolated PEG (polyethylene glycol) offer a multi-functional environment for insulin encapsulation and targeted release, enhancing diabetes treatment. These nanoparticles improve insulin stability and bioavailability, permitting a gradual and regulated release. They lessen negative effects and increase the effectiveness of insulin delivery by focusing on particular cells or tissues. This innovative approach can potentially eliminate the need for frequent insulin injections, making diabetes management more effective and convenient for patients. [27]

**MWCNTs & Electrospun PLA Nanofibers:** These structures serve as advanced reservoirs for insulin, leveraging their nanoscale design for controlled release. Multi-Walled Carbon Nanotubes (MWCNTs) and Electrospun PLA (Poly Lactic Acid) Nanofibers are revolutionizing diabetes treatment, especially in wound healing. By imitating the extracellular matrix, these substances provide dressings that promote wound healing by offering a platform for tissue regeneration and cell proliferation. They can be loaded with medicinal substances for controlled medication release, which promotes healing, and functioning with antimicrobial substances that prevent infections in diabetic wounds. Furthermore, they control the inflammatory response in order to lessen persistent inflammation and encourage angiogenesis, which creates new blood vessels that are essential for delivering oxygen and nutrients to the healing tissue. Patients with diabetes benefit greatly from this mix of qualities in terms of wound healing. [28]

**Nano emulsions:** Using surfactants, these emulsions enhance the oral bioavailability of insulin by encapsulating it within nanodroplets. Nano emulsions, using surfactants to encapsulate insulin within nanodroplets, enhance its oral bioavailability, making diabetes treatment more effective. These emulsions shield insulin from gastrointestinal tract deterioration, ensuring it reaches the bloodstream intact. This innovative approach simplifies insulin administration, potentially eliminating the need for injections and improving patient compliance and quality of life. [29]

**Chitosan Nanoparticles:** Derived from chitin, these nanoparticles improve mucoadhesive properties and oral insulin delivery. By encasing insulin or other antidiabetic medications, shielding them from deterioration, and improving their stability and bioavailability, chitosan nanoparticles are transforming the treatment of diabetes. They offer regulated and prolonged medication release, lowering the requirement for frequent dosing and preserving stable blood glucose levels. These nanoparticles can be engineered for targeted delivery to specific cells, such as pancreatic cells, improving drug efficiency and reducing side effects. Their biocompatibility and biodegradability make them safe for use, minimizing immune reactions. Additionally, some

chitosan nanoparticles are designed for pH-sensitive release, ensuring drugs are delivered precisely when and where needed in the body, significantly improving diabetes management.

**Peptide-Based Therapies:**

Peptide-based therapies are making significant strides in diabetes mellitus management. Here are some notable innovations:

**Incretin Mimetics**: These peptides, such as GLP-1 analogues (e.g., Semaglutide) and GIP analogues, mimic natural hormones. These hormones promote the production of insulin, which helps control blood glucose levels, and produce insulin in response to meal intake. Incretin mimetics thus offer a more natural method of controlling blood sugar levels in diabetics. This novel approach offers additional advantages including weight loss and maybe cardiovascular protection in addition to helping with improved glucose control. [30]

**Amylin Analogues**: **Pramlintide** offer innovative approaches to diabetes treatment by addressing several key aspects of glucose regulation. Pancreatic beta cells co-secrete insulin with a synthetic analogue of the human the amylin hormone called pramlintide. By delaying stomach emptying, preventing glucagon secretion, and encouraging satiety, which can lead to a decrease in food intake, it aids in blood sugar regulation. This comprehensive strategy reduces the risk of hypoglycemia and weight gain while enhancing postprandial (after-meal) control of glucose and overall glycemic management. Patients with both types of diabetes who are currently receiving insulin therapy but have difficulty achieving ideal glucose control will benefit most from pramlintide. [31,32]

**Insulin Analogues**: One of the latest innovations in insulin analogues is the approval of Merilog (insulin-aspart-szjj), the first biosimilar product of rapid-acting insulin. FDA-approved in February 2025, Merilog is highly similar to Novolog (insulin aspart) and helps lower mealtime blood sugar spikes, improving glycemic control for both adults and pediatric patients with diabetes. This approval is part of ongoing efforts to increase access to insulin treatments by offering more affordable options. [33]

**Peptide Hormones**: Research into peptide hormones like GEP44 is indeed promising for diabetes treatment. GEP44 is a novel chimeric multi-agonist peptide that targets multiple receptors, including Neuropeptide Y1, neuropeptide Y2, and GLP-1 receptors. This multi-target approach helps enhance insulin sensitivity and improve pancreatic function. Studies have shown that GEP44 can reduce energy intake and body weight, promote glycemic control, and even increase energy expenditure. This makes it a potential game-changer in diabetes management, offering a more comprehensive treatment option. [34,35]

**Continuous Glucose Monitoring (CGM):**

Here are some of the recent advancements in Continuous Glucose Monitoring (CGM).

**Extended Wear Time**: One major development in the management of diabetes is the longer wear time of modern Continuous Glucose Monitoring (CGM) devices, including the Dexcom G7. With up to 10 days of wear time and an additional 12-hour grace period, users experience less hassle and discomfort from frequent sensor replacements. This extended duration ensures continuous glucose monitoring without interruptions, leading to more accurate and consistent data for better diabetes management. Additionally, fewer sensor

changes mean less frequent skin punctures, reducing the risk of irritation and infection. While the initial cost of these systems might be higher, the reduced frequency of sensor changes can lead to cost savings over time. Overall, the convenience and improved quality of life offered by these systems make diabetes management more manageable and less intrusive for individuals. [36,37]

**Implantable CGM**: The Eversense 365 is an implantable CGM that can be worn for up to 365 days, providing continuous glucose monitoring without the need for daily sensor replacements. The Eversense 365 is a groundbreaking innovation in diabetes treatment, offering a long-term solution to the challenges of traditional Continuous Glucose Monitoring (CGM) systems. Unlike other CGMs that require frequent sensor changes, the Eversense 365 sensor is implanted under the skin and lasts for up to a year. This significantly reduces the inconvenience and discomfort associated with regular sensor replacements. The system includes a removable transmitter that can be taken off and put back on without wasting the sensor, providing flexibility and ease of use. Additionally, the Eversense 365 offers exceptional accuracy and minimal skin irritation, thanks to its gentle, silicone-based adhesive. By offering consistent, dependable monitoring of glucose with fewer disruptions and fewer sensor changes, this new technology improves the quality of life for diabetics. [38]

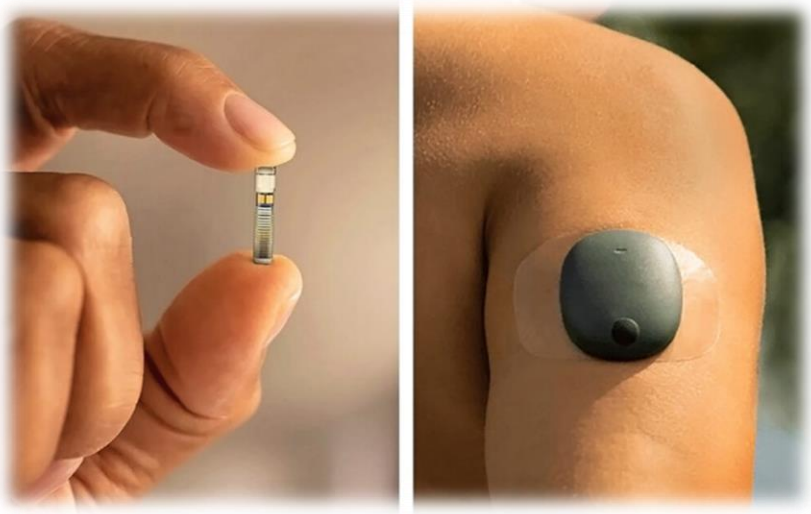


**Figure 4: Implantable Continuous Glucose Monitoring**

**Self-Powered Sensors**: Researchers are developing self-powered Continuous Glucose Monitoring (CGM) sensors using microbial fuel cells (MFCs). These sensors harness the metabolic activity of bacteria to generate electrical signals in response to glucose levels. By integrating spore-forming bacteria, such as Bacillus subtilis, into a micro engineered paper-based platform, these sensors can produce continuous electrical signals without the need for battery replacements or frequent maintenance. [39]

**Integration with Insulin Pumps**: Integrating Continuous Glucose Monitoring (CGM) systems A closed-loop device that automatically modifies insulin delivery in response to actual time glucose readings is created with insulin pumps. This advancement offers automated insulin delivery, improved glycemic control, enhanced convenience with fewer finger pricks and manual injections, and better data-driven decisions for managing diet, exercise, and medication. Additionally, it provides personalized care tailored

to individual needs, significantly improving diabetes management and patient quality of life. [40]

**Wireless Data Transmission**: Modern CGM devices offer secure wireless data transmission, enabling users to quickly supply caretakers and medical professionals with glucose data.

## CONCLUSIONS:

Diabetes mellitus is a rapidly growing global health challenge, requiring innovative solutions to manage its diverse forms and associated complications. From addressing its root causes to improving treatment options, advancements like smart insulin, beta-cell regeneration, gene therapy, and nanotechnology promise transformative impacts. Ongoing research, awareness, and effective interventions are essential to curb the rising prevalence of diabetes and improve the lives of people who are impacted. Through collective efforts, the future of diabetes care holds the potential for improved. Diabetes mellitus continues to be a global health challenge, with its prevalence rising at alarming rates. Innovative solutions are critical to addressing this multifaceted condition and improving outcomes for affected individuals. Among these advancements, smart insulin like NNC2215 represents a promising breakthrough, offering glucose-responsive insulin delivery that mimics natural bodily responses and reduces the need for constant monitoring. Preclinical studies have shown its potential, but further human trials are necessary to confirm its efficacy and safety. Beta-cell regeneration research aims to restore natural insulin production in the pancreas, particularly for type 1 diabetes patients. Strategies such as stem cell transplantation, gene therapy, and drugs like harmine show promise in increasing beta-cell mass and reducing reliance on insulin therapy. While these approaches remain experimental, they have the capacity to greatly raise living standards. Gene therapy provides transformative possibilities by targeting genetic causes of diabetes. Techniques like CRISPR-Cas9 and viral vectors aim to restore insulin production and reduce insulin resistance. Advances such as chimeric MHC-I receptors for T-cell reprogramming offer hope for long-term solutions to diabetes management. Nanotechnology has revolutionized diabetes treatment by enabling controlled drug delivery systems, improving insulin stability, and enhancing bioavailability. Innovations like glucose-responsive nanoparticles and lipid-based carriers ensure automated insulin release and better glycemic control, making treatment more convenient and effective. Peptide-based treatments, such as amylin mimetics and GLP-1 analogs, improve glucose regulation while offering additional benefits like weight loss and cardiovascular protection. These therapies are expanding Options for treating patients with both types of diabetes. Through the provision of real-time glucose readings and integration with insulin pumps for automatic delivery, Continuous Glucose Monitoring (CGM) system have revolutionized the treatment of diabetes.Devices like Dexcom G7 and Eversense 365 enhance convenience, accuracy, and patient adherence while reducing complications. Notwithstanding these developments, diabetes continues to be a major global problem that disproportionately affects low- and middle-income nations. Collective efforts in research, awareness campaigns, policy implementation, and equitable access to innovative treatments are essential to curb its prevalence. By embracing these transformative technologies and strategies, the future of diabetes care has the potential to significantly enhance patient results and the level of life.

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