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Review Article

## Advancements in Diabetes Mellitus: Pathogenesis, Current Therapies, and Emerging Treatment Strategies

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### Abstract

The incidence of diabetes mellitus is sharply increasing globally, making it a serious public health concern. More than 463 million people were impacted in 2019, and estimates indicate that by 2045, that figure may rise to 700 million. Diabetes causes serious consequences, such as retinopathy, nephropathy, and cardiovascular illnesses. It is characterised by persistent hyperglycemia brought on by either inadequate insulin secretion, impaired insulin action, or both. Type 1 diabetes mellitus (T1DM) and Type 2 diabetes mellitus (T2DM), both with unique aetiologies and treatment needs, are part of the complicated pathophysiology of diabetes. In contrast, T2DM is primarily associated with insulin resistance and is influenced by both genetic and environmental factors, T1DM, which is often autoimmune in nature, results in total insulin insufficiency. Insulin therapy, oral hypoglycemic medications, and lifestyle changes are examples of traditional management techniques; however, they frequently fall short of providing the best possible glycaemic control. Recent developments in diabetes treatment have led to novel therapeutic approaches, including immunological therapies, novel pharmacological agents, and nanotechnology-based drug delivery systems. The goals of these new therapies are to reduce the risk of complications, enhance patient compliance, and improve glycemic management. This overview provides an overview of the development of diabetes treatments, the pathophysiology of the condition, available treatment options, and the promise of new drugs and methods for managing the condition. We can gain a better understanding of the future of diabetes care and the significance of creating individualised treatment plans to improve patient outcomes and quality of life by investigating these developments.

**Keywords:** Diabetes Mellitus; Hyperglycemia; Type 1 Diabetes (T1DM); Type 2 Diabetes (T2DM); Novel Therapeutic Strategies

### Introduction

Diabetes mellitus is a significant health issue that necessitates continuous research or the creation of novel treatment strategies due to its increasing prevalence worldwide. Diabetes is indicated by persistently elevated blood glucose levels conduct on by either inadequate insulin secretion, compromised insulin action, or both. Beyond its immediate metabolic effects, it has several complexities. The background of diabetes is thoroughly covered in this introduction, followed by a discussion of the evolution of diabetic therapies over time. It ends with a detailed analysis of the necessity of novel therapeutic strategies. The International Diabetes Federation (IDF) reports that more than 463 million people worldwide underwent diabetes in 2019, and projections suggest that figure would rise to 700 million by 2045, underscoring the disease's significance in the context of global health.<sup>1</sup>

There is substantial healthcare, societal, and economic repercussions from this pandemic that go beyond simple data. Diabetes is a condition that predicts serious

illness and mortality rather than being a single health issue. It is directly related to small blood vessel problems like retinopathy and nephropathy as well as significant issues affecting large blood vessels like cardiovascular diseases. Complex disruptions in glucose balance fundamentally characterise the pathophysiology of diabetes. The different causes and mechanisms that contribute to this complex disorder are represented by the variety of symptoms, which include Type 1 and Type 2 diabetes.<sup>2</sup>

Regarding insulin insufficiency, diabetes mellitus has been classified such as type 1 diabetes (T1DM), sometimes referred to as insulin-dependent diabetes mellitus or juvenile-onset diabetes, which affects 5–10% of diabetic individuals and is linked to the autoimmune destruction of pancreatic beta cells.<sup>3</sup> These individuals, who also have autoimmune hepatitis, grave's disease, vitiligo, need insulin injections to maintain blood glucose levels. Type 1 Diabetes Mellitus (T1DM) is inherited, and its prevalence varies worldwide based on the interaction of genetic predisposition and other environmental factors.<sup>4</sup>

There have been recent reports linking low sociodemographic status to higher T1DM mortality and morbidity rates.<sup>5, 6</sup> Along with the risk of heart conditions like coronary heart disease and stroke, type 2 diabetes mellitus (T2DM), also known as insulin-nondependent diabetes mellitus (NIDDM) or mature-onset diabetes, is the fourth leading cause of mortality in many developed nations.<sup>7</sup> Genetic predisposition is covered by idiopathic diabetes, and people with this condition require insulin replacement medication for an hour. Despite having almost no causal factor, certain patients with T1DM of Oriental or Nigerian ancestry are nevertheless at risk of developing diabetic ketoacidosis with insulinopenia.<sup>8</sup> An elevated insulin demand, typically up to four times, is the outcome of prolonged hyperglycemia.<sup>9</sup> The pathogenesis is still uncertain, albeit.<sup>10</sup> Pregnancy causes gestational diabetes mellitus which is characterised by insulin intolerance and hyperglycemia of varying degrees of severity.<sup>11</sup>

Insulin therapy, oral medicines, and lifestyle changes are all part of the traditional treatment for diabetes mellitus. Weight loss, nutritional control, and regular exercise are examples of lifestyle changes that are more successful in managing type 2 diabetes than type 1 diabetes.<sup>12</sup> Several pills for diabetes target certain pathogenic regions that contribute to hyperglycemia.<sup>13</sup> Biguanides, which specifically decrease hepatic glycogenolysis and increase peripheral insulin sensitivity, are among the most widely used oral hyperglycaemic medications.<sup>14</sup> Sulfonylureas are medications that work on the beta cells in the pancreas to produce extra insulin.<sup>15</sup> Thiazolidinediones also increase peripheral tissues' sensitivity to insulin.<sup>16</sup> Insulin therapy has been recommended for sufferer who are unable to meet their glycaemic goals with lifestyle changes and oral hypoglycemic medications. Recently, a number of innovative strategies have been used to treat diabetes mellitus, such as insulin delivery systems based on nanotechnology, which aim to increase insulin therapy's accuracy, effectiveness, and patient compliance.<sup>17-20</sup>

**Pathogenesis:** The following can cause hyperglycemia, depending on the cause of DM:

- A decrease in the release of insulin.
- The body uses less glucose.
- A higher production of glucose.

**Type 1 DM:** In most cases, type 1 diabetes leads to total insulin insufficiency due to the loss of  $\beta$ -cell mass. The HLA area of chromosome 6 (MHC class II region) contains the type 1A DM susceptibility gene, which is located in the HLA DR3, HLA DR4, and HLA DQ loci. Multiple genes that contribute sensitivity to the condition are inherited in a familial way to type 1A DM [identical twins-has odds of 50% of inheriting Type1A DM to second twin]. T cell-mediated immunity, specific  $\beta$ cell damage, insulinitis (a disorder in which lymphocytes invade the pancreatic islets), islet cell antibodies against insulin therapy and an enzyme known as glutamic acid decarboxylase (GAD), and other autoimmune disorders factors or immunologic abnormalities.

### Type 2 DM

**Genetic factors:** The growth of type 2 diabetes has not been linked to any clear-cut, reliable genes. The substantial contribution factor to the growth of type 2 diabetes is multifactorial inheritance. Constitutional considerations: Several environmental factors, including physical activity level, obesity, and hypertension, influence the disease's phenotype and play a contributing role.

**Reduced insulin secretion:** The function of islet cells is exacerbated by hyperinsulinemia,  $\beta$ -cell dysfunction, glucose toxicity, and lipotoxicity.

**Increased hepatic glucose production:** Hyperglycemia is a result of increased hepatic sugar synthesis.<sup>21</sup>

### Current Treatment Plans for Diabetes

Many oral hypoglycemic medications are available as pharmacotherapy for the treatment of diabetes mellitus (DM) (table 1).<sup>22</sup>

**Table 1: Oral hypoglycemic agents used for the treatment of Diabetes Mellitus**

Class	Generic name	Mode of action	Side effects
Sulfonylureas	Gliclazide Gliclazide Glyburide Glimepiride	Encourage the production of more insulin by the pancreas	A low blood sugar level, or hypoglycemia
Meglitinides	Nateglinide Repaglinide	Increase the pancreas's ability to produce insulin	Hypoglycemia, low blood sugar
Biguanides	Metformin	Reduce the liver's synthesis of glucose	Diarrhea, metallic aftertaste, nausea
Thiazolidinediones (TZD)	Pioglitazone Rosiglitazone	Boost body cells' sensitivity to insulin and decrease the	Increased risk of bladder cancer, weight gain, swelling

		liver's synthesis of glucose	from water retention
Alpha- glucosidases inhibitor	Acarbose Voglibose	Reduce the rate at which ingested sugar or carbs are absorbed	Bloating and flatulence
Dipeptidyl-peptidase-4 (DPP- 4) inhibitors	Linagliptin Sitagliptin Sitagliptin Alogliptin	Improve the impact of intestinal hormones that regulate blood sugar levels	Pharyngitis, headache
Glucagon-like peptide-1 (GLP-1) agonist	Exenatide Liraglutide Dulaglutide	mimic the actions of specific intestinal hormone that regulate blood sugar levels.	Nausea, diarrhea, vomiting
Sodium glucose cotransporter2 (SGLT2) inhibitors	Canagliflozin Dapagliflozin Empagliflozin	aid in the removal of glucose from the urine	Urinary tract and genital diseases, increased frequency of urination

## Innovative Agents Under Development

### Amylin/GLP-1 dual receptor agonists

In response to dietary intake, beta cells co-secrete the pancreatic islet cell hormone amylin along with insulin. It delays the emptying of the stomach and inhibits postprandial glucagon. Cagrilintide is a weekly, long-acting analogue of amylin that is injected beneath the skin. It can be used both alone and in conjunction by semaglutide, a long-acting GLP-1 RA.

### GIP/glucagon/GLP-1 triple receptor agonists

The pancreatic islets' alpha cells emit the 29-amino-acid peptide glucagon, which promotes gluconeogenesis and glycogenolysis. The goal of T2D therapy is antagonism rather than agonism because the physiology of insulin raises blood glucose. Another study determines how insulin affects consumption of food, satiety, and consumption of energy. Retatrutide is an injectable multiple hormone agonist that acts on the GIP/GLP-1/glucagon receptor once every seven days. In a phase 2 study, participants had type 2 diabetes.

### Non-peptide glucagon-like peptide-1 (GLP-1) receptor agonist

Orforglipron, a member of the non-peptide GLP1-receptor agonist class, is one little drug used to treat type 2 diabetes. In developmental and early clinical studies, orforglipron shows an excellent oral absorption (20–40%) and pharmacological profile (29–49 hours of dose-dependent half-life). Type 2 diabetes are now being treated with the medication orforglipron.

### Once-weekly basal insulin analog

Although glycaemic control is the primary objective in the treatment of type 2 diabetes, new antidiabetic treatments lead to significant weight loss and organ protection. For people with type 2 diabetes, insulin is crucial in regulating blood glucose levels that are uncontrollable with traditional antidiabetic medications. Weekly basal insulin injections should

enhance individuals' quality of life, encourage adherence to therapy, and reduce clinical lethargy during the time as the potential of hypoglycemia remains low. Insulin icodex is a C20 fatty diacid side-chained acylated insulin analogue that binds to albumin strongly and reversibly, but it has a reduced selectivity for the insulin receptors and is less cleared by the insulin receptor.<sup>23</sup>

## Emerging Treatment Techniques

### Treatment with Oral Hypoglycemics Using Nanocarriers

Excellent uses of nanotechnology can be found in the creation of drug delivery systems (DDS). Most biological functions depend on nanoscale components like viruses and ribosomes.<sup>24</sup> Direct interactions between nanoparticles (NPs) and subcellular entities have the ability to trigger intracellular events. Because of their promising uses, therapeutic DDS based on nanocarriers is gaining more attention than traditional DDS. Consequently, a lower dosage can lessen the harmful effects of medications, while the same dosage can increase the effectiveness of the DDS. Additionally, nanocarriers exhibit external characteristics that can be adjusted for a range of therapeutic medicines and targeting methods.<sup>25</sup> Because pharmacological therapy has limits and nanocarriers (NPs) are superior in administration of drugs and imaging, researchers are very interested in using NPs to treat and maintain diabetes mellitus.<sup>26</sup>

The most widely used nano-based drug delivery systems in the treatment of diabetes mellitus include liposomes, polymer-based NPs, and artificial NPs. Nanocapsules, dendrimers, micelles, and nanospheres are among the several polymer-based NPs that have been proven to be effective drug transporters.<sup>27</sup>

### Liposomes

Liposomes are composed of a core of water and a lipid bilayer structure. A liposome that can transport

hydrophilic and hydrophobic drugs is created by the combination of the lipid bilayer and aqueous core. During storage, liposomes increase the solubility of medicines and stop chemical and biological deterioration.<sup>28-30</sup> Joshi *et al.* used a microfluidics-based production approach to load hydrophilic pharmaceuticals (metformin) and lipophilic medications (glipizide) in a single liposome ( $64 \pm 6$  nm). The release rate of both medications was greatly increased by co-delivery; in one hour, glipizide release increased from 3 to 12% while MET release increased from 35 to 65%. This was linked to glipizide's presence inside the tiny, highly curved lipid bilayers, which altered the lipids' packing density and boosted the drug's permeability throughout the liposomes. Synergistic activity is the outcome of these two characteristics, which lead to better and synchronised drug release.<sup>31</sup> Nevertheless, liposomes have many drawbacks, including limited biological and physical stability brought on by phospholipid hydrolysis, oxidation, fusion sedimentation, and aggregation. Additionally, liposomes can initiate complement process-based pseudo allergy and opsonise defence responses. Furthermore, the commercialisation of liposomes is limited by issues with sterilisation and large-scale manufacture.<sup>32,33</sup>

### Niosomes

Niosomes are bilayered, self-assembling nanostructures composed of non-ionic surfactants and cholesterol. A hydrophilic head orientated towards the aqueous solvent and a hydrophobic tail orientated away from the solvent make up the bilayered structure. Their distinct structure aids in the entrapment of hydrophilic medications within chemical medications and the water-based core within the lipid bilayer.<sup>34, 35</sup> Their prolonged drug release, which lowers dose frequency and toxicity, is their primary selling advantage. In one study, metformin-loaded niosomes reduced the BGL for just two to four hours while exhibiting prolonged hypoglycemic activity for six to eight hours when compared to MET solution. The hydrophobic phospholipid barriers of niosomes are responsible for the continuous drug release.<sup>36</sup>

### Micelles

Micelles are groups of amphiphilic molecules that can aid in the solubilisation of medications that are hydrophobic. Furthermore, when the attained concentration matches the critical micelle concentration (CMC), clusters may develop. Micelles stabilise the straightforward drug solution manufacturing procedure, and their molecular structure and assembly behaviour are clearly described.<sup>37,38</sup>

Over the past few decades, insulin delivery systems for the treatment of diabetes have been widely adopted. Polymeric micelles having dual reactivity to hydrogen peroxide (H<sub>2</sub>O<sub>2</sub>) and glucose were investigated by Liu *et al.* for insulin transmission. The poly (ethylene glycol)-block-poly (amino phenylboronic ester) (PEG-b-PAPBE) self-assembled the polymeric micelles, with the hydrophilic PEG acting as the shell and the hydrophobic PAPBE providing the micelles with dual sensitivity to

H<sub>2</sub>O<sub>2</sub> and glucose. After the integrated phenylboronic ester (PBE) was dissolved by H<sub>2</sub>O<sub>2</sub> and dissolved by glucose, the polymeric micelles broke apart and released insulin that was responsive to glucose. Insulin release was greatly enhanced by the co-encapsulation of glucose oxidase (GOx) in the micelles. The H<sub>2</sub>O<sub>2</sub> generated by the Gox-mediated catalytic oxidation of glucose hydrolysed the PBE. Insulin/GOx-co-loaded polymeric micelles injected subcutaneously into diabetic mice showed a better hypoglycemic impact *in vivo* than either free insulin or micelles carrying only insulin. With its dual glucose and H<sub>2</sub>O<sub>2</sub> tolerance, this polymeric micelle offered a promising avenue for the treatment of diabetes.<sup>39</sup>

### Nanoemulsion

A thermodynamically unstable nanosized emulsion, nanoemulsion (NE) differs from microemulsion.<sup>40</sup> Berberine (BBR)-loaded NE was created by Xu *et al.* to investigate the hypoglycemic potential of BBR in mice with STZ-induced diabetes. It was discovered that diabetic mice's BGL was three times lower in the BBR-loaded NE treatment group than in the BBR-only group. In order to increase the hypoglycemic potency of BBR for diabetes treatment, this novel NE provided a potent delivery vehicle.<sup>41</sup>

NE's potential for peptide oral delivery is yet in its infancy. In order to administer hydrophobically modified insulin (HM-insulin) orally, Santalices *et al.* created and thoroughly described NE. A hybrid system comprising NE and micelles that was designed showed 100% HM-insulin association efficiency. The nano system demonstrated satisfactory mucodiffusive behaviour in pig mucus and demonstrated high stability and miscibility in many biorelevant conditions.<sup>42</sup>

Abelmoschus esculentus, or okra, may have anti-diabetic properties. Djamil *et al.* prepared an okra extract (NOE) nanoemulsion and investigated its effects on mice with alloxan-induced diabetes mellitus. 35 male mice (*Mus musculus* L.) were split into seven groups: a normal control group that was not diabetic and six diabetic mouse categories untreated negative control, glibenclamide-treated positive control, and four different treatments with okra ethanol extract (OEE) at 200 and 400 mg/kg bw and NOE at 200 and 400 mg/kg bw. In mice with alloxan-induced hyperglycemia, NOE was more effective than OEE at lowering BGL. By enhancing the penetration of active chemicals into interstitial space, the NE may enhance the okra extract's antidiabetic efficacy by improving their transport and bioavailability.<sup>43</sup>

### Polymeric Nanoparticles

Nanoparticles (NPs) are nanoscopic, colloidal DDS with a length of 10–1000 nm. In reservoir systems, the phrase "nanocapsule" or "matrix system" describes polymeric nanoparticles (NP) in which the drug is enclosed by a polymer film and contained within a cavity, whereas the term "nanosphere" describes the drug that is dispersed throughout all of the particles.<sup>44</sup> This results in a lower dosage and less harmful effects of

the medication on cells that are not the intended target. By using NP, targeted or smart DDS reduces harmful effects, increases drug concentration in the localised area, and promotes a quick commencement of action.<sup>45</sup>

NPs made of polylactic acid (PLA), a biodegradable and biocompatible polymer, are frequently used to administer drugs orally for the treatment of diabetes-related issues.<sup>46</sup> Notwithstanding the many intriguing aspects, there are some toxicity issues with NPs. Unintentional inhalation of NPs can cause them to build up in various human organs, particularly the lungs. For example, NPs that are deposited in the tubercular system may result in oxidative stress-related inflammatory responses. By direct absorption or olfactory receptors across the blood-brain barrier, they can also enter the central nervous system by inhalation.<sup>47</sup> In addition to their harmful effects, NPs have a short shelf life, unstable stability, and expensive production costs.<sup>48</sup>

### Solid Lipid Nanoparticles

Solid lipid nanoparticles, colloidal carriers composed of solid fats such as high melting fat matrix with a nanosize (50–1000 nm), can improve drug bioavailability and solubility.<sup>49</sup> Anchan *et al.* investigated the possibility of using chitosan-coated, insulin-loaded SLN for consumption as a viable alternative to subcutaneous injection.<sup>50</sup>

### Dendrimers

Dendrimers are tree-like, three-dimensional (3D) formations that are uniform and well defined. Dendrimers have received a lot of interest as a means of achieving controlled medication delivery. The chemical structure of dendrimers is more diverse than that of polyester dendrimers, poly (etherhydroxylamine) (PEHAM), poly (propylene imine) (PPI), poly(amidoamine) (PAMAM), and poly(L-lysine) (PLL).<sup>51</sup>

### Carbon Nanotubes

The physicochemical characteristics of carbon nanotubes (CNTs) have made them a promising DDS. To investigate the CNTs' potential in medicine, they can be functionalised with a variety of therapeutically active compounds. Functionalised carbon nanotubes (f-CNTs) have been shown to have antidiabetic properties by Zaman *et al.*<sup>52</sup>

### Immunological Approach<sup>53</sup>

Immunological therapy has become very popular these days for the treatment of diabetes, particularly type 1 diabetes. The two immunological techniques that are typically used are antigen-specific and non-antigen-specific. The most often used immunomodulatory medications that are gaining popularity are cyclosporine A, cytotoxic T cells, anti-CD3 cells, anti-thymocyte globulin, insulin, heat shock protein, anti-TNF, glutamic acid decarboxylase, and mycophenolate mofetil.

### Cyclosporin A (CsA)

Its significant immune-suppressive action against type 1 diabetes has made cyclosporine A (calcineurin

inhibitor) one of the first and most important immunosuppressive medications. It works by interfering with the signal transduction that the TCR (T cell receptors) mediates. This stops T cell activation and, as a result, helper T cells secrete less IL-2.

Regulatory T cells, or Tregs, have demonstrated promise as a potential treatment strategy in the setting of type 1 diabetes (T1D). Through the suppression of overactive immune responses and the prevention of autoimmune reactions, Tregs are essential for preserving immunological homeostasis. To maintain beta cell function, Tregs may play a role in modulating the immune response.

### Rituximab

Monoclonal antibodies aimed at the outermost marker B-lymphocyte antigen-CD-20, which is produced by both immature and mature B cells, are examples of antigen-specific immunomodulatory drugs. In a recent phase II study, people with type 1 diabetes had their  $\beta$  cell patency monitored with rituximab.

### Anti-TNF- $\alpha$

The most common usage of these substances is as treatments for rheumatoid arthritis and other chronic inflammatory autoimmune diseases. Nevertheless, a double-blind study employing etanercept (anti-TNF- $\alpha$ ) revealed that reducing the amount of insulin needed in children promotes the growth of pancreatic  $\beta$  cells. But more recently, it was also noted that anti-TNF- $\alpha$  reduces the progression and development of DM by binding to the TNF- $\alpha$  receptor. These substances have been shown to have the ability to deactivate T lymphocytes, which will prevent pancreatic  $\beta$  cells from undergoing apoptosis.

### GAD-65 (Glutamic Acid Decarboxylase 65)

GAD65 peptides administered intranasally to NOD mice produced a Th2 cell response that prevents autoreactive Th1 responses from developing spontaneously and  $\beta$  cell autoimmunity from progressing in NOD animals. As a result, the incidence of T1DM and pancreatic apoptosis is decreased.

### Insulin Secretagogues (TAK-875)

The surface receptor known as G-protein-coupled receptor-40 (GpcR-40) is most highly expressed in pancreatic  $\beta$  cells. Insulin secretion is stimulated when fatty acids or synthetic ligands activate GpcR-40, but only when there is an increase in glucose levels. Recent additions to the class of new medications include TAK-875, which acts on GpcR-40 to cause hypoglycemia and raise the insulinogenic index in diabetic individuals.

### Conclusion

Diabetes mellitus care is changing quickly due to the pressing need to address the chronic disease's rising prevalence and related consequences. Despite their effectiveness, traditional treatment methods frequently fail to provide the best glycaemic control and patient adherence. The incorporation of innovative therapeutic approaches, such as immunological therapy and delivery

systems for medicines based on nanotechnology, presents encouraging opportunities to improve patient outcomes and treatment efficacy. These novel techniques not only attempt to enhance glycemic control but also focus on minimising the risk of complications and boosting the quality of life for those living with diabetes. Continued research and development in this sector are required to fully realize the potential of these developing medicines, ultimately leading to more effective and individualised diabetes control techniques.

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