

Precision Medicine Approaches in Diabetes Management: Targeting Individualized Pathways

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Abstract

This article primarily focuses on novel approaches for managing diabetes, with a particular emphasis on type 2 diabetes. Insulin- and glucagon-secretagogue-stimulating peptide-1 (GLP-1) is an essential element of incretin-based therapies. Its function is contingent upon the levels of glucose in the body. Incretin-based treatments consist of orally active dipeptidyl peptidase-IV inhibitors and injectable GLP-1 receptor agonists. The main objective of current treatments for DM is to achieve glycemic control. However, this strategy overlooks other pathogenic variables that have a role in treatment failure and the development of the illness. Moreover, the existing anti-diabetic drugs now in use have a range of adverse effects with prolonged use. Consequently, researchers will continue to actively seek novel approaches to address DM. Diverse research conducted globally has proposed novel therapy techniques that target various and alternative pathogenic hotspots associated with DM. This review article aims to examine novel therapy options that have significant potential for transforming these revolutionary candidate drugs into effective therapies for DM. It will offer compelling evidence of their safety and assess the associated adverse effects.

Keywords: diabetes, treatment, nanotechnology, gene therapy, statin

Introduction

With its prevalence quickly increasing to epidemic proportions, type 2 diabetes mellitus presents a severe threat to the health of the general population. By the year 2030, it is anticipated that more than 360 million people all over the globe will be affected with type 2 diabetes. This information comes from the Globe Health Organization (WHO) [1]. Without a doubt, diabetes and the effects of the disease will put a strain on the resources available for public health. Over sixty percent of patients are unable to achieve the required glycated hemoglobin (HbA1C) level of seven percent or

below, even though there are various drugs available to treat diabetes. Factors contributing to this phenomenon include nonadherence, adverse reactions to therapies, apprehension about hypoglycemia, weight increase, and challenges in adjusting the dosage of antidiabetic medications, and the imposition of increasingly rigorous HbA1C goals by healthcare institutions, which often undergo modifications [2]. These clinical constraints need the development of additional therapeutic techniques that are capable of successfully addressing them. Sulfonylureas, which are known to stimulate insulin release from pancreatic islets, biguanides, which are known to decrease hepatic glucose production, peroxisome proliferator-activated receptor- γ (PPAR γ) agonists, which are known to enhance insulin action, and α -glucosidase inhibitors, which are known to hinder glucose absorption in the gut, are the primary drug classes that are utilized for the treatment of hyperglycemia [3]. It is possible to employ these pharmacological categories on their own or in combination with other hypoglycemic drugs. The use of conventional drugs, which were discussed earlier, is linked to several significant drawbacks, such as severe hypoglycemia, weight gain, decreased therapeutic efficacy as a result of an improper or ineffective dosage regimen, low potency, altered side effects brought on by drug metabolism and a lack of target specificity, as well as problems with solubility and permeability [4]. Although there have been breakthroughs in anti-hyperglycemic drugs, the primary challenges in providing successful diabetes treatment include the need to improve the treatments that are now available to guarantee optimum and balanced glucose levels while also minimizing the long-term repercussions that are inherently connected with diabetes [5]. Here we discuss some therapeutic approaches that counter the diabetics.

Insulin secretagogues

These drugs, in particular sulfonylureas and metiglinides, work by increasing the amount of insulin that is produced by the pancreas. They do this by

establishing a connection with the sulfonylurea receptor (SUR) of the ATP-sensitive potassium channel that is situated on the β cells of the pancreas. Tolbutamide, chlorpropamide, tolazamide, and acetohexamide are the four medications that make up the first generation of sulfonylurea medications. Glibenclamide, Glipizide, and Glimepiride are the three medications that make up the second generation [6]. The second generation of sulfonylurea was developed as a result of the need for higher potency, a speedier onset of action, shorter plasma half-lives, and a longer period of activity. These requirements were driving forces behind the development of the drug. Sulfonylurea exposure may result in a number of adverse consequences, one of the most prevalent of which is the emergence of symptoms that signal low blood sugar levels. Anxiety, confusion, perspiration, and dizziness are some of the symptoms that may be experienced. There are a number of other symptoms that may be connected with this disorder. Some of these include a loss of appetite, an increase in body mass, a sensitivity to the skin, discomfort in the gastrointestinal system, and the appearance of urine that is black in colour [7].

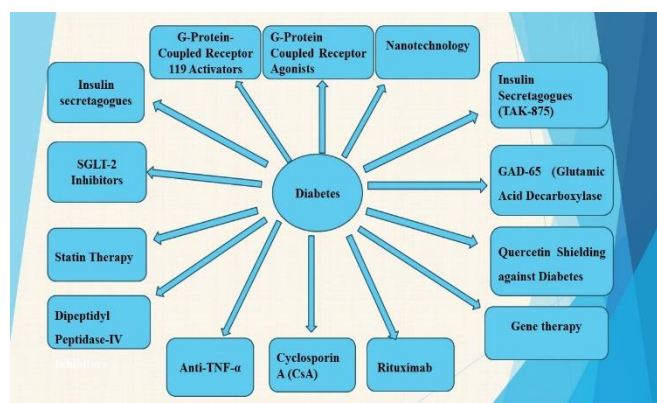


Figure 1: Different therapeutics for the management of diabetics

Statin Therapy

Statins are considered to be among the most cutting-edge medical tools in the battle against diabetes and in the treatment of the disease. The category of pharmaceuticals that are referred to as 3-hydroxy-3-methyl-glutaryl-coenzyme. For example, statins are considered reductase inhibitors. Among the well-known benefits of statins is the ability to filter out low-density lipoprotein (LDL), which in turn reduces blood levels and assists in maintaining the strength of their blood vessels. Following this, they provide the twin advantage of lowering the risk of diabetic ketoacidosis and decreasing the likelihood of developing cardiovascular disease (CVD), which is the most visible and significant consequence of type 2 diabetes [8]. These well-known lipid-lowering vehicles bring about a reduction in cholesterol levels by obstructing the pathway that ultimately leads to the formation of cholesterol and by converting HMG-CoA into mevalonic acids [9]. Importantly, a clinical investigation that included 6,000 patients who were using statins discovered that these medications prevent angiopathy in diabetic patients by acting on the lipolytic pathway. As a consequence, these medications have a therapeutic benefit because they

preserve the integrity of the microvascular system [10]. On the other hand, chronic use was associated with myositis, liver problems, and renal difficulties. In a substantial body of research, the anti-diabetic potential of statins has been shown on several occasions. There is a significant reduction in the possibility of cellular and subcellular damage brought on by hyperglycemia when the levels of LDL cholesterol are effectively reduced by medications belonging to this class. Statins, on the other hand, have been linked to an increased risk of developing type 2 diabetes, which has caused some individuals to express concern [11]. For those who use statins, there is some evidence to suggest that they have a somewhat elevated risk of developing diabetes. Numerous large-scale studies, like JUPITER (Justification for the Use of Statins in Prevention: An Intervention Trial Evaluating Rosuvastatin) and meta-analyses, have provided evidence in support of this assertion.

Dipeptidyl Peptidase-IV Inhibitors

DPP-4 inhibitors that are taken orally were included in the treatment plan for type 2 diabetes during the year 2006. These pharmaceuticals slow down the process of the incretin hormone GLP-1 being broken down and rendered inactive. DPP-4 inhibitors may be classified into two distinct classes, each of which has a molecular structure that is distinct from the other. 'Peptidergic' DPP-4 inhibitors, such as saxagliptin, Onglyza®, manufactured by AstraZeneca Pharmaceuticals; sitagliptin, manufactured by MSD Pharmaceuticals; and vildagliptin, manufactured by Novartis Pharmaceuticals, are included in one category. DPP-4 inhibitors having a 'xanthine' structure are included in the other class [11]. Examples of these inhibitors are linagliptin, Trajenta®, manufactured by Boehringer Ingelheim Pharmaceuticals, and alogliptin, manufactured by Takeda and Furiex Pharmaceuticals (see an illustration of this in figure 4). You may be able to find a variety of DPP-4 inhibitors in your region. As a result of the fact that all DPP-4 inhibitors are able to effectively block DPP-4 by 80 to 90 percent, the amount of endogenous GLP-1 that is produced after a meal rises by a factor of two to three [12]. This multimodal action, which starts with an increase in GLP-1 and continues with stimulation of glucose-dependent pathways and inhibition of glucagon production, is responsible for mediating the effects that are supposed to be achieved on glucose reduction. DPP-4 inhibitors have a local impact on the intestinal mucosa by inhibiting the breakdown of rapidly produced GLP-1. This is in addition to the systemic humoral or "endocrine" effects that they have. At that location, elevated levels of GLP-1 stimulate the afferent autonomic nerve fibres that regulate the postprandial stage of metabolism [13]. There is a low probability that DPP-4 inhibitors are the cause of hypoglycemia. Each and every one of the DPP-4 inhibitors has an unrivalled level of specificity, and they do not have any impact whatsoever on the activity of any other peptidases or members of the dipeptidyl peptidase community. Because of their pharmacological features, all of these inhibitors, with the exception of vildagliptin, allow for a regular dose to be taken once daily without the need for any modifications to the dosage. This effectively inhibits DPP-4 for a period of twenty-four hours [14].

Quercetin Shielding against Diabetes

There are many different foods that include flavonoids, such as quercetin. Some of these foods include berries, onions, seeds, nuts, barks, tea, flowers, leaves, brassica vegetables, and flowers. It has recently been shown via research conducted in the area of pharmacology that quercetin has biological properties that are pertinent to human health. Protection against cardiovascular disease, allergies, cancer, ulcers, inflammation, diabetes, and the development of cataracts are some of the properties that are included in this category [15]. One of the mechanisms by which quercetin acts as an antioxidant by inhibiting xanthine oxidase is not yet fully understood. It is believed that the presence of the sugar moiety in quercetin is the cause of its decreased oral bioavailability, which is the principal obstacle that prevents its utilisation. As more time passes, it becomes

more and more obvious that quercetin decreases the difficulties associated with diabetes by working on a variety of signal pathways [16]. Following oral administration of different quercetin doses to streptozotocin (STZ) and alloxan-induced diabetic rats, both the levels of glycosylated haemoglobin (HbA1C) and blood glucose were shown to be lowered. The therapeutic mechanism was assumed to be owing to quercetin's capacity to regenerate the islet of Langerhans, which in turn elevated serum insulin levels and promoted insulin release. This was shown in a diabetic rat model, where quercetin was administered orally and resulted in a considerable reduction in blood glucose levels [17].

Table 1: Summary of Drug Mechanisms, Advantages, and Side-effects for Diabetes Management

Drugs	Mechanism of action	Advantages	Side-Effects	Reference
Biguanides	Metformin alters cell energy metabolism. Metformin lowers glucose via inhibiting hepatic gluconeogenesis and reducing glucagon.	Biguanides are anti-hypertriglyceridemia, Vaso protective,	Gastrointestinal Distress, Such As Diarrhea, Cramps and Nausea	[18]
Insulin Sensitizers or Peroxisome Proliferator Activated Receptor agonists (PPARs).	PPAR γ agonists may decrease inflammation and oxidative stress, possibly via mitochondrial protection.	PPAR γ activation improves the absorption of glucose by skeletal muscle.	Edema, Weight Gain, Macular Edema and Heart Failure	
Alpha-glucosidase inhibitors (AGIs)	Anti-gastric-reflux (AGI) medicines divert undigested carbohydrate to the colon and small intestine, delaying GI absorption.	Reduce the blood glucose after meal	Bloating, Flatulence and Gastrointestinal Irritation	[19]
Insulin secretagogues	Drugs like sulfonylureas and metglinides increase insulin release by binding to the SUR of ATP-sensitive potassium channels on pancreatic β cells.	lower blood glucose level	Such As Dizziness, Sweating, Confusion and Nervousness	
Amylin analogues	Many ways to maintain glucose homeostasis. Delaying stomach emptying, preventing post-meal glucagon release, and controlling appetite to minimise food intake and weight gain	keeps blood glucose levels steady while fasting and after eating.	Vomiting, Headache and Hypoglycemia	[20]
Incretin mimetics (GLP-1 agonists and DPP-IV inhibitors)	GLP-1 works similarly to insulin in pancreatic beta cells. GLP-1 increases insulin release in pancreatic β cells. ATP-sensitive potassium channels shut and membranes depolarize during intestinal L cell glucose metabolism, letting calcium ions in.	(GLP-1RAs) improve glycaemic control with a low risk of hypoglycaemia	Diarrhoea, Nausea, Vomiting, Headaches, Dizziness	
Sodium glucose co-transporter 2 antagonists/ inhibitors	In PCT, SGLT2 inhibition decreases glucose reabsorption and increases urine glucose excretion. When urine excretes glucose, blood glucose and glycaemic indicators stay steady.	Improves A1C levels, reduces blood pressure	SGLT2 Inhibitors May Sometimes Cause Diabetic Ketoacidosis.	

Cyclosporin A (CsA)

One of the first and most prominent immunosuppressant drugs was cyclosporine A, more often known as a calcineurin inhibitor. The substantial immune suppressive impact it exerts against type 1 diabetes may be associated with this connection. How it does this is by preventing TCR-mediated signal transduction, which in turn stops T cell activation and, ultimately, reduces IL-2 secretion by helper T cells [21]. However, there are a few of downsides to treating individuals with type 1 diabetes with long-term medicine, including the high expense and significant harm to pancreatic β cells [22].

Tregs, or regulatory T cells: In the context of type 1 diabetes (T1D), regulatory T cells (Tregs) have shown promise as useful therapeutic agents. An important part of regulatory T cells' (Tregs) job is to keep the immune system from getting out of hand by reducing overreactions and autoimmune reactions [23]. The immune response may be better managed with the help of regulatory T cells (Tregs), which help keep beta cells functioning. Some authors have even suggested a therapeutic vaccination to combat type 1 diabetes, and the role of regulatory T cells (Tregs) has come under scrutiny. Similarly, CD4+ CD25+ CD127- Tregs promote pancreatic islet survival.

Rituximab

Antigen-CD-20 is a surface marker that is present on both immature and mature B lymphocytes. Antigen-specific immunomodulatory medicines, such as monoclonal antibodies, have the potential to target this surface marker [24]. The use of rituximab in a phase II trial was recently conducted with the purpose of monitoring the patency of β cells in individuals who have type 1 diabetes. There were a total of 87 individuals with type 1 diabetes who received four doses of the medication on a weekly basis. At the end of the year, it was observed that the average C-peptide AUC (area under the curve) seemed to be greater than the one that was seen in the placebo group [25].

Anti-TNF- α

When it comes to the use of these drugs as therapies, the most common indications for their use are rheumatoid arthritis and other chronic inflammatory autoimmune disorders [26]. Despite this, a research conducted using etanercept, an anti-TNF- α , shown that decreasing the insulin dose required for children is beneficial in promoting the proliferation of pancreatic β cells. The study was conducted in a double-blind fashion. In spite of this, recent research has shown that the anti-TNF- α binds to the TNF- α receptor, therefore inhibiting the progression and development of diabetes mellitus (DM) [27]. Because these medications possess the capability to deactivate T lymphocytes, they have the potential to block the process of apoptosis that occurs in pancreatic β cells.

Glutamic Acid Decarboxylase 65 (GAD-65)

The administration of a single intranasal dosage of GAD65 peptides to NOD mice generated a Th2 cell response, which was then used to reduce the incidence of pancreatic apoptosis and T1DM. The Th2 cell

response in NOD mice is responsible for preventing the spontaneous production of autoreactive Th1 responses and the progression of β cell autoimmunity [28].

Insulin Secretagogues (TAK-875)

The G protein-coupled receptor-40 (GpcR-40) is the most highly expressed surface receptor inside the pancreatic β cells. Fatty acids or synthetic ligands activate GpcR-40, which in turn increases insulin production, but only in the presence of a high glucose concentration [29]. Hypoglycemia and a significant rise in the insulinogenic index in diabetic individuals are caused by TAK-875, a relatively new class of novel medicines. Phase 2 randomized, double-blind, placebo- and active comparator-controlled 12-week trial ended after 10 weeks, despite the candidate chemical showing encouraging results [30]. The conclusion was taken due to the fact that the candidate drug was linked to hepatotoxicity when used persistently. But current preclinical and clinical investigations are exploring several GpcR-40 agonists as potential new diabetic treatments. GPR-119 agonists have shown promise as diabetic treatments due to their ability to increase insulin and incretin production via direct action on the β cell and enteroendocrine K- and L cells [31].

Sodium-Glucose Transporter-2 Inhibitors

The year 2012 was the year when a new category of medications known as sodium-glucose transporter (SGLT)-2 inhibitors were granted approval for the treatment of type 2 diabetes. Particularly in the proximal tubule of the kidney, epithelial cells are responsible for the expression of the sodium-glucose transporter SGLT-2 [32]. The renal glomeruli are responsible for the passive filtering of glucose, which most of the time is present in the primary filtrate. However, since glucose is such an important substrate for the body, efforts have been made over the course of evolution to find ways to keep it stable. Because of this, the SGLTs, which are mostly located in the kidneys and the intestines, are responsible for recycling glucose into the circulation. SGLT-1 is found in a significant amount in 10% of kidney tubular epithelial cells, but the SGLT-2 subtype is found in more than 90% of these cells. SGLT-1 in the intestines is much more prevalent [33].

In the nineteenth century, it was discovered that the alkaloid phlorizin, which is generated from the bark of the apple tree, had the potential to cause high levels of glucose in the urine. In the end, it was shown that phlorizin acts in a manner that is comparable to that of an inefficient SGLT inhibitor [34]. Unfortunately, phlorizin has not been further investigated as a potential therapy for diabetes because of its negative side effects, particularly diarrhoea, which may be attributed to the suppression of SGLT-1. The concept of inhibiting the reabsorption of glucose by the kidneys in order to enhance glycemic control in diabetics has lately garnered a lot of interest for three primary reasons: Increased glucosuria eliminates excess caloric equivalents, which results in a moderate loss of body weight; the reabsorption of filtered glucose from the proximal renal tubules is actually increased in diabetics in comparison to the non-diabetic state; and (1) increasing glucose disposal through the urine can reduce the glucose load in

diabetics and in people who have chronic glucose toxicity [35].

G-Protein-Coupled Receptor Agonists

Activators for G-Protein-Coupled Receptor 40 are accessible. A variety of dietary, hormonal, and pharmaceutical factors may modulate the glucose-dependent activation of insulin synthesis. Fatty acids increase insulin secretion via a number of pathways, including the synthesis of intracellular signalling molecules and the activation of receptors on the surface of cells. Research has shown that G-protein-coupled receptor (GPR) 40, also known as free fatty acid receptor 1, plays a role in the enhancement of insulin production by fatty acids. This receptor is now considered crucial. The primary mechanism by which GPR40 communicates is via Gαq/11. It raises intracellular calcium levels and activates phospholipases, which generate diacylglycerols and, ultimately, boost insulin production [36].

G-Protein-Coupled Receptor 119 Activators. In addition to other GPRs, there is evidence that GPR119 is involved in the process of mediating systemic metabolic homeostasis. Due to the fact that it has the ability to promote normoglycemia, the majority of the research that has been conducted on GPR119 has been on its potential as a therapeutic target for type 2 diabetes [37]. Prior research has shown that GPR119 increases glucose-stimulated insulin secretion and GLP-1 release, which lends credence to the notion that it may be able to improve the homeostasis of glucose levels throughout the body. On the other hand, emerging research suggests that these class of agonists can have an adverse effect on the muscle level. In the event that this occurs, metabolic diseases, such as type 2 diabetes, may have a more rapid beginning and development. As a consequence of this, further research is required in order to develop GPR119 receptor agonists into therapies that treat diabetes [38].

Gene therapy

Gene therapy is a potential new technique to treating diabetes mellitus. This treatment method works by effectively replacing or repairing the defective genes that are responsible for the condition [39]. This process includes the transfer of genes via the use of either a viral vector or a gene transfer approach that does not entail the use of viruses. The reduction of auto reactive T cells, which will ultimately prevent the death of islet cells, is the objective of this endeavor. Altering the insulin gene or performing this procedure as a prophylactic treatment are both viable options. Based on their capacity to proliferate in culture, stem cells have the potential to be used as surrogate β-cells in the treatment of diabetes, as shown by a research study. In addition, researchers have shown that mice who had stem cells transplanted had considerably reduced blood glucose levels after undergoing the transplant by intrahepatic injection [40]. Through the use of a fluorescent microscope, the histopathological examinations that include the sacrifice of mice show the dispersion of stem cells as green fluorescence. Brown staining, which was performed following staining with an anti-human insulin polyclonal antibody, was responsible for determining whether or not insulin was present [41].

Mesenchymal stem cells were proven to be capable of normalising blood glucose levels and producing human insulin after being subjected to testing for a period of forty-two days. A comparison was made between these mice and mice that did not get gene therapy. As a result, gene therapy shows promise as a potentially useful new approach to the treatment of diabetes mellitus [42].

Nanotechnology

Insulin injections, when provided in the usual manner for the treatment of type 1 and type 2 diabetes, are known to cause pain during the delivery process, infections after the injection, and results that are not favourable for the patient [43]. Because of this, the nanotarget strategy is being used in order to sidestep these issues. This approach is now highly trendy owing to the fact that it is favourable, specific, effective, and accurate. Nanotechnology has been used extensively in the treatment of diabetes mellitus (DM) due to the miniaturisation of glucose sensors and closed-loop insulin delivery devices. As a consequence of this, glucose sensors are an essential component of smart nanoparticles (NPs) as a method of administering medication [44]. These sensors are helpful in determining the amounts of glucose in the blood, which in turn increases the amount of insulin that is transported. Insulin has the ability to go through the minute pores that are present in the microcapsules of these bioengineered molecules. Researchers made the discovery that the compositions of these nanoparticles boosted the bioavailability of medications and made it possible to give maximum quantities of medications in a targeted manner [45]. However, due to the fact that they possess poisonous qualities and have the ability to expand to harmful dimensions, they pose a possible risk. A nanotechnology-based insulin delivery system that precisely targets pathogenic hotspots involved in the etiology of diabetes mellitus at low doses has been shown to enhance the pharmacokinetics of insulin while simultaneously reducing the intensity of its adverse effects. In addition, nanoparticles of mesoporous silica and quantum dots have been used in the development of glucose sensors that are very sensitive and selective [46]. In a similar vein, technologically advanced insulin delivery systems that make use of nanotechnology make it possible to release insulin that is responsive to glucose levels. There are several challenges that need to be conquered before clinical translation can take place in the area of nanotechnology for the management of diabetes. Some of these challenges include biocompatibility, long-term safety, and scaling limitations [47].

Stem Cell Therapy in diabetics

Some researchers in the field of stem cells have created therapies for type 1 diabetes by using stem cells to generate completely mature cells using this technique [48]. Because the pancreas is incapable of regeneration, it is of the utmost importance to acquire the particular kind and number of stem cells that are required to treat the problem. Pancreatic necrosis in mice was also found to be a probable location of pancreatic damage recovery when embryonic-like stem cells (VSELs) were administered intravenously (IV). This was shown by both the animals and the researchers [39].

Conclusion

Diabetes, a condition that has lately expanded to become an epidemic on a worldwide scale, is now causing a great number of individuals to struggle with the catastrophic repercussions of the illness. In the treatment of diabetes mellitus, the primary goal of all therapy is to get blood glucose levels as near as possible to normal levels. While the therapies that are now available for diabetes may only delay the progression of the condition and relieve its symptoms, they are not capable of curing the disease and come with a wide range of unwelcome side effects. The search for new compounds that might be used as a therapy for diabetes mellitus and the complications that come along with it is ongoing among scientists. In addition to this, they are looking for a treatment that would have the fewest possible adverse effects on the patient. When it comes to treating diabetes mellitus, insulin treatment is one of the standard approaches that has been used for a considerable amount of time.

Declarations

Ethical Consideration

No underlying data was collected or produced in this study.

Data Availability

N/A

Conflict of interest

The authors declared no conflict of interest.

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Author Contributions

The manuscript supervision and critical review was done by A.Z and S.M; introduction and certain other portion was written by N.A while S.T.V drafted the manuscript, drew tables and figure.

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