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A Review Study for the Treatment of Diabetes Using New Biotechnological Methods

Parinaz Shaqaqi[1*], Nastaran Shojaei-Barjoei[1]

[1]Department of Biology, Faculty of Basic Sciences, East Tehran Branch, Islamic Azad University, Tehran, Iran.

**Corresponding author: Parinaz Shaqaqi, Department of Biology, Faculty of Basic Sciences, East Tehran Branch, Islamic Azad University, Tehran, Iran. Email: p.shaghaghiiiiiiii@gmail.com.*

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Abstract:

A metabolic disease known as diabetes mellitus (DM) is brought on by a reduction in insulin production and activity. Nephropathy, retinopathy, and cardiovascular problems are among the pathological alterations that the body will unavoidably experience as the condition progresses. Type I DM and Type II DM are the two basic subtypes of DM. Oral hypoglycemics are used to treat type II diabetes, while insulin replacement treatment is often used to treat type I diabetes. Insulin secretagogues, biguanides, insulin sensitizers, alpha-glucosidase inhibitors, incretin mimetics, amylin antagonists, and sodium-glucose co-transporter-2 (SGLT2) inhibitors are the main medications used to treat type II diabetes. When first-line oral hypoglycemic medications are not as effective as monotherapy, dual-drug treatments are often advised for patients. Despite the significant therapeutic advantages, traditional dosage forms have a short half-life and varied bioavailability, which require frequent dosing and increased side effects. This may render treatment ineffective and result in patient non-compliance. With the extra benefit of site-specific medication delivery with increased bioavailability and a lower dose regimen, nanotechnology-based techniques are more alluring, given the pathological intricacy of the condition above. In this review study, we have attempted to examine the biology of type II diabetes, traditional treatment modalities (mono and combination therapy), and drug delivery methods based on nanotechnology.

INTRODUCTION

Diabetes is a prevalent chronic illness. The International Diabetes Federation reports that 463 million people worldwide had diabetes in 2019; by 2030, that number is expected to rise to 578 million individuals (1). Diabetes is a condition that is characterized by high blood glucose amounts; it is brought on by inadequate production of insulin or impaired insulin action (2). Type 2 diabetes is the most common type of diabetes, accounting for over 90% of cases (3). Persistently high blood glucose levels may lead to damage to the kidneys, eyes, cardiovascular system, nervous system, and other organs. Diabetes frequently leads to numerous complications, including diabetic nephropathy, diabetic neuropathy, and diabetic foot problems (4). These problems put human health in grave peril since they often result in blindness, incapacity, and even death (4).

A review of new diabetes treatments

Diabetes management has changed dramatically over the past few thousand years. The option preferred by the "experts" of the Egyptian pharaoh 3500 years ago was a mixture of "bird pond water," elderberry, ascites plant fiber, milk, beer, cucumber flowers, and green dates. Although our treatment options are significantly more effective today, if the current path of treatment development continues, they will likely be considered secret by our successors in the next 100 years. However, the current drug arsenal used to manage diabetes has resulted in a significant reduction in mortality (5).

Insulin

Before the 1920s, there were no effective drugs to manage diabetes; That is why type 1 diabetes is a disease. It was fatal. This changed dramatically with the work of Frederick Bunting. In addition to the formulation changes that later resulted in the structure

of insulin, countless improvements in the field of insulin delivery devices and Prescription ways have been done or are in progress, including better syringes, insulin Pulmonary, insulin pumps, and closed-loop insulin delivery systems. Insulin today Widely in patients with diabetes Type 1 or Type 2 is used and arguably the most effective and predictable (in most, but not all) cases of all current antihyperglycemic drugs (6).

Biguanids

French lilac or goat (officinalis Galega) was used as a folk medicine for diabetes in Eastern and Southern Europe in the Middle Ages. In the early 20th century, the antihyperglycemic part of this plant, guanidine, was isolated. Researchers Synthesized a guanidine compound called cynthalin in Germany and used it to treat diabetes in the 1920s. Hyguanidine homologs (e.g., cynthalin) were used for a short time but had hepatotoxicity, and the use of these compounds ended with the discovery and proliferation of insulin (7). However, in the following years, interest in biguanides increased again. In the 1960s and 1970s, phenformin was studied extensively in the United States, While Metformin was studied in France and Buforminder in Germany. Although phenformin and buformin were used clinically, their association with lactic acid led to their withdrawal from the market in most countries (8). Metformin was introduced as an antihyperglycemic agent in 1959 but was not approved in the United States until 1990. Today, metformin is the only clinically important biguanide and the most widely used antihyperglycemic agent in the world. The main mechanism of its effect is its ability to reduce hepatic glucose production, but also, through A slight increase in insulin-stimulated glucose uptake, lowers glucose. This drug is generally well tolerated and is usually accompanied by a significant reduction in A1C levels (~1.5%) (9).

Sulfonylureas

The history of sulfonylureas (Sus) began in 1937 with the observation of the hypoglycemic activity of synthetic sulfur compounds. Five years later, Marcel Janbon and his colleagues treated patients with the antibiotic amino sulfonamide isopropyl thiadiazole and observed hypoglycemia. In August 1946, Lobatieres confirmed that Aryl compounds of SU stimulate the release of insulin and, therefore, induce effects on some β-cell functions. In 1950, the first SU, tolbutamide, was marketed in Germany. Following this, other first-generation agents were chlorpropamide, acetohexamide and tolazamide. Further advances in the treatment of SU in the United States only occurred once the release of the more potent second-generation agent's glipizide and glyburide in 1984. These agents had been used in Europe for several years before this. The next SU agent, glimepiride, which is sometimes known as a third-generation agent, was released in 1995 (10).

Thiazolidinediones

Thiazolidinediones (TZDs), also known simply as "glitazones," were first introduced to the US market in 1996. These receptor-activating agents Γ are activated by peroxisome proliferators whose mechanism of action is to increase skeletal muscle insulin sensitivity and decrease it. Hepatic glucose production, these agents do not increase the risk of hypoglycaemia, and it has a more lasting effect than troglitazone, the only agent in this category that the FDA approved. With increasing use of troglitazone, specific liver failure was reported. By March 2000, the FDA had received reports of 63 cases of fatal liver failure in patients treated with troglitazone, and shortly after that, the drug was withdrawn from the market. Two other TZDs, pioglitazone and rosiglitazone, are currently on the market. Are they associated with non-hypoglycaemic problems? Both factors are associated with fluid retention and should be used in patients with congestive heart failure (11).

The heart should be used with caution. Pioglitazone has been shown to have a potentially beneficial effect on cardiovascular disease, but it is also associated with a possible increase in the incidence of bladder cancer. It was not α-glucosidase inhibitors A-glucosidases (AGIs) that have a local effect on Ruymerz applying the brush of the small intestine and They inhibit α-glucosidase enzymes (12).

They are saccharides and disaccharides. These enzymes include maltase, isomaltose, and glucoamylase, and they are sucrose. Control these systems. Enzyme effectively speeds up absorption. Carbohydrates reduce, but absorption does not change the absolute. Reduction results in Postprandial glucose level, with effect, it is moderate on fasting glucose. The FDA, which previously imposed restrictions on Rosiglitazone, began easing those restrictions in November 2013. Their change of position was based on the findings of the large Rosiglitazone Evaluated for Cardiovascular Outcomes and Blood Glucose Regulation in Diabetes (RECORD) study, which concluded that subjects treated with Rosiglitazone compared with patients treated with other antidiabetic drugs. There is no significance in A1C reduction between pioglitazone and rosiglitazone (13).

α-glucosidase inhibitors

α-glucosidases (AGIs) have a local effect on Ruymerz applying the brush of the small intestine, and they inhibit α-glucosidase enzymes. Responsible for the breakdown of oligosaccharides, they are saccharides and disaccharides. These enzymes include maltase,

isomaltase, glucoamylase, and sucrose (14).

Meglitinides

Meg Lytin Ida (the so-called "Glinides" are called) has the same mechanism of action as they have SU. This class of drugs irritates Insulin secretion from the pancreas and glucose levels. They reduce blood. The second generation has a faster onset and a shorter duration of action that requires multiple doses of glinides and can cause hypoglycemia. However, they do it at a slower rate than SUs. Decrease the A1C of glinides, which is generally between 1 and 5.1% sucrose (15).

Glucagon-like peptide-1

The idea of the "incretin effect" has been around for a long time. Budo, based on experimental data, shows that there is more insulin response with the administration of glucose ingestion than with an intravenous injection. Incretin pathway overview Insulin was identified in the 1980s. A key study evaluated the effect of native GLP-1 receptor agonists, all of which are administered subcutaneously. One of the benefits of treatment with incretin-based drugs is a 5.0% to 1% reduction in Treatments and 11.7 weight loss. However, these compounds can cause complications and create significant side effects in the digestive system, especially in early treatment (15).

4-DPP inhibitors

As mentioned above, researchers can develop 4-DPP inhibitors by turning on the incretin-insulin pathway. These factors can be taken orally, and the circulating half-life of incretin is too long. The first of these agents is not available in the United States. Sitagliptin was included in 2006, and after that, Saxagliptin and linagliptin were produced (16).

Pathophysiology of diabetes

Many hormones are responsible for maintaining the body's glucose homeostasis. However, glucose homeostasis is primarily regulated by two hormones, insulin and glucagon (16). β cells release insulin as the glucose concentration increases. Insulin lowers blood glucose levels either a) by preventing the liver from producing glucose via gluconeogenesis and glycogenolysis (17) or b) by promoting the liver, muscle, and adipose tissue to absorb glucose more readily.

When the amount of glucose is low, the pancreatic α cells produce glucagon. Glucagon works by: a) Counteracting the effects of insulin by promoting the liver's gluconeogenesis and glycogenolysis (18).

b) Plasma glucose levels are likewise raised by catecholamines, cortisol, and glucagon (18).

Amylin, a 37 amino acid peptide, glucagon-like peptide-1 (GLP-1), a 30 amino acid peptide, and glucose-dependent insulinotropic polypeptide (GIP), a 42 amino acid peptide, are additional hormones that contribute to the maintenance of normal glucose levels (18). Insulin and amylin are secreted together. It improves the absorption of glucose after a meal by reducing stomach emptying. The gut produces the peptides or incretins GLP and GIP. These incretins help the pancreatic β cells synthesize and secrete insulin (19). Neither the intestinal tract nor cells in need of energy can readily absorb glucose. Therefore, glucose transporters are responsible for distributing glucose to the cells. There are two categories for the family of membrane-bound glycoproteins known as glucose transporters.

- Sodium-glucose co-transporter (SGLT)
- Facilitative glucose transporter (GLUT)

There are two basic subtypes of diabetes mellitus, and the underlying causes of each are distinct (20).

•Type I diabetes (T1DM): In this condition, the immune system unintentionally targets the pancreatic β cells, where genes are essential.

•Type-II DM (T2DM): Genetics and lifestyle factors interact to cause this condition. Being overweight or obese raises the hazards involved.

Advanced treatment now includes new medication classes

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• Type-II DM (T2DM): Genetics and lifestyle factors interact to cause this condition. Being overweight or obese raises the hazards involved.

Alpha-glucosidase inhibitors (AGIs)

The two main enzymes in charge of the metabolism of carbohydrates are alpha-amylase and alpha-glucosidase (22). The alpha-glucosidase Oral anti-diabetic medications called AGIs are mostly used to treat type 2 diabetes. By relocating the undigested carbohydrates to the distal portion of the small intestine and colon, AGIs slow down the absorption of carbohydrates in the gastrointestinal system. Postprandial hyperglycaemia is reduced by this family of medications (23). AGIs are saccharides that work as competitive inhibitors of the small intestine's enzymes to slow down the breakdown of starch and other carbs. This causes glucose from meals to reach the circulation more slowly, which lowers postprandial hyperglycaemia. When used in conjunction with other diabetes medications, these medications help reduce post-meal blood sugar levels, which in turn lowers HbA1c (23).

They aid in increasing GLP-1 levels after meals, which postpones digestion and reduces appetite (60).

Bloating, flatulence, and gastrointestinal discomfort are common AGI side effects that may go away in a few weeks (24).

Alpha-glucosidase inhibitors are not advised for those with inflammatory bowel diseases such as Crohn's disease or ulcerative colitis, intestinal obstruction, intestinal digesting disorders, or diabetic ketoacidosis, a condition in which the body burns fat for energy rather than carbs (25). Acarbose is not advised for pregnant women, those with large intestinal ulcers, or those with liver cirrhosis.

Amylin analogues

The hormone amylin is made up of a single chain of 37 amino acids. It is co-secreted by the pancreatic β cells with insulin (25). It keeps blood glucose levels stable during fasting and after meals by delaying stomach emptying and inhibiting glucagon secretion. Adjusting the brain's appetite center controls how much food is consumed (25). Since both T1DM and T2DM lack amylin, research, and development of amylin analogs that preserve glucose homeostasis by any one of the following pathways were conducted.

i) Postponing stomach emptying ii) Preventing glucagon release after meals iii) Restricting food intake and weight gain by regulating appetite

Biochemical analogs that mimic amylin's effect were created since amylin aggregates and is insoluble in solution, making it unsuitable as a medication Amylin analogs may be administered parenterally to treat both type 1 and type 2 diabetes (25). This sort of molecule is given before meals and functions similarly to amylin. The available medication in this class is pramlintide acetate, which is marketed under the Symlin® brand and is given subcutaneously.

Amylin analogs most often cause headaches, nausea, vomiting, and hypoglycemia when used with insulin. Once the patient gets used to the drug, these adverse effects disappear (25).

Incretin mimetics (GLP-1 agonists and DPP-IV inhibitors)

The gut produces the incretins, or peptides, glucose-dependent insulinotropic polypeptide (GIP) and glucagon-like peptide (GLP). A class of naturally occurring metabolic hormones known as incretins promotes a drop in blood glucose levels (26). After a meal, several hormones are released. After a meal is introduced, the gut's L cells release a peptide called GLP-1, which is composed of 36 amino acids. GLP-1 secretion is comparable to insulin secretion from the pancreatic β cells (27). GLP-1 causes the pancreatic β cells to synthesize and secrete insulin. In intestinal L cells, the metabolism of carbohydrates results in the depolarization of the membrane and the closure of the ATP-sensitive potassium channel, which allows calcium ions (Ca2+) to enter. This results in GLP secretion. Dipeptidyl peptide-IV (DPP-IV) enzymes rapidly metabolize GLP-1, resulting in a half-life of around 1-2 minutes (28, 29). Therefore, one method for treating T1DM and T2DM may be the creation of GLP-1 analogs with longer half-lives. Once again, DPP-IV inhibitors exhibit incretin mimic behavior.

Sodium-glucose co-transporter 2 antagonists/ inhibitors

Facilitative glucose transporter (GLUT), a passive transporter, and sodium-glucose co-transporter (SGLT), an active co-transporter, are responsible for the reabsorption of glucose in the proximal convoluted tubule (PCT) (30).

By blocking the SGLT2 found in PCT, SGLT2 inhibitors stop glucose from being reabsorbed and increase its excretion in urine. The blood glucose level and other glycaemic indicators are maintained. In contrast, glucose is eliminated in the urine (31). Canagliflozin, Dapagliflozin, Empagliflozin, Ipragliflozin, Luseogliflozin, and Tofogliflozin are the compounds that currently fall within this group (31).

SGLT2 inhibitors may be administered alone, in conjunction with insulin, sulfonylureas, metformin, or thiazolidinediones, or as an adjuvant.

An innovative method of delivering antidiabetic medications for type 2 diabetes

Some drawbacks of traditional drug delivery methods include reduced potency or altered effects as a result of drug metabolism, lack of target specificity, and ineffectiveness owing to incorrect or inefficient doses (33). Because of its advantages in lowering the frequency of doses, improving bioavailability, preventing degradation in an acidic stomach environment, and providing tailored therapeutic effectiveness with fewer adverse effects, novel drug delivery systems, or NDDSs, have been a rapidly developing topic in recent years (34). Few NDDSs have been documented to treat type 2 diabetes, even though several are being studied for the treatment of other illnesses. They may be categorized as:

The first kind of particle system is the microparticulate system, followed by the nanoparticulate system.

Niosomes and Liposomes in the Vesicular System

Other: i) Drug delivery system that self-emulsifies (SNEDDS), ii) Transdermal medication administration

The particulate system is made up of tiny particles that may carry drugs into cells and are identified by certain receptors via ligand coupling. As a result, these systems are seen to be the best options for delivering medications that prevent diabetes (35).

Microparticle-based treatment allows for the controlled release of entrapped medications at the

Table 1. novel drug delivery of antidiabetic drug delivery for T2DM.

Type of delivery system	Class of drug	Drug	Polymer used	References
Niosome	insulin Secretagogues	Repaglinide	Span 60, cholesterol	40
Liposome	Incretin Mimetics	Glucagon-like peptide-1 (GLP-1)	Anionic liposomes Containing DSPEPG8G (10%), DPPC (27%), Cholesterol (36%) and DPPG (27%)	41
Polymeric Nanoparticles	Biguanides	Metformin	Chitosan-PLGA	42
Carbon Nanotubes	Biguanides	Metformin	---	43

desired location. Mechanisms control the drug's release rate to maintain its concentration in plasma. Because of their greater surface-to-volume ratio and smaller size, microparticles are used to improve the dissolving of insoluble medications. Receptor-mediated endocytosis is the transcellular transport mechanism for microparticulate systems. Because of their size, microparticles are unable to pass through the mucosal membrane's tight junctions and enter cells by paracellular transport; in contrast, nanoparticulate systems have greater intracellular absorption than microparticulate systems (36). The nanoparticles are divided into four categories: metallic, lipid-based, polymeric, and biological nanoparticles (NPs) (36). Drugs that are encapsulated in nanoparticles are delivered by both transcellular and paracellular pathways during cellular absorption (37). In addition, since the positively charged NPs interact electrostatically with the negatively charged mucus and endothelium layer to stay in the gastrointestinal system, they exhibit enhanced mucoadhesion. Sometimes, the mucous physically captures the NPs.

The transdermal delivery system (TDS) is an alternate method of medication administration to oral and parenteral routes. It is administrable, noninvasive, affordable, and patient-compliant. TDS may solve the issue of first-pass metabolism's premature drug metabolism (38). Using penetration enhancers, TDS may be a viable method for delivering hydrophilic medications, macromolecules, and vaccinations (39, 44). Table 1 shows several reports on innovative antidiabetic medication administration.

CONCLUSION

An ever-increasing number of people have diabetes as a result of the increasing incidence of obesity and sedentary lifestyles. This has led to a huge demand for anti-diabetic medications and increased investment by companies in research and development to create targeted formulations. Nanotechnology promises to introduce several real, revolutionary medicinal breakthroughs into our everyday lives. The development of nanoparticulate drug delivery systems for anti-diabetic medications has advanced significantly as a result of years of thorough nanoformulation research. The implementation of the most recent FDA rules for the regulation of these goods, together with long-term safety and ethical problems about nanoformulations, is necessary to facilitate the safety of said products and improve their effectiveness.

Longer-term glucose regulation may be possible with active targeting techniques that functionalize appropriate ligands or with combinatorial medication treatment that combines two or more antidiabetic medications. Such ongoing developments in nanotechnology provide promising opportunities for the creation of an effective treatment modality that lowers blood sugar levels in the near future.

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Authors' contributions

Conceptualization and writing the draft of manuscript Parinaz Shaqaqi, Nastaran Shojaei-Barjoei; All authors reviewed the manuscript.

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Availability of data and materials

The datasets analysed during the current study are available from the corresponding author upon reasonable request.

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Not applicable.

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