

REVIEW ARTICLE

ANALOGUES IN DIABETES MANAGEMENT: CURRENT AND FUTURE PROSPECTS

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ABSTRACT

Diabetes, Type 2 diabetes, is the biggest challenge for people all around the world. Time goes by, and it gets worse! It results in more health issues. Unfortunately, diabetes is a disease, and the typical treatments are not effective. Thus, there is a need to find methods to treat it. A type of medication that may be beneficial is a GLP-1 receptor agonist. These medicines help our bodies control blood sugar levels. When our blood sugar levels are too high, they help our bodies make insulin. They also help to reduce the amount of the hormone glucagon, which raises our blood sugar levels. These drugs also help to reduce the rate at which food is moved from the stomach to the intestine. They may help people feel fuller. Our bodies create GLP-1, which isn't long-lasting; however, these drugs are designed to be long-lasting. They are meant to remain in our bodies for a while. This review presents an overview of the GLP-1 receptor agents that we have today. It compares the way they work, the extent to which they work well and their safety. There are types of these medicines. Some work for a short period of time, some work for a long period of time. The GLP-1 receptor agonists are not only used for blood sugar control. They can also assist people in losing weight and in decreasing the risk of heart problems. There have been advancements in medicine that are altering the way diabetes is treated. We are finding ways to make medicines that're easier to

take. We are also finding medicines that can do more than one thing. We need to keep an eye out for side effects like stomach problems. We have to make sure GLP-1 receptor agonists are safe for people to take over time. We have to keep watching to see how GLP-1 receptor agonists work, if they are safe.

Keyword – Pharmacokinetics, GLP-1 receptor, Diabetes, incretin therapy, Pharmacology

INTRODUCTION

Diabetes mellitus is a disease that people have to live with over time. It gets worse slowly. Affects how the body handles food. This happens because the body does not make insulin, or it does not use insulin properly, or maybe a little bit of both. There are different kinds of diabetes mellitus, and one of them is called Type 2 diabetes mellitus. This type is the most common, and it is often linked to not being active, being overweight and having family members who have it. The number of people with diabetes is going up fast all around the world. This is causing a lot of problems for the people who take care of health. It means we really need to find new ways to treat diabetes that will work better and last longer. Diabetes mellitus is a concern, and diabetes mellitus needs to be taken seriously [1].

Doctors usually use medicine to help people with blood sugar levels. This includes insulin shots and special pills. The main goal of these treatments is to lower blood sugar levels. However, these treatments do not always work well to fix the complicated problems that cause Type 2 Diabetes. Type 2 Diabetes is caused by things, including problems with the cells in

the body that make insulin, problems with the way the body releases a hormone called glucagon, and problems with the way the body responds to special helpers called incretins. Moreover, Type 2 Diabetes treatments can have bad side effects, such as blood sugar, weight gain, and patients not taking their medicine as they should. This means that these treatments may not work well in the long run for people with Type 2 Diabetes [2-3].

People have been paying a lot of attention to the incretin system over the past few years. The incretin system is a deal because the incretin hormones, especially glucagon-like peptide-1, help keep our blood sugar levels in check. Glucagon-like peptide-1 does a lot of things. It helps our body make insulin when we need it. It also stops our body from making much glucagon. Glucagon-like peptide-1 slows down how fast our stomach empties. It helps us feel full. The incretin system and glucagon-like peptide-1 are really important. There is a problem with using glucagon-like peptide-1 to help people. The problem is that glucagon-like peptide-1 does not last long in our body. This is because an enzyme called dipeptidyl peptidase-4 breaks it down fast. The dipeptidyl peptidase-4 enzyme is the

reason why glucagon-like peptide-1 has a short half-life [4].

The GLP-1 receptor agonists, or GLP-1RA, have been changed to make them better. These changes help the GLP-1RA stay longer in the body and work more effectively. The GLP-1RAs are good at helping people control their blood sugar levels. The GLP-1RA also have benefits, such as helping people lose weight and protecting the heart. For people who need additional support for their metabolism and health, these traditional treatments do not always give them the help they need, which is why people can opt for the GLP-1RA, which will provide them with such support [5].

The clinical interest in GLP-1RAs is getting bigger. It is not all about

controlling diabetes. We are finding out that GLP-1RAs can also be used for obesity, heart disease and problems with the brain. This indicates that GLP-1RAs can have various applications for individuals. GLP-1RAs, such as those taken orally, have become more beneficial for doctors to prescribe and use. It has occurred in the past few years, and it's significant for GLP-1RAs [6].

The purpose of this article is to discuss the GLP-1 receptor agonists, their mechanism of action, clinical efficacy, safety profile and future therapeutic potential [7]. The global prevalence of diabetes continues to increase at an alarming rate, placing a substantial burden on healthcare systems worldwide. Figure 1. Represent the global burden and projected prevalence of diabetes mellitus worldwide [8-9].

Share of people with diabetes, 2024

The share of people aged 20-79 who have type I or type II diabetes. Diabetes is both a major chronic disease and a risk factor for complications such as cardiovascular and kidney disease.



Fig.1: Global burden and projected prevalence of diabetes mellitus worldwide.

MECHANISM OF ACTION OF GLP-1 RECEPTOR AGONISTS

GLP-1 Receptor Activation and Intracellular Signalling

The pharmacological action of glucagon-like peptide-1 (GLP-1) receptor agonists is mediated by the activation of the GLP-1 receptor, which is a type B G protein-coupled receptor in pancreatic β -cell, the gastrointestinal tract, and the central nervous system. The agonist binding causes the receptor to change its conformation, thus activating several intracellular signalling pathways that all work together to regulate glucose homeostasis [10].

One of the mechanisms is the stimulation of adenylate cyclase that leads to the elevation of intracellular levels of cyclic adenosine monophosphate (cAMP). The increase in cAMP activates the downstream effectors like protein kinase A

and exchange proteins that are directly stimulated by cAMP, and increases insulin granules release by pancreatic β -cells. Notably, such a process is still reliant on the levels of glucose in the ambient, thus restricting the chances of hypoglycemia [11].

Simultaneously, the activation of GLP-1 receptors has an effect on the phosphatidylinositol-3-kinase/Akt signal transduction that contributes to improvements in β -cell survival and alleviates apoptotic mechanisms. Further participation of the mitogen-activated protein kinase pathway helps in cellular growth, differentiation, and the maintenance of pancreatic functions. These signalling events, triggered by GLP-1 receptor agonists, not only motivate insulin release but also help maintain the integrity of the β -cell in the long run. Figure 2 depicts the mechanism of action of GLP-1 receptor agonists in glucose regulation and metabolic control [12-13].

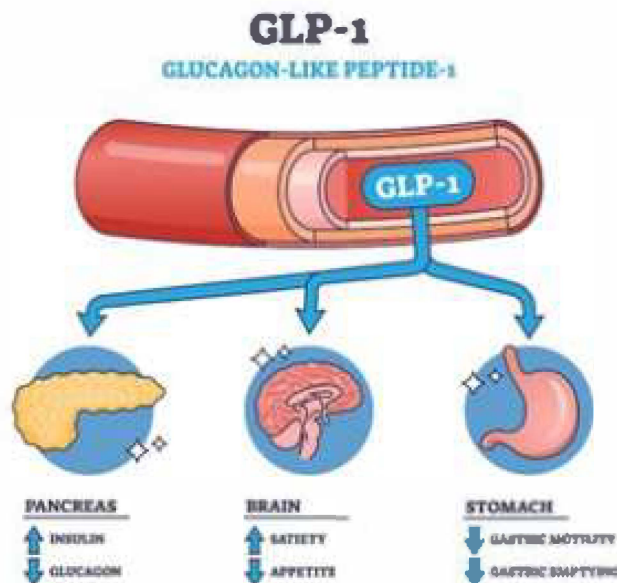


Fig 2: Mechanism of action of GLP-1 receptor agonists in glucose regulation and metabolic control.

Effects on Glucose Regulation and Energy Homeostasis

GLP-1 receptor agonists have been associated with clinical effectiveness because of their capacity to regulate a number of physiological processes at the same time.

GLP-1 receptor stimulation augments glucose-dependent hyperglycemic insulin release, so insulin release is augmented only in high-glucose situations. This is a mechanism which largely decreases the chances of hypoglycemic events in contrast to the conventional insulin secretagogues.

Besides insulintropic effects, these drugs inhibit the release of glucagon by pancreatic α -cells. Given that hepatic glucose production is activated by glucagon, its inhibition is involved in the better control of fasting and postprandial glucose.

The other notable impact is the retardation of gastric emptying, which slows down the speed of nutrient absorption and decreases the postprandial glucose spikes. This helps in creating a more stable glycemic profile during the day.

Central appetite-regulating pathways are also mediated by GLP-1 receptor agonists. They are able to induce satiety and decrease the volume of food taken by modifying the activity of hypothalamic signalling, resulting in clinically significant weight loss. This twin effect on

controlling body weight and glucose is a great benefit compared to most traditional treatments [14-16].

Comparison with Native GLP-1 and Advantages of Synthetic Analogues

Despite its very important physiological role, the therapeutic use of endogenous GLP-1 is hampered by its very short half-life, which is quickly broken down by an enzyme known as dipeptidyl peptidase-4. This quick inactivation limits its clinical application to the process of long-term glycemic regulation.

In order to eliminate this weakness, GLP-1 receptor agonists have been engineered to withstand the effects of enzymes and prolong their action. The amino acid substitution strategy, fatty acid conjugation to facilitate albumin binding, and fusion to larger protein structures have been used to increase molecular stability [17-18].

CURRENT GLP-1 RECEPTOR AGONISTS

GLP-1 receptor agonists are a major therapeutic category in the treatment of Type 2 diabetes mellitus, which has more than just glycemic control. These drugs have a more integrated metabolic effect, such as weight loss and cardiovascular risk alteration, unlike the traditional agents, which mainly target blood glucose levels. Currently available agents could be categorised into short-acting and long-acting formulations, with a specific pharmacological profile, based on their

duration of action [19-20].

Short-Acting GLP-1 Receptor Agonists

Agonists of GLP-1 receptors may be short-acting and have a shorter half-life in circulation. The agents are mostly given once or twice a day, and they have a strong influence on postprandial glucose levels.

Their main effects are due to slowing gastric emptying, which decreases the rate of glucose uptake after meals and decreases postprandial glycemic variability. They also cause insulin secretion and glucagon release suppression, but their short time span does not allow long-term effects on fasting glucose levels.

Short-acting agents could be especially helpful in patients with postprandial hyperglycemia as the first-line issue because of their properties. Nevertheless, the necessity of regular administration and the rather low effect on long-term glycemic indicators may influence patient compliance and the overall treatment efficacy [21].

Long-Acting GLP-1 Receptor Agonists

In order to address the shortcomings of short-acting formulations, long-acting GLP-1 receptor agonists have been created. These agents can be used once daily or once weekly due to structural changes that increase stability and systemic exposure.

In contrast to short-acting agents, long-acting formulations have a more prolonged influence on both the postprandial and the fasting glucose levels. Their sustained receptor activity results in better glycemic regulation in the long run, as seen in greater changes in the level of glycated haemoglobin.

Besides the regulation of glucose, long-acting GLP-1 receptor agonists have been shown to have much impact on body weight loss. This is highly explained by their effects on appetite control and energy consumption, and hence they are highly useful in patients who have obesity as a comorbid condition [22].

Dual and Multi-Receptor Agonists

People have made some progress with the design of agents that work on incretin pathways at the same time. This is what happens when we use agents that're a mix of GLP-1 and other metabolic hormones. These hormones work together to make the treatment better. The agents work by using pathways that help the body respond to insulin and balance energy. This means that the agents can lower blood glucose levels and help people lose weight more than if we just used one type of hormone. This new way of treating people is different from what we used to do. Now we do not just focus on one thing; we try to help the body in ways [23].

Comparative Clinical Considerations

The selection of a suitable GLP-1 receptor agonist will be influenced by factors, including the patient and the physician's objectives. When the main goal is to control blood sugar after meals, acting agents are usually the best choice. Long-acting GLP-1 receptor agonist formulations are often prescribed as they are easier to administer, more likely to be taken and have more whole-body effects. The combination of GLP-1 receptor agonist drugs that target both receptors is highly promising, particularly for people who need to lose a considerable amount of weight or maintain their blood sugar more closely. Doctors should be careful in using these drugs that stimulate the GLP-1 receptors. Consider each patient's response and the GLP-1 receptor agonist's safety [24-25].

CLINICAL BENEFITS AND THERAPEUTIC OUTCOMES

GLP-1 receptor agonists have been the subject of much interest because of their glucose-lowering properties and the metabolic and clinical benefits. These agents occur in contrast to traditional antidiabetic treatment, which mainly focuses on glycemic control, and have an effect on various physiological pathways, leading to a more complete therapeutic profile. An important advantage of using them in clinical practice is their beneficial effect on the glycemic parameters, weight and cardiovascular outcomes, and

therefore they should be incorporated into the modern management of diabetes [26].

Glycemic Control and HbA1c Effects.

Achieving sustained glycemic control is one of the key therapeutic benefits of GLP-1 receptor agonists. These agents increase the secretion of insulin in response to high glucose levels and also inhibit the secretion of glucagon, hence correcting the fasting and postprandial hyperglycemia.

The decrease in the level of glycated haemoglobin with the agents is an indicator of the long-term efficacy in the regulation of glucose. Notably, this is done without having to substantially raise the risk of hypoglycemia because their mechanism also relies on ambient glucose levels. This is a definite benefit compared to some of the more conventional treatment options that can cause glucose-independent insulin secretion.

The clinical practice shows that the extent of glycemic decrease differs according to the particular agent, dose, and treatment time. The long-acting formulations tend to show more consistent and pronounced effects since they have a prolonged receptor activity [27-29].

Impact on Body weight and Appetite regulation.

Besides glycemic control, GLP-1 receptor agonists have also been found to induce a uniform effect of weight loss, which is especially useful with patients with Type 2

diabetes who are usually overweight or obese. The effect is mainly mediated by central and peripheral mechanisms that control appetite and energy intake.

GLP-1 receptors in the hypothalamus increase the signal of satiety and decrease hunger after being activated, which results in a reduction of caloric intake. Moreover, the slow gastric emptying is a cause of protracted postprandial fullness. All this leads to a slow and long-term loss of weight.

Not all agents have the same degree of weight loss and some of the more recent formulations have shown stronger effects. This has seen the application of some GLP-1 receptor agonists as a treatment therapy in obesity management, even in non-diabetic individuals [30-32].

Cardiovascular Outcomes and Risk Reduction.

In addition to metabolic control, GLP-1 receptor agonists have demonstrated significant advantages in cardiovascular risk reduction, which is a significant issue in Type 2 diabetes patients. The results of substantial clinical studies suggest that some of the agents in this group are related to a decrease in major adverse cardiovascular events, such as myocardial infarction, stroke, and cardiovascular mortality.

These benefits have mechanisms that may be multifactorial. GLP-1 receptor agonists can also have anti-inflammatory properties, enhance endothelial functionality, and have a modest effect on blood pressure and lipid levels, in addition to enhancing glycemic control. All these actions contribute to their effectiveness in overall cardiovascular risk management.

Consequently, these agents are increasingly being viewed as agents of glucose control and cardioprotection, especially in patients with known cardiovascular disease or high risk [33].

Effects on Pancreatic Function and Disease Progression

Recent data indicate that GLP-1 receptor agonists also have a potential positive impact on the functioning of pancreatic β -cells. These agents can potentially preserve insulin-secreting capacity with ageing by minimising cellular stress and apoptotic events.

The better functioning of the β -cell can help to reduce the progression of Type 2 diabetes, which is a disease of progressive deterioration of endogenous insulin synthesis. Though these results are encouraging, the clinical implications of β -cell preservation over the long-term in humans are a subject of ongoing research [34].

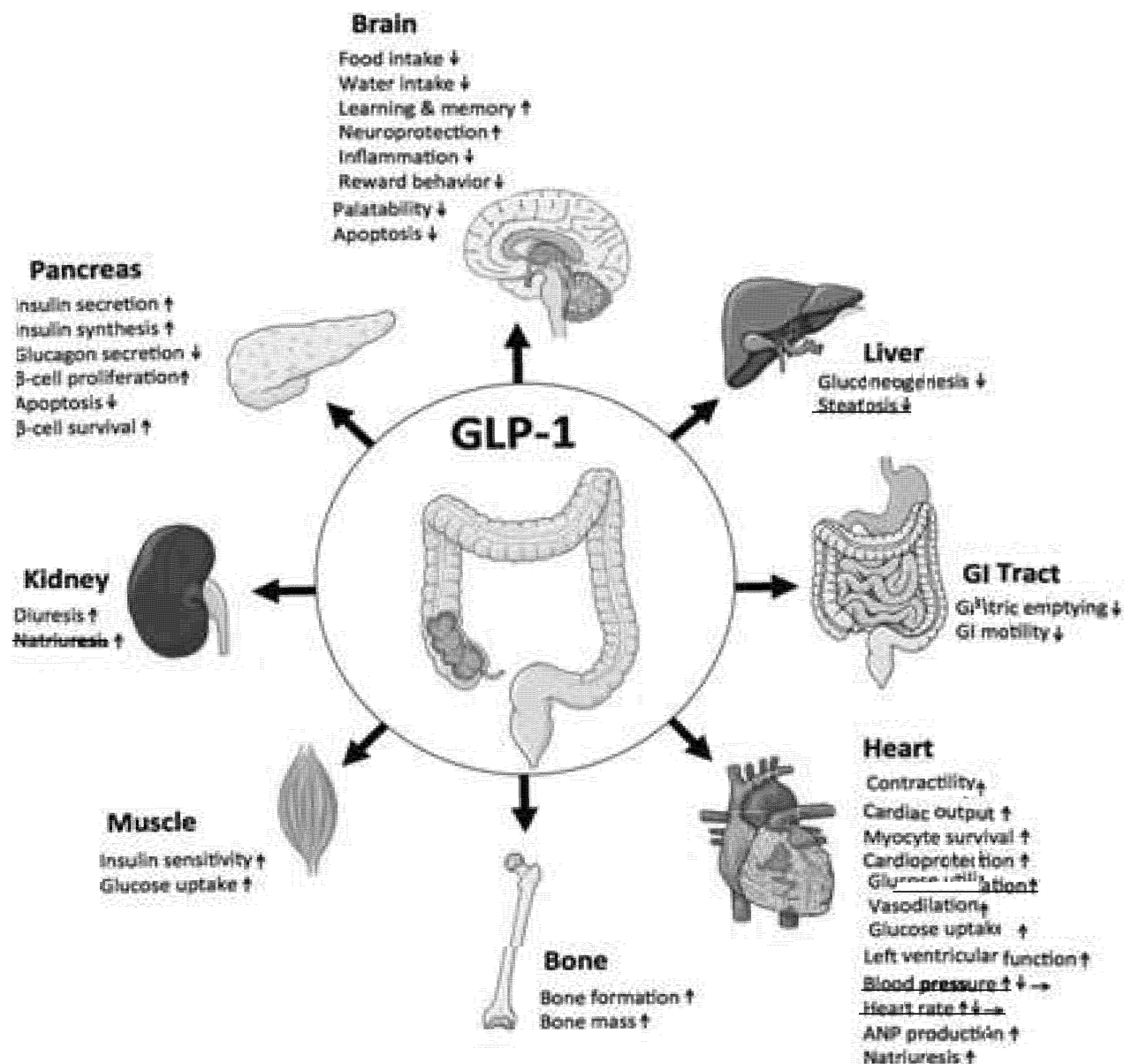


Fig 3: Key clinical benefits of GLP-1 receptor agonists in metabolic disease management.

SIDE EFFECTS AND SAFETY CONCERNS.

GLP-1 receptor agonists are tolerable and considered safe during long-term interventions in Type 2 diabetes management. Nevertheless, like all

medications, their use is connected with some side effects that are to be taken into account and closely observed during the choice of therapy and patient observation. These aspects of safety need to be understood on a balanced level to maximise clinical outcomes [35-37].

Table 1. Adverse Effects and Safety Profile of GLP-1 Receptor Agonists.

Category	Adverse Effect / Concern	Description	Clinical Considerations
Gastrointestinal Effects	Nausea, vomiting, diarrhea	Most commonly reported adverse effects, especially during treatment initiation	Usually transient and dose-dependent; gradual dose escalation improves tolerability
Gastrointestinal Effects	Abdominal discomfort	May occur due to delayed gastric emptying	Typically mild; rarely requires discontinuation
Pancreatic Safety	Acute pancreatitis (suspected)	Early reports suggested a possible association	No definitive causal link established; use caution in patients with prior pancreatitis
Pancreatic Safety	Pancreatic cancer (debated)	Concerns raised in observational studies	Current evidence is inconclusive; long-term monitoring is recommended
Endocrine Safety	Medullary thyroid carcinoma (MTC) risk	Observed in animal studies but not confirmed in humans	Contraindicated in patients with a history of MTC or MEN2
Metabolic Effects	Hypoglycemia (low risk)	Rare when used alone due to glucose-dependent action	Risk increases when combined with insulin or sulfonylureas
Immunogenicity	Anti-drug antibody formation	Possible due to the peptide nature of drugs	Generally does not affect efficacy significantly
General Tolerability	Injection-site reactions	Mild irritation or discomfort at the injection site	Usually self-limiting
Long-Term Safety	Unknown rare adverse effects	Limited long-term data for newer agents	Requires ongoing surveillance and post-marketing studies

EMERGING AND NEXT-GENERATION GLP-1 RECEPTOR AGONISTS

There is a rapid development in the therapeutic landscape of GLP-1 receptor agonists, which is necessitated by the need to enhance efficacy, convenience and long-term outcomes for patients. Although the currently existing agents have shown significant clinical advantages, there is continuous study on how to overcome the current weaknesses of these drugs, which include injectable delivery, unreliable effectiveness in patients, and a lack of control over their metabolic process. The recent innovations in the field of drug design and delivery have resulted in the emergence of next-generation therapies with improved drug pharmacology [38].

Oral GLP-1 Receptor Agonists

The conversion of injectable to oral formulations is one of the greatest innovations in this area. Traditionally, peptide-based drugs have been limited to parenteral administration due to their susceptibility to enzymatic degradation and poor gastrointestinal absorption.

Emerging oral GLP-1 receptor agonists are a significant breakthrough, which allows patients to be more convenient and compliant. This has been done by the use of absorption enhancers, which prevent degradation of the peptide and enable it to be transported across the gastrointestinal lining.

Although these breakthroughs have been made, there are still difficulties regarding the attainment of uniform bioavailability and reduction of inter-individual differences. The future study will probably centre on the best way to optimise formulation to guarantee more predictable absorption and therapeutic efficacy [39-40].

Dual and Triple Receptor Agonists

The idea of attacking more than one metabolic pathway at a time has resulted in the creation of dual and triple receptor agonists. They are peptides that will activate GLP-1 receptors and other similar receptors, such as glucose-dependent insulinotropic polypeptide (GIP) and glucagon receptors.

These therapies provide greater metabolic control by combining the actions of several hormones. They show more blood glucose reductions and more weight loss as compared to single-receptor agonists. Moreover, they can enhance energy expenditure and lipid metabolism, covering more comprehensive areas of metabolic dysfunction.

Nevertheless, the augmented pharmacological intricacy of these agents can likewise be linked to an augmented incidence of gastrointestinal side effects. Optimisation of dosage and safety assessment will be critical to their successful clinical integration [41].

Development of Drug Delivery and Peptide Engineering.

Advancements in drug delivery systems and molecular design have been really important for developing GLP-1 receptor agonists. These molecules are chemically modified to make them more stable, so they remain in the body for longer and can be administered more frequently, such as by attaching fat to them, with a special coating called PEG, or by mixing proteins together. More research is being done on using particles and technology to help deliver drugs better. This includes using nanoparticles, liposomes and special carriers made of polymers. These help keep the drug safe from breaking down and allow it to be released slowly. These advancements will not only make GLP-1 receptor agonists work better in the body but also make it easier for patients to take their medicine. By making it so patients do not have to take drugs all the time, these developments will improve how well patients follow their treatment plans (Example GLP-1 receptor agonists) [42].

Gene Therapy and Long-term Therapeutic Interventions.

The modern way to do this is to use gene therapy so our bodies can make GLP-1 for a long time. This is a plan to fix the problem of having to take medicine over again because our bodies will be able to make GLP-1 all the time. The ideas that people are thinking about are using viruses to deliver genes and technologies that can

edit genes to help our bodies make GLP-1. People are also looking at using stem cells to make systems that can make GLP-1. Even though these methods sound really good, they are not ready yet. Need to be studied very carefully to make sure they are safe, work well and do not have bad effects after a long time, and that is why GLP-1 is still being researched [43-44].

Clinical Translation and Future Challenges.

Although significant gains have been made in the translation of next-generation GLP-1 therapies into standard clinical practice, there are still a number of challenges. These consist of the problems of cost, access, long-term safety and variable patient response.

Moreover, a more personalised selection of therapies is required due to the growing complexity of those therapies. Future research will be focused on the identification of the patient groups that will benefit most from specific formulations or combination therapies [45].

FUTURE DIRECTIONS IN GLP-1-BASED THERAPIES

GLP-1 receptor agonists have been a step forward in gaining control over metabolic disorders. These drugs can be made more effective, and more people can be helped by taking advantage of opportunities. A potential area of research involving these drugs is their use in combination with other drugs that act in a different manner.

For instance, GLP-1 receptor agonists and sodium-glucose co-transporter-2 inhibitors have synergistic effects. They help the body make insulin, decrease appetite and get rid of extra glucose in the urine. This is not a good combination to regulate blood sugar levels, but it is also beneficial for weight loss and maintaining a healthy heart, which is particularly beneficial for patients with complicated metabolic issues [46-47].

GLP-1 receptor agonists have applications beyond those for people with Type 2 diabetes. They can also assist individuals suffering from illnesses. They are effective in controlling appetite and maintaining energy balance, and are useful in the treatment of obesity. Other studies indicate that GLP-1 receptor agonists may also benefit individuals suffering from other conditions, such as Alzheimer's disease, as they may help lower inflammation and shield the brain. They may also be beneficial for individuals who suffer from liver diseases, such as alcoholic fatty liver disease, by enhancing metabolic and inflammatory pathways. These are all new applications for GLP-1-based treatments, indicating that they are remarkably versatile and may be used to treat a variety of metabolic disorders.

Personalised medicine is yet another area of study that is significant. Individuals have different reactions to GLP-1 receptor agonists, and this may be due to genetic and physiological factors. New advances in pharmacogenomics may lead to the

identification of biomarkers that could help us determine if a patient will respond to treatment or not. This will enable us to select treatment strategies exactly. Personalised medicine can help to make treatments more effective, reduce side effects, and help us determine the dosage for each patient. Although GLP-1 receptor agonists have advantages, there are still issues to be addressed. They can be expensive. Not everyone can get them. Some people might not take their medicine as they should. We need to find ways to make these treatments more affordable, easier to use and make sure patients understand how to take them. We also need to collect data on how well these treatments work in the long term, especially for new agents and different populations. This will help us make sure that everyone can get the treatment they need and that it is safe and effective [49-50].

CONCLUSION

GLP-1 receptor agonists are an effective and appropriate kind of medication to control Type 2 diabetes. They do a lot more than lower glucose levels. GLP-1 receptor agonists act on the body parts, such as assisting insulin in its efficacy to lower glucagon, to slow down the gastrointestinal emptying, and to regulate the appetite. This implies that they can assist in managing metabolism somehow. They assist in the enhancement of blood sugar, they assist individuals in losing weight, and they assist in lessening the

danger of heart issues. All these advantages render GLP-1 receptor agonists helpful in patients.

Developments of these medicines, such as various forms and oral delivery systems, have made them even more convenient and easy to administer to patients. The question of how GLP-1 receptor agonists can be used, and in combination with other therapies, is also being researched. This implies that GLP-1 receptor agonists may not only be applied in the future in treating diabetes. However, there are still some problems with GLP-1 receptor agonists. We still need to know more about their long-term safety they can be expensive. They are not effective with all patients. To achieve the results, we have to continue research and discover ways to make treatments specific to each patient.

All GLP-1 receptor agonists are a step in the right direction in medicine and can truly assist individuals with metabolic illnesses such as diabetes to live better lives. The agonists of the GLP-1 receptor have the potential to transform how the conditions are treated and improve the situation for patients.

ABBREVIATIONS

GLP-1 – Glucagon-Like Peptide-1

DPP-4 – Dipeptidyl Peptidase-4

GIP – Glucose-Dependent Insulinotropic Polypeptide

NAFLD – Non-Alcoholic Fatty Liver Disease

NASH – Non-Alcoholic Steatohepatitis

HbA1c – Glycated Hemoglobin

FDA – Food and Drug Administration

MTC – Medullary Thyroid Carcinoma

SGLT2 – Sodium-Glucose Co-Transporter-2

T2DM – Type 2 Diabetes Mellitus

T1DM – Type 1 Diabetes Mellitus

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