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A REVIEW ON GLP-1 RECEPTOR AGONISTS IN OBESITY AND TYPE 2 DIABETES MANAGEMENT

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ABSTRACT
GLP-1 receptor agonists have proven to be a major therapeutic class in the treatment of obesity and T2DM due to their multi-metabolic mechanism of action. The pharmacological agents function in the same way as the endogenously produced GLP-1 by improving glucose-dependent insulin secretion, inhibition of glucagon secretion, slowing down of gastric emptying, and increasing satiety. As such, the agents result in better glycemic regulation as well as sustained weight loss. In addition to the multi-metabolic effects, GLP-1 receptor agonists have also been found to offer cardiovascular and kidney protection, and hence, are useful in individuals with multiple cardiometabolic risks. The agents have found application in areas other than the treatment of diabetes as well. In addition to being used in diabetes, the drugs are also used in chronic weight management and other obesity-related diseases. Current research is trying to investigate the utility of the drugs in metabolic dysfunction-associated steatotic liver disease, neurodegeneration, and precision medicine among other areas.

KEYWORDS: GLP-1 receptor agonists, obesity, type 2 diabetes mellitus, incretin therapy, glycemic control, weight management, insulin resistance, cardiovascular protection, renal protection, metabolic disorders.

INTRODUCTION

Obesity and Type 2 Diabetes Mellitus (T2DM) are currently among the most prevalent chronic ailments throughout the world, regardless of age group. Rapid urbanization, poor diet, lack of exercise, stress, and sedentary lifestyle are some of the factors responsible for increasing cases of these diseases over the last couple of decades. Being overweight is only one of the characteristics of obesity, which is a multi-systemic disorder causing many other problems such as insulin resistance, cardiovascular disorders, high blood pressure, high lipids, fatty liver and several types of cancer. On the other hand, T2DM is marked by persistent high glucose levels due to decreased insulin secretion and its low sensitivity. The connection between obesity and T2DM made them interlinked diseases with a strong tendency to go hand in hand.[1]

The standard medical treatments for obesity and type 2 diabetes mainly consist of lifestyle modifications that include proper dieting, exercising, behavior modification, and medication. While these treatment

methods are still considered to be the key to successful treatment, there is no doubt that numerous patients are unable to lose their weight and maintain their glycemia at the required levels. Traditional drugs for the treatment of type 2 diabetes prove to be efficient in lowering blood glucose levels; however, they can also be accompanied by such negative consequences as weight gain, constant hypoglycemia, or a lack of cardioprotection. Thus, it became necessary to look for treatment methods that would not only regulate glucose levels in the blood but also correct the metabolic abnormalities caused by obesity.[2]

In the modern era of metabolism science, GLP-1 receptor agonists represent one of the most effective and advanced methods for the treatment of people suffering from obesity and type 2 diabetes mellitus. The mechanism of action of these drugs is based on imitating the action of endogenous incretin hormone, glucagon-like peptide-1, which takes part in glucose homeostasis regulation. The drugs activate the secretion of insulin in glucose-dependent manner, inhibit the secretion of glucagon, decrease gastric emptying time, and decrease appetite through CNS receptors. This allows the patients to achieve lowering of blood glucose and remarkable weight loss without a high risk of hypoglycemia. Also, it has been shown that some of the GLP-1 receptor agonists possess cardiorenal protective effects.[3]

However, the increased clinical application of GLP-1 receptor agonists has attracted significant attention by virtue of their many benefits and therapeutic properties. Clinical trials and evidence-based practices have shown that GLP-1 receptor agonists are highly effective in managing blood sugar levels, decreasing body weight, lowering cardiovascular disease risk, and improving quality of life in people who have obesity and type 2 diabetes. The development of novel products such as once-a-week administration and oral drugs has also made treatment more convenient for patients. Nonetheless, there are some factors such as side effects, cost, and safety that still affect their clinical use.[4]

GLUCAGON-LIKE PEPTIDE-1 (GLP-1)

GLP-1 is an incretin hormone that is found within the body, and it is crucial for the maintenance of glucose balance, energy metabolism, and appetite control. It is a member of the glucagon peptide family and is primarily synthesized in enteroendocrine L-cells located in the distal small intestine and colon after eating nutrients. The functions of GLP-1 go beyond regulating the glucose level in the body as it also affects motility of the gastrointestinal tract, cardiovascular function, renal physiology, and the activities of the central nervous system. From the discovery of GLP-1 until now, it has been one of the most extensively studied metabolic hormones because of its ability to regulate glucose concentrations in a glucose-dependent fashion and causing weight loss. Such features have resulted in the synthesis of GLP-1 receptor agonists, which are currently being used in the management of type 2 diabetes mellitus and obesity.[5]

Structure of GLP-1

GLP-1 is a peptide hormone arising from the proglucagon precursor protein transcribed by the proglucagon (GCG) gene. Processing of proglucagon in a tissue-specific manner leads to the formation of a number of biologically active peptides, with GLP-1 being synthesized mainly by the intestinal L-cells via the activity of prohormone convertase 1/3. The biologically active variants of GLP-1 are GLP-1 (7-37) and GLP-1 (7-36 amide), where GLP-1 (7-36 amide) represents the dominant form in circulation in humans. Structurally, GLP-1 is composed of 30 amino acids arranged in such a way that allows high-affinity interaction with the GLP-1 receptor, which is a class B G-protein-coupled receptor. Native GLP-1 is extremely labile and prone to degradation by the enzyme dipeptidyl peptidase-4 (DPP-4). Specifically, DPP-4 hydrolyzes GLP-1 almost immediately after it is secreted into the blood. Thus, the biological half-life of endogenous GLP-1 is estimated to be around 1-2 minutes. Such enzymatic instability has led to the development of long-acting GLP-1 receptor agonists resistant to DPP-4-mediated degradation.[6]

Synthesis of GLP-1

GLP-1 synthesis starts with the transcription of the proglucagon gene that is found on chromosome 2 of human beings. The proglucagon gene is expressed in a number of body tissues, such as the pancreas, intestine, and central nervous system. Translation of the messenger RNA results in formation of a large proglucagon precursor protein. Upon removal of the signal peptide in the endoplasmic reticulum, preproglucagon becomes proglucagon. Products of proglucagon after tissue-specific post-translational processing are dependent on the enzyme that processes proglucagon in various tissues. For instance, the processing of proglucagon in pancreatic α-cells is through the action of prohormone convertase 2 to form glucagon. Proglucagon is processed by prohormone convertase 1/3 in the intestine L cells and some brain stem neurons to form GLP-1, GLP-2, oxyntomodulin, glicentin, among others. The result is that GLP-1 is synthesized mostly in the digestive system where it acts as an endocrine hormone.[7]

Secretion of GLP-1

The secretion of GLP-1 takes place very fast after the consumption of food, hence serving as an important constituent of the incretin pathway. GLP-1 is secreted from enteroendocrine L-cells that detect the nutrients that are available in the intestinal lumen immediately after the consumption of the food. Glucose, fats, proteins, and specific amino acids trigger the secretion of GLP-1; however, a mixed meal causes maximal release of the hormone. Both direct and indirect mechanisms are involved in the secretion of GLP-1. Direct secretion involves nutrient detection in the L-cells with the help of transporters and receptors; on the other hand, indirect

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mechanism involves the stimulation of hormones in the proximal intestine mediated by the vagal nerve. Once GLP-1 is secreted, it enters the portal circulation and reaches the target organs such as the pancreas, gut, brain, heart, and kidneys. However, nearly fifty percent of the GLP-1 that is released gets degraded via DPP-4 before it reaches the systemic circulation due to its short half-life. Despite the short half-life of GLP-1, it serves as a very important hormone in terms of controlling blood sugar and appetite.[8]

GLP-1 RECEPTORS AND TISSUE DISTRIBUTION

The physiological action of GLP-1 occurs via interaction with the glucagon-like peptide-1 receptor (GLP-1R), a member of the class B subfamily of GPCRs. The GLP-1 receptors are highly distributed in various tissues of the body, giving GLP-1 the ability to perform numerous actions both metabolically and non-metabolically. The GLP-1 receptors are abundantly expressed on β-cells, and their stimulation increases the secretion of insulin in a glucose-dependent manner, enhances β-cell survival, and increases insulin synthesis. These receptors are also expressed on α-cells in the pancreas, and GLP-1 decreases glucagon secretion when blood glucose is high.

Beyond the gastrointestinal tract, GLP-1 receptors are densely distributed within multiple areas of the central nervous system, such as the hypothalamus and brainstem, where they exert control over appetite, satiety, feeding behavior, and energy expenditure. Receptor activation in the brain lowers appetite and enhances sensations of satiety; therefore, GLP-1 is involved in the regulation of body weight. GLP-1 receptors are also found in the heart and vasculature, where they have favorable effects on the function of the heart, the integrity of the endothelium, and protection against cardiovascular diseases. Activation of the GLP-1 receptors in the kidneys leads to increased natriuresis, enhanced renal blood flow, and delay in the development of kidney injury due to diabetes. GLP-1 receptors have been found in other organs, such as the lungs, liver, fat, immune cells, and peripheral nervous system, indicating possible additional functions of the GLP-1 system. These include regulation of inflammation, lipid metabolism, and neuroprotection.[9]

PHYSIOLOGICAL FUNCTIONS OF GLP-1

Enhancement of Glucose-Dependent Insulin Secretion

Insulin is secreted by pancreatic beta cells when there is an elevation in blood glucose concentration through GLP-1 in a glucose-dependent manner, which ensures maintenance of normal blood glucose levels without increased insulin secretion when fasting. Moreover, GLP-1 increases insulin production and preserves beta cell function. Due to glucose-dependent insulin secretion, there is less possibility of hypoglycemia in comparison to many common antidiabetics.

Suppression of Glucagon Secretion

GLP-1 blocks the secretion of glucagon from the pancreas' alpha cells when there is increased glucose in the bloodstream. Glucagon promotes the production of glucose by the liver; hence, blocking it ensures that less glucose is produced and secreted into the bloodstream. The complementary effect works with the enhanced secretion of insulin in order to ensure optimal glucose balance.[10]

Delay in Gastric Emptying

GLP-1 delays gastric emptying, which causes the slowing of passage of nutrients, mainly glucose, from the stomach into the intestines. It causes gradual release of nutrients and glucose into the bloodstream, thus avoiding postprandial hyperglycemia. Delayed gastric emptying also ensures prolonged post-meal satiation, which helps to minimize eating habits. It is an important effect used in the treatment of obesity.

Regulation of Appetite and Satiety

The other effect of GLP-1 on the brain is in the regulation of appetite and satiety. GLP-1 targets the areas in the hypothalamus and brain stem that regulate hunger; it reduces hunger and increases satiety. The effect does not influence energy expenditure, but reduces food cravings and food intake significantly.

Preservation of Pancreatic β-Cell Function

According to experimental research, the GLP-1 stimulates pancreatic β-cell survival through increasing cell proliferation, increasing insulin production, and decreasing programmed cell death (apoptosis). Such mechanisms could lead to the maintenance of endogenous insulin production capacity and decrease the rate of β-cell dysfunction, which is characteristic of type 2 diabetes mellitus. Nevertheless, long-term clinical studies about β-cell protection are still being carried out.[11]

Cardiovascular Protective Effects

GLP-1 produces various positive effects on the cardiovascular system, which include improving endothelial function, reducing oxidative stress, decreasing inflammation, and increasing myocardial glucose uptake. GLP-1 may also result in slight lowering of blood pressure and body mass index. All these effects decrease cardiovascular risks, and there are various GLP-1 receptor agonists that have shown the reduction of major adverse cardiovascular events in patients with type 2 diabetes.

Renal Protective and Anti-inflammatory Effects

GLP-1 affects the kidneys through natriuresis (increasing sodium excretion), diuresis (urine production), and improvement of renal blood flow. In addition, GLP-1 exhibits anti-inflammatory and antioxidant action, which decreases chronic metabolic inflammation, thus protecting organs from injury due to obesity and type 2 diabetes mellitus.[12]

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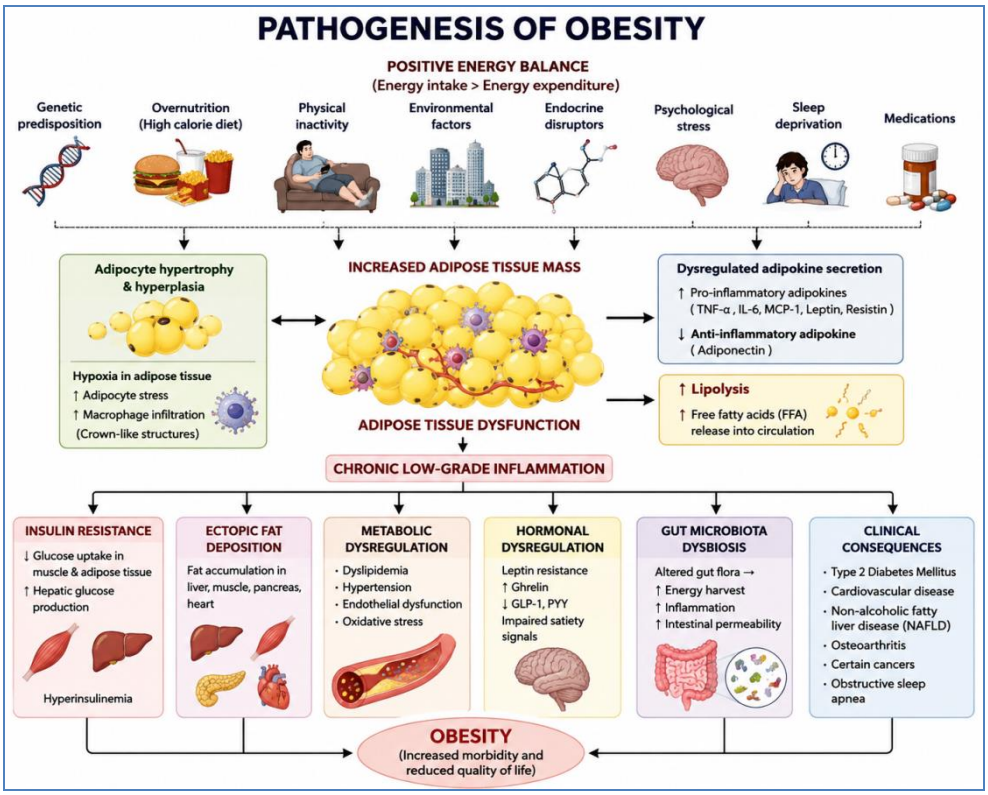
PATHOPHYSIOLOGY OF OBESITY

Obesity can be defined as a chronic and complex metabolic condition, which results due to the continuous imbalance between energy intake and output, resulting in excessive deposition of body fats, especially visceral adiposity. While excess calorie consumption and a sedentary lifestyle are the two important contributing factors for the development of obesity, genetic predisposition, hormone imbalances, environmental factors, psychological stress, insufficient sleep, certain drugs, and socioeconomic status also contribute to the condition. It is now understood that adipose tissue is an active endocrine organ producing many adipokines and inflammatory agents responsible for metabolic control. With increase in the amount of body fat, there occurs hypotrophy of the adipocytes and their dysfunction, which leads to increased secretion of free fatty acids, leptin, tumor necrosis factor-alpha (TNF-α), interleukin-6 (IL-6), resistin, and decrease in adiponectin levels.

Among other key pathophysiological outcomes resulting from obesity, there is insulin resistance, when the response to insulin decreases in skeletal muscles, liver, and adipose tissue. The high levels of free fatty acids and inflammatory cytokines affect the process of intracellular signaling by insulin, resulting in impaired peripheral utilization of glucose and higher glucose output from the liver. In addition, the chronic inflammation, oxidative stress, hormone imbalance, and ectopic fat accumulation in such organs as liver, pancreas, and skeletal muscles also exacerbate metabolic disorders. Imbalanced secretion of appetite modulating hormones such as leptin, ghrelin, and GLP-1 can be considered among others the factors that contribute to higher food consumption and lower satiety. These mechanisms not only cause additional weight gain, but also increase the risk of developing other obesity-associated diseases including type 2 diabetes mellitus, cardiovascular disease, MASLD, hypertension, etc.[13]



PATHOPHYSIOLOGY OF TYPE 2 DIABETES

Type 2 diabetes mellitus (T2DM) is a metabolic disease where there is an ongoing state of hyperglycemia due to insulin resistance along with the malfunctioning of pancreatic β cells. It is an insidious disease developing over a period of several years and highly associated with factors like obesity, sedentary lifestyle, poor eating habits, old age, and genetic predisposition. At the initial stage, insulin sensitivity in target organs, which include skeletal muscles, liver, and fat tissues, decreases, leading to insulin resistance. As a compensatory measure, pancreas secretes higher amounts of insulin in order to normalize blood sugar level. Over a period of time, high blood glucose level, free fatty acid, oxidative stress, and inflammatory state negatively affect the functioning of β cells causing lower secretion of insulin and consequently persistent hyperglycemia.

Other than the insulin resistance and β-cell dysfunction, there are various metabolic factors that play an important role in the development of T2DM. The increased hepatic glucose production, caused by abnormality in the secretion of the glucagon hormone, raises the blood glucose levels in fasting state. Impairment in the function of the incretin hormones, particularly glucagon-like peptide-1 (GLP-1), reduces insulin secretion in a glucose-dependent manner. There is also chronic inflammation, adipokine dysregulation, mitochondrial

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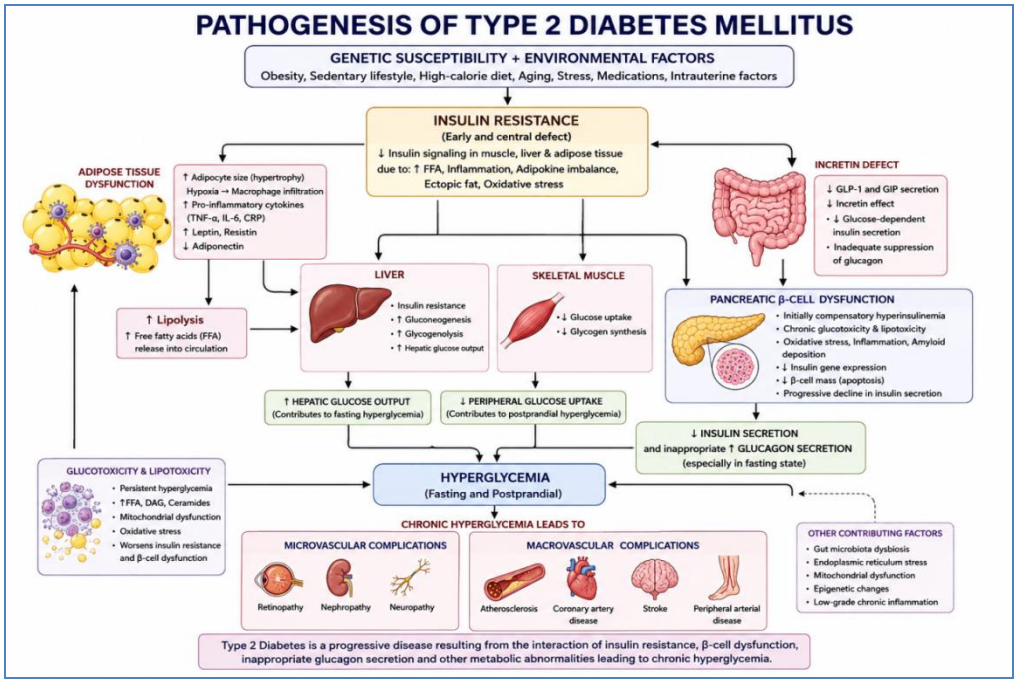
dysfunction, and ectopic fat deposition in the liver and pancreas. These metabolic factors worsen the insulin resistance and β-cell impairment. All these metabolic factors lead to glucose disturbance and increase the likelihood of developing the microvascular complications (retinopathy, nephropathy, and neuropathy) and macrovascular complications (cardiovascular disease and stroke). Due to this understanding, GLP-1 receptor agonist drugs have been developed.[14]



GLP-1 RECEPTOR AGONISTS

Glucagon-like peptide-1 receptor agonists (GLP-1 RAs) are one of the incretin therapies which aim at mimicking the physiological effect of the hormone, glucagon-like peptide-1 (GLP-1). Endogenous GLP-1 is crucial in glucose homeostasis through its mechanism which includes; stimulation of insulin secretion that is dependent on glucose, suppression of glucagon secretion, slowing of gastric emptying, and induction of satiety. Nevertheless, endogenous GLP-1 has a very short half-life of about 1 to 2 minutes as a result of rapid degradation by dipeptidyl peptidase-4 (DPP-4). In order to overcome this problem, GLP-1 receptor agonists were designed in such a way that they resist DPP-4 degradation, hence extending their effect. GLP-1 RAs have revolutionized the treatment of type 2 diabetes mellitus (T2DM) and obesity by tackling several metabolic disorders at once, contrary to glucose reduction alone.

In addition to enhancing the glycemic control, GLP-1 receptor agonists have also exhibited a wide array of other positive impacts such as weight loss, cardio-protection, kidney sparing, and enhanced metabolic profile. Different from conventional anti-diabetes drugs, GLP-1 receptor agonists induce insulin secretion when blood sugar levels are high, and thus there is little likelihood of developing hypoglycemia. Some clinical studies involving large numbers of participants have found some GLP-1 receptor agonists to be effective in decreasing the rate of major cardiovascular events and progression of chronic kidney diseases. The availability of these agents as oral as well as injectable preparations along with their once weekly dose regimen have enhanced adherence among patients.[15]

CLASSIFICATION OF GLP-1 RECEPTOR AGONISTS[16]

Classification	Drug	Brand Name	Route of Administration	Dosing Frequency	Approximate Half-life
Short-Acting GLP-1 Receptor Agonists	Exenatide	Byetta	Subcutaneous injection	Twice daily	2–4 hours
	Lixisenatide	Adlyxin (Lyxumia)	Subcutaneous injection	Once daily	~3 hours
Long-Acting GLP-1 Receptor Agonists	Liraglutide	Victoza / Saxenda	Subcutaneous injection	Once daily	~13 hours
	Exenatide Extended Release	Bydureon BCise	Subcutaneous injection	Once weekly	~2 weeks (extended release)

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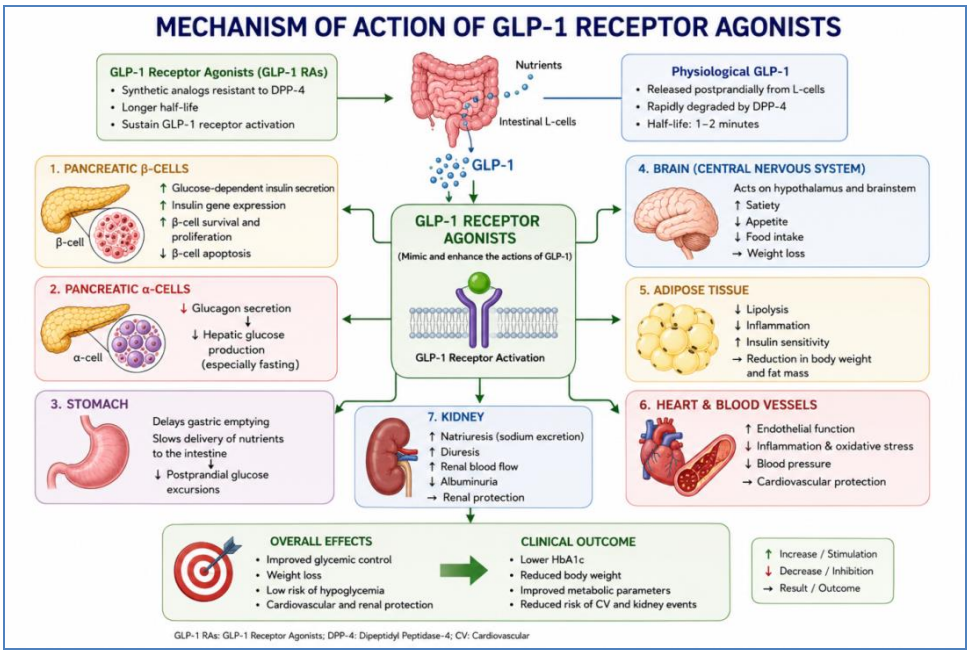
	Dulaglutide	Trulicity	Subcutaneous injection	Once weekly	~5 days
	Semaglutide (Injectable)	Ozempic / Wegovy	Subcutaneous injection	Once weekly	~7 days
	Semaglutide (Oral)	Rybelsus	Oral tablet	Once daily	~7 days
Dual Incretin Receptor Agonist*	Tirzepatide	Mounjaro / Zepbound	Subcutaneous injection	Once weekly	~5 days

MECHANISM OF ACTION OF GLP-1 RECEPTOR AGONISTS

The action mechanism of GLP-1 receptor agonists is associated with their binding to GLP-1 receptors which are distributed in several organs such as pancreas, digestive tract, brain, heart, kidneys, and blood vessels. Upon stimulation of the receptors, GLP-1 receptor agonists cause insulin secretion in response to increased blood glucose levels only from pancreatic β-cells. At the same time, GLP-1 receptor agonists inhibit the secretion of glucagon from pancreatic α-cells leading to reduction of hepatic glucose production. As insulin secretion is glucose-dependent, there is low likelihood of developing hypoglycemia.

In addition to their roles in regulating pancreatic hormones, the actions of GLP-1 receptor agonists include slowing of gastric emptying, thus ensuring that nutrients slowly enter the small intestine and postprandial glucose levels are stabilized. They exert actions on the centers that regulate appetite in the hypothalamus and brain stem, causing decreased appetite, increased satiety, and reduced food intake, resulting in weight loss. Additionally, they improve endothelial function, decrease inflammation and oxidative stress, lower blood pressure, enhance sodium excretion by the kidneys, and protect the heart and kidneys. The wide variety of actions of GLP-1 receptor agonists makes them ideal therapeutic drugs for obesity and type 2 diabetes mellitus.[17]



CLINICAL APPLICATIONS OF GLP-1 RECEPTOR AGONISTS IN TYPE 2 DIABETES

1. Glycemic Control

The GLP-1 receptor agonists are highly efficient in improving glycemic control in patients with type 2 diabetes mellitus. They cause glucose-stimulated insulin secretion, inhibit glucagon secretion, and slow gastric motility, which leads to the reduction in fasting and postprandial blood glucose levels. Due to their glucose-dependent action, the risk of hypoglycemia is minimized; thus, the efficiency of blood glucose control is significantly increased.

2. Reduction of HbA1c Levels

One of the major clinical benefits provided by GLP-1 receptor agonists is a significant lowering of glycated hemoglobin (HbA1c), which is an indicator of long-term glycemic control. Most GLP-1 receptor agonists can reduce HbA1c by about 1-2%. The lowering of the level of glycated hemoglobin provides lower risks of microvascular complications of diabetes mellitus.[18]

3. Weight Reduction in Patients with Type 2 Diabetes

Unlike a number of conventional antidiabetic drugs which result in weight gain, GLP-1 receptor agonists cause substantial weight loss. This is due to reduced

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appetite, increased satiety, and reduced calorie consumption through actions on the centers that control appetite in the brain. The loss of weight improves insulin sensitivity, reduces blood pressure, improves lipid profile, and improves the overall metabolism in such a way that they are especially useful for diabetics who are overweight.

4. Reduction of Cardiovascular Risk

A number of GLP-1 receptor agonists have shown cardiovascular benefit in type 2 diabetic patients with established cardiovascular disease or who are at high cardiovascular risk. They reduce the occurrence of cardiovascular diseases, such as cardiovascular death, myocardial infarction, and non-fatal stroke.[19]

5. Renal Protection

One of the key advantages of GLP-1 receptor agonists is their renal protective activity through the reduction of albuminuria, increased renal perfusion, natriuresis, and delaying of progression of diabetic nephropathy. The improvement of glucose control, blood pressure, and weight also plays a role in renal protection. Taken together, these properties make GLP-1 receptor agonists promising therapeutic options for patients with type 2 diabetes and chronic kidney disease.

6. Combination Therapy with Other Antidiabetic Agents

The use of GLP-1 receptor agonists in combination with other antidiabetic drugs (for example, metformin, SGLT2 inhibitors, and basal insulin) is common practice. In combination therapy, the correction of multiple pathophysiologic mechanisms of diabetes leads to more pronounced decreases in HbA1c, weight control, and insulin needs. In addition, the complementary actions of drugs increase treatment effectiveness while preserving a relatively low risk of hypoglycemia.[20]

7. Low Risk of Hypoglycemia

As GLP-1 receptor agonists are designed to induce insulin release when blood sugar levels are high, their risk of hypoglycemia is significantly lower than that of sulfonylureas and insulin. In turn, it allows for achieving satisfactory glycemic control with a reduced number of occurrences of hypoglycemia and increased patient satisfaction, compliance with treatment, and, consequently, better quality of life.

8. Early Intervention and Disease Progression Management

The current recommendations state that GLP-1 receptor agonists should be administered early, depending on indications in a patient, especially in obese, cardiovascular, or chronic kidney disease patients. The early administration of the drugs leads to better glycemic control, weight loss, and potentially to the prevention of loss of pancreatic β-cells caused by excessive metabolic pressure.[21]

CLINICAL APPLICATIONS OF GLP-1 RECEPTOR AGONISTS IN OBESITY

1. Promotion of Significant Weight Loss

GLP-1 receptor agonists are very useful when it comes to significant weight loss among people with obesity. They work on the center that regulates the appetite, and they lead to a reduction in hunger and increased satiety, hence reduced calorie consumption. In clinical studies, it has been seen that these agents lead to significant body weight loss even with prolonged treatment.

2. Appetite Suppression and Increased Satiety

One of the most common uses of GLP-1 receptor agonists is their capability of suppressing appetite and increasing satiety after eating. These drugs act on the receptors of GLP-1 in the brainstem and hypothalamus, thus reducing hunger and the amount of food consumed. Through this, patients get to eat less energy without feeling excessively hungry.[22]

3. Reduction in Caloric Intake

GLP-1 receptor agonists play an essential role in weight loss through reducing daily caloric intake. Gastric emptying delay results in increased satiety sensation, while central nervous system activity reduces hunger. Patients tend to eat smaller portions of food less often, which contributes to a negative energy balance that helps lose weight gradually without imposing excessive dietary limitations.

4. Improvement in Metabolic Health

Obesity-related metabolic health problems can be alleviated by using GLP-1 receptor agonists to lose weight. The use of such drugs is accompanied by enhanced insulin sensitivity, decreased fasting plasma glucose, improved lipid profile, reduced blood pressure, and decreased systemic inflammation. The metabolic health improvement reduces the risks of development of obesity-associated diseases, such as type 2 diabetes, cardiovascular disease, and MASLD.[23]

5. Reduction of Visceral and Ectopic Fat

Along with body mass loss, GLP-1 receptor agonists promote the loss of visceral and ectopic fats, including those found in the liver and pancreas. Fat loss from visceral tissues leads to increased insulin sensitivity and reduced levels of chronic inflammation. Fat loss from the liver contributes to the better functioning of the liver and lower risks of developing obesity-associated complications.

6. Long-Term Weight Maintenance

Weight maintenance is rather challenging after intervention through lifestyle change. GLP-1 receptor agonists can maintain the weight reduction due to the continuous regulation of appetite and lowering food consumption. This, together with diet and physical activity, can considerably reduce the chances of gaining the lost weight back.[24]

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7. Prevention of Obesity-Related Complications
The use of GLP-1 receptor agonists lowers the risk of development of many obesity related complications through their favorable effects on weight and metabolism. Losing weight is associated with a lower risk of development of type 2 diabetes, hypertension, dyslipidemia, obstructive sleep apnea, cardiovascular disease, osteoarthritis, and MASLD. These effects benefit general health and functional ability and help in achieving better clinical outcomes in patients suffering from obesity.

8. Enhancement of Quality of Life
Weight loss due to the usage of GLP-1 receptor agonists contributes to marked improvement in physical, mental, and social well-being of patients. Better mobility, higher exercise tolerance, improved self-confidence, diminished obesity-related symptoms and overall quality of life are common experiences of patients on this therapy.[25]

EFFECTS BEYOND GLYCEMIC CONTROL

1. Cardiovascular Protection
GLP-1 receptor agonists have been shown to offer several benefits for heart health aside from reducing blood sugar levels. Such benefits include improved endothelial function, reduction in blood pressure, decreased oxidative stress and inflammation, and minor positive changes in lipid profiles. The results from cardiovascular outcome studies have shown reduced occurrence of major adverse cardiovascular events such as cardiovascular death, non-fatal myocardial infarction, and stroke. These properties make GLP-1 receptor agonists useful in treating patients with type 2 diabetes and established or high cardiovascular risks.

2. Renal Protection
GLP-1 receptor agonists have nephroprotective effects due to their ability to decrease albuminuria, increase natriuresis and diuresis, increase renal blood flow, and slow down the progression of diabetic nephropathy. Improved glycemic control, weight loss, and blood pressure also help maintain kidney function. The combination of these properties lowers the chances of chronic kidney disease development in obese patients and patients with type 2 diabetes mellitus.

3. Improvement in Metabolic Dysfunction-Associated Steatotic Liver Disease (MASLD)
The use of GLP-1 receptor agonists has shown great potential in patients with MASLD. Due to their ability to result in significant weight loss, enhance insulin sensitivity and reduce hepatic fat content, such drugs reduce inflammation in the liver and help increase liver enzymes. Clinical trials indicate the reduction of liver steatosis and improved metabolism, which makes GLP-1 receptor agonists a great option for the treatment of obesity-induced liver disease.[26]

4. Benefits in Polycystic Ovary Syndrome (PCOS)
Polycystic ovary syndrome often presents with obesity, insulin resistance, and predisposition to type 2 diabetes. GLP-1 receptor agonists increase insulin sensitivity, facilitate weight loss, reduce visceral obesity, and optimize metabolism. Such physiological changes might positively affect menstrual cycles, ovulation, and fertility and avoid complications associated with PCOS and metabolic health issues.

5. Neuroprotective and Anti-inflammatory Effects
There are several brain areas that express GLP-1 receptors, including those responsible for cognition and survival of neurons. According to experimental research, GLP-1 receptor agonists decrease neuroinflammation, oxidative stress, neuronal cell death, and improve mitochondrial function. Neuroprotective properties of GLP-1 receptor agonists raised interest in their possible application in neurodegenerative disorders such as Alzheimer's disease and Parkinson's disease.

6. Improvement in Obstructive Sleep Apnea and Quality of Life
The notable amount of weight loss obtained through the use of GLP-1 receptor agonists is capable of treating obstructive sleep apnea caused by obesity by reducing the deposition of fat within the upper airways of the body, thus minimizing airway obstruction. The patient may benefit from good sleep quality, decreased daytime fatigue, increased physical ability, and improved general well-being.[27]

COMPARISON WITH OTHER ANTIDIABETIC AGENTS

1. GLP-1 Receptor Agonists vs Metformin
Metformin continues to be the drug of choice for the majority of type 2 diabetes patients since it is effective, cheap, and has a safe record of use. This drug mainly decreases the production of glucose from the liver and increases insulin sensitivity without inducing hypoglycemia. The benefit of GLP-1 receptor agonists is that it causes more weight loss, better HbA1c lowering in some patients and cardioprotective effect. However, it is very expensive and prescribed after the failure to reach optimal glycemic levels with the use of metformin in combination with high obesity and cardiovascular problems in patients.

2. GLP-1 Receptor Agonists vs Sulfonylureas
Sulfonylureas reduce blood sugar level through increased production of insulin irrespective of the glucose level in the blood. Although sulfonylureas are cheap and effective, they are linked with risks of hypoglycemia and weight gain. Unlike this group of drugs, GLP-1 receptor agonists induce the production of insulin only in case of hyperglycemia. Thus, the risk of hypoglycemia is minimized while weight loss is gained.[28]

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3. GLP-1 Receptor Agonists vs DPP-4 Inhibitors
Both GLP-1 receptor agonists and DPP-4 inhibitors act on the incretin pathway; however, their approaches differ greatly. DPP-4 inhibitors stop the breakdown of the natural GLP-1 to provide mild efficacy regarding glycemic improvement with weight neutrality. Conversely, GLP-1 receptor agonists stimulate GLP-1 receptors directly and provide better decreases in HbA1c, greater weight loss, and cardiovascular benefits. Nevertheless, GLP-1 receptor agonists are primarily injectable (except for oral semaglutide) and are known to have more adverse gastrointestinal effects.

4. GLP-1 Receptor Agonists vs SGLT2 Inhibitors
The mechanism of action of SGLT2 inhibitors involves increasing the urinary output of glucose due to blocking its reuptake in the kidneys. Both drug types have similar cardiorenal benefits and a minimal chance of developing hypoglycemia. GLP-1 receptor agonists lead to greater weight loss and larger HbA1c decreases compared to SGLT2 inhibitors; SGLT2 inhibitors have the advantage in decreasing the risk of heart failure hospitalizations and slowing the progression of chronic kidney disease.

5. GLP-1 Receptor Agonists vs Insulin Therapy
Insulin is the most powerful antidiabetic agent and is mandatory in patients with β-cell dysfunction or extreme hyperglycemia. Nevertheless, insulin treatment is often accompanied by weight gain and an increased risk of hypoglycemia. GLP-1 receptor agonists effectively reduce blood glucose levels and induce weight loss without increasing the risk of hypoglycemia since their insulinotropic activity depends on glucose concentration. In some cases, the addition of GLP-1 receptor agonists delays insulin use or decreases insulin dosage while enhancing the metabolic profile of patients.

6. GLP-1 Receptor Agonists vs Dual GIP/GLP-1 Receptor Agonists (Tirzepatide)
Dual GIP/GLP-1 receptor agonists, for example, tirzepatide, are the newest generation of incretin drugs that activate both glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 receptors. As compared to conventional GLP-1 receptor agonists, the effectiveness of tirzepatide was proved to be greater concerning lowering HbA1c levels and inducing weight loss. The safety and cardiometabolic benefits of both types of agents are similar; however, dual GIP/GLP-1 receptor agonists could be preferable for selected patients. Further research continues in this field.[29]

SAFETY PROFILE

GLP-1 receptor agonists are usually regarded as safe and well-tolerated drugs with a good benefit-to-risk ratio in the treatment of obesity and type 2 diabetes mellitus. Being glucose dependent, their side effect is minimized by the absence of hypoglycemia when GLP-1 receptor agonists are taken either alone or in conjunction with those drugs that do not cause hypoglycemia on their own. The most common side effects include gastrointestinal issues such as nausea, vomiting, diarrhea, constipation, abdominal pain, and decreased appetite. They are mostly mild and occur at the beginning of treatment or increasing dose and are gradually overcome by further treatment. Starting treatment with low doses and raising the doses slowly helps to overcome side effects.

Despite rare cases, proper selection of patients along with continuous monitoring is highly required. Some rare cases of acute pancreatitis, cholelithiasis, dehydration-related renal dysfunction, hypersensitivity reaction, and aggravation of diabetic retinopathy due to rapid glucose reduction have been found in certain patients. GLP-1 receptor agonists should not be used in people with a personal or familial history of medullary thyroid cancer and multiple endocrine neoplasia type 2 due to the presence of thyroid C-cell tumors seen in rodents; however, no causality has been found yet in humans. In general, numerous clinical studies and experience show that the advantages of GLP-1 receptor agonists are greater than their risks if used properly along with close clinical monitoring.[30]

FUTURE PERSPECTIVES

The future of GLP-1 receptor agonists in treatment will go way beyond type 2 diabetes mellitus and obesity. Current research is geared towards the development of novel incretin drugs with higher potency, longer duration of action, and enhanced patient convenience. These include new generation GLP-1 receptor agonists that target other receptors apart from GLP-1 like glucose-dependent insulinotropic polypeptide (GIP) and glucagon receptors. The new drugs are proving effective in producing more weight loss and better glycemic outcomes than the current generation of agents. Improvements in oral delivery of these drugs, monthly dosing by injection, and implantation techniques are some of the approaches being developed to ensure better compliance and satisfaction in patients. Additionally, research efforts are ongoing towards the use of GLP-1 receptor agonists in the prevention of type 2 diabetes mellitus and treatment of pediatric obesity.

GLP-1 receptor agonists can also serve as therapeutic agents in various other chronic diseases due to their anti-inflammatory, antioxidant, and organ-protecting properties aside from being used in the treatment of metabolic disorders. The current clinical trials aim to determine their efficacy in the treatment of MASLD, chronic kidney disease, heart failure, Alzheimer's disease, Parkinson's disease, PCOS, and obstructive sleep apnea. Future precision medicine strategies using the support of genetic profiling, biomarkers, and artificial intelligence might be useful to pinpoint patients that can gain benefits from certain GLP-1 therapies while avoiding adverse events. Based on the growing clinical data, GLP-1 receptor agonists will undoubtedly serve an increasingly significant role in the management of cardiometabolic disorders in the future.[31]

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CONCLUSION

Glucagon-like Peptide-1 (GLP-1) receptor agonists have revolutionized the treatment of obesity and Type 2 Diabetes Mellitus through their ability to influence a variety of pathophysiologic processes involved in disease processes other than controlling blood glucose levels. This includes increased glucose-mediated insulin secretion, suppression of glucagon production, slowing of the stomach emptying rate and induction of satiety, among others, to ensure efficient glycemic management along with weight loss. Due to their cardioprotective and renoprotective properties and minimal risk of causing hypoglycemia, GLP-1 receptor agonists have become an essential part of modern cardiometabolic treatment strategy. Clinical evidence proves that these medications are beneficial for improving metabolic parameters and reducing complications of obesity.

The increasing significance of GLP-1 receptor agonists in the treatment field not only covers diabetes and obesity but is also gaining momentum in the area of treatment of metabolic dysfunction-associated steatotic liver disease (MASLD), cardiovascular diseases, chronic kidney disease, and many others metabolic disorders. With further improvements in the drug design field such as oral drugs and dual/triple incretin receptor agonists, their efficacy and compliance will be enhanced further. Despite some limitations in terms of side effects in the gastrointestinal tract and cost of therapy, their risk-benefit ratio is very promising. With growing studies about their increasing clinical importance, GLP-1 receptor agonists will keep on maintaining their leading position in the personalized metabolic therapy for obesity and type 2 diabetes mellitus.

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