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# A REVIEW ON GLUCAGON LIKE PEPTIDE-1 RECEPTOR AGONISTS: A NEW ERA IN DIABETES CARE

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**ABSTRACT:**

Type 2 diabetes mellitus (T2DM) is a chronic hyperglycaemic metabolic disorder due to insulin resistance and insulin deficiency. The glucagon-like peptide-1 (GLP-1) receptor agonists are an important therapeutic choice for the management of T2DM because of their glucose-dependent insulinotropic effects and their ability to reduce glucagon secretion. These agents also result in reduced gastric emptying and increased satiety, which leads to weight loss and reduced incidence of hypoglycemia when compared with certain conventional antidiabetic agents. GLP-1 receptor agonists, such as liraglutide, semaglutide and dulaglutide, have either been clinically proven to (or are expected to) significantly decrease glycated hemoglobin, or HbA1C, and have beneficial cardiovascular effects. While they are effective, there are some limitations, such as gastrointestinal side effects, cost of treatment, and difficulties with adherence, which can impact their use. New studies are targeting the formulation and combinations to further increase effectiveness as well as compliance with the patient. In conclusion, GLP-1 receptor agonists are a valuable addition to the T2DM treatment armamentarium, with glycemic and cardiometabolic effects, and will remain important in contemporary diabetes management strategies.

**Keywords:** GLP-1, glucagon peptide receptor agonist, type 2 diabetes mellitus, glucose homeostasis, GLP-1Ras

## 1.INTRODUCTION:

The glucagon-like peptide-1 receptor (GLP-1R) and its agonists have been a highlight of the medical and scientific field because of their wide range of therapeutic uses. GLP-1R is a member of the G protein-coupled receptor (GPCR) family that is expressed at high levels across a variety of cell types in the human body and is a highly important therapeutic target, reshaping treatment paradigms for numerous diseases, including diabetes mellitus, cardiovascular diseases, and neurodegenerative disorders, among others.[1,2] GLP-1 is a peptide hormone formed by the enzymatic processing of proglucagon, mainly produced by L-cells of the intestine, islet α-cells of the pancreas and neuronal cells in the nucleus of the solitary tract (NST). The diverse physiological actions mediated by GLP-1 receptor agonists (GLP-1RAs) make them highly effective in controlling blood glucose levels and improving metabolic dysfunction.[3,4] They have already been shown to be useful in diabetes management, but their various biological actions warrant their use in other known and unknown metabolic disorders. They are important advances in biomedical research because they started from the discovery of the GLP-1(7–37) fragment and culminated in the development of metabolically stable longacting GLP-1 analogues. This review outlines the complex mechanisms by which GLP-1RAs exert their effect and explores the more recent development of GLP-1RAs for the treatment of various diseases, such as musculoskeletal inflammatory conditions, cardiovascular diseases, neurodegenerative diseases, and some cancers, as well as obesity.[5-7] In some disorders, including Alzheimer's disease (AD) and Parkinson's disease, GLP-1RAs have shown some potential to slow the progression of the disease and have neuroprotective activity. Similarly, they have anti-inflammatory properties that may be beneficial for various inflammatory diseases such as, cardiovascular diseases, and osteoarthritis and rheumatoid arthritis (RA).[7-8] Despite the

promising potential of GLP-1 as a therapeutic agent for diabetes treatment, its clinical use is hampered by its rapid degradation in vivo, which requires frequent administration and potentially high doses with a risk of side effects. Exendin-4 is a 39-amino-acid peptide that circulates for more than two hours, as opposed to the native GLP-1, which is rapidly metabolized in the circulation (<1 minute). The results of these groundbreaking studies were then published in the Journal of Biological Chemistry (JBC).[9]

## 1.1 HISTORY AND MILESTONES IN GLP-1 RESEARCH

Richard Goodman had found that anglerfish are an ideal source for pancreatic mRNA because of their concentrated cells. He isolated mRNA, spliced anglerfish DNA into bacteria, and used radioactive probes to find the somatostatin gene. In 1982, they published a paper in Proceedings of the National Academy of Sciences (PNAS), revealing that the glucagon precursor gene actually encodes three peptides-glucagon and two new hormones expressed in intestine.[10]

## 1.2 GLP-1

GLP-1 is a peptide hormone produced through the enzymatic processing of proglucagon. It is synthesized by L-cells within the intestinal mucosa, α-cells of the pancreatic islets, and neurons situated in the nucleus of the solitary tract.[11] As an endocrine hormone, GLP-1 is secreted by enteroendocrine L-cells located primarily in the distal jejunum, ileum, and colon in response to nutrient intake and neuroendocrine stimulation. It originates from the preproglucagon precursor molecule, which undergoes enzymatic cleavage within intestinal L-cells to generate GLP-1(1–37) and the biologically active forms GLP-1(7–36) amide and GLP-1(7–37). [12,13] Subsequently, GLP-1 is rapidly degraded by the enzyme dipeptidyl peptidase-4 (DPP-4), resulting in the loss of its biological activity.[14]

## 1.3 GLP-1R

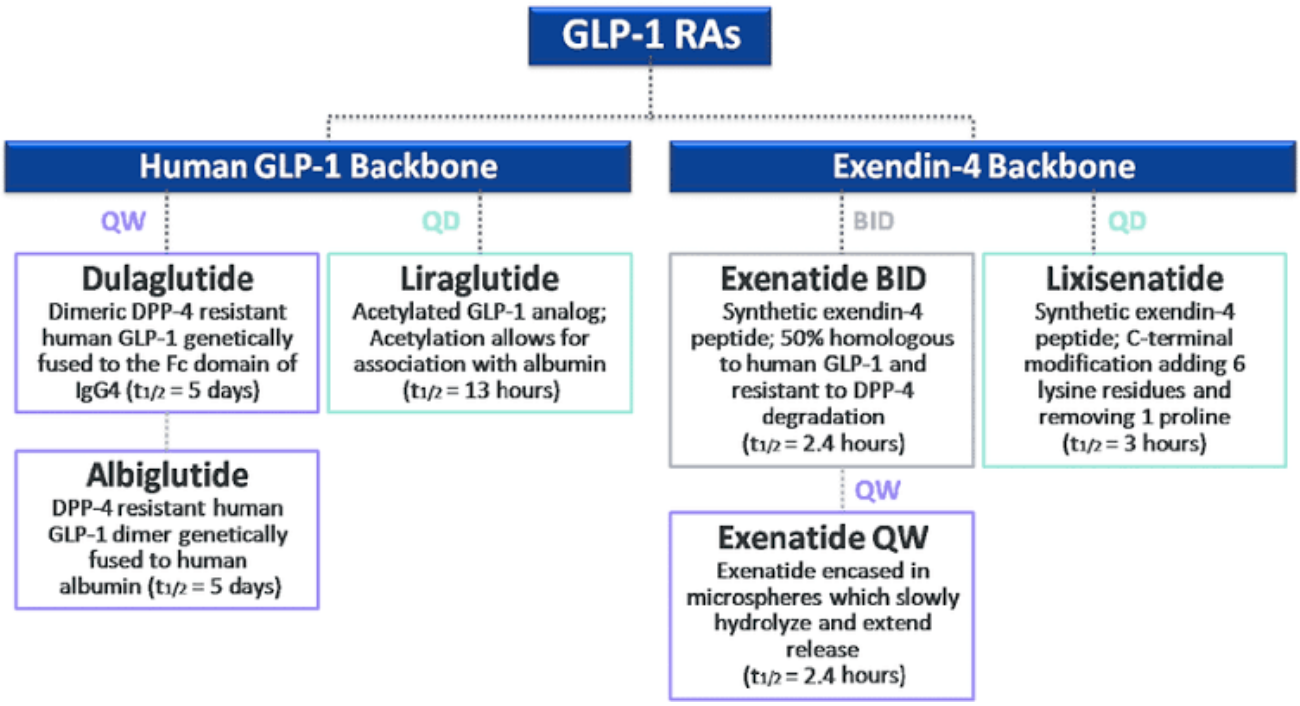
It a member of the GPCR family, exhibits specific affinity for GLP-1. It predominantly localizes to the cellular membrane of diverse cell types throughout the human body.[15] Indeed, GLP-1R is present beyond the confines of the pancreas and extends to a multitude of organs and tissues throughout the body. Its extensive distribution and involvement in diverse physiological processes emphasize the important role of GLP-1R beyond the regulation of glucose metabolism. [16-18]

## 1.4 GLP-1RAS

It result from intricate structural modifications to GLP-1, enabling them to not only replicate the pharmacological functions of GLP-1 but also impede its hydrolysis by DPP-4, thereby extending the drug's half-life. [19,20].

## EXENATIDE

Exenatide is the medication which belongs to the class of drugs called as GLP-1RAs. It is a synthetic version of the hormone exendin-4, which is found in the saliva of the Gilamonster, a venomous lizard native to the southwestern United States.[21] Exenatide is consists of 39 amino acids and it shares 53% sequence identity to human GLP-1. The second position of its N-terminus is glycine (alanine in GLP-1), which is not easily degraded by the DPP-4 enzyme.[22] Compared with GLP-1, the C-terminus of its amino acid sequence contains 9 additional amino acid residues (PSSGAPPPS), which are not easily degraded by peptide chain endonucleases; thus, it has a long half-life and strong biological activity.[23] The average half-life of exenatide is 2.4h, 2to3 times per day.[23]




**LIRAGLUTIDE**

Liraglutide is a medication usedtotreatT2DMand obesity. [24,25] In the treatment of T2DM, liraglutide helps lower blood sugar levels b by increasing insulin production and reducing glucose production by the liver.[26] It also slows stomach emptying, which helps control appetite and reduce food intake. [27,28] In addition to lowering blood sugar levels, liraglutide helps to reduce body weight by suppressing appetite and reducing energy intake.[29]

**LIXISENATIDE**

Lixisenatide was developed by Sanofi to treat T2DM. [30,31] Structurally, lixisenatide is based on the exenatide structure but lacks proline at position 38, and six lysines are linked after serine at position 39.[32] The six lysine residues increase the rigidity of the molecule's structure, thus allowing its drug properties to be improved.[33]

**1.5 CLASSICAL PATHOPHYSIOLOGICAL MECHANISMS OF GLP-1**

GLP-1 initiates signaling by binding to its receptor, GLP-1R, which is a G-protein-coupled receptor.[34,35] When GLP-1 binds to GLP 1R, it triggers the activation of G-proteins, leading to an increase in the intracellular second messenger cAMP.[36,37,38]The rise in cAMP activates protein kinase A (PKA), which then promotes the synthesis and secretion of insulin and inhibits the release of glucagon.[37,38]Additionally, cAMP can activate Rap1 through EPAC (Exchange Protein directly Activated by cAMP).[39,40]

**Interactions with other pathways GLP-1:**

It activates the release of insulin as well as increases the responsiveness of pancreatic β-cells to insulin via the PI3K/Akt signalling pathway, which increases insulin signal transduction and improves peripheral insulin sensitivity. [1,41] These effects include interactions with other satiety and hunger signals, including PYY, CCK, insulin, and leptin.[42 ,43] And GLP-1's role in the brain to reduce appetite may interact with other factors that affect energy expenditure.

**ROLE OF GLP IN T2DM:**

GLP-1 is an important incretin hormone that stimulates insulin secretion in a glucose-dependent manner and also stimulates the proliferation and prevents apoptosis of pancreatic β-cells, keeping their quality and

functionality. [3,44,78] GLP-1 activates the PI3K/Akt pathway, which is a key pathway that regulates the survival and proliferation of pancreatic β-cells.[45,46] This pathway activates a number of downstream effector molecules including Fork box protein O1 (FoxO1) and glucose transporter type 2 (GLUT2) which promote insulin secretion, reduce apoptosis and stimulate β-cell proliferation.[47,48] GLP-1 also inhibits glucagon release from α-cells, which is beneficial for reducing blood glucose levels since glucagon promotes hepatic gluconeogenesis.[49,51] GLP-1's action on α-cells regulates glucagon release.[51] The direct impact of GLP-1 on these cells slows the secretion of glucagon, essential for maintaining glucose stability, especially postprandially.[50,51]

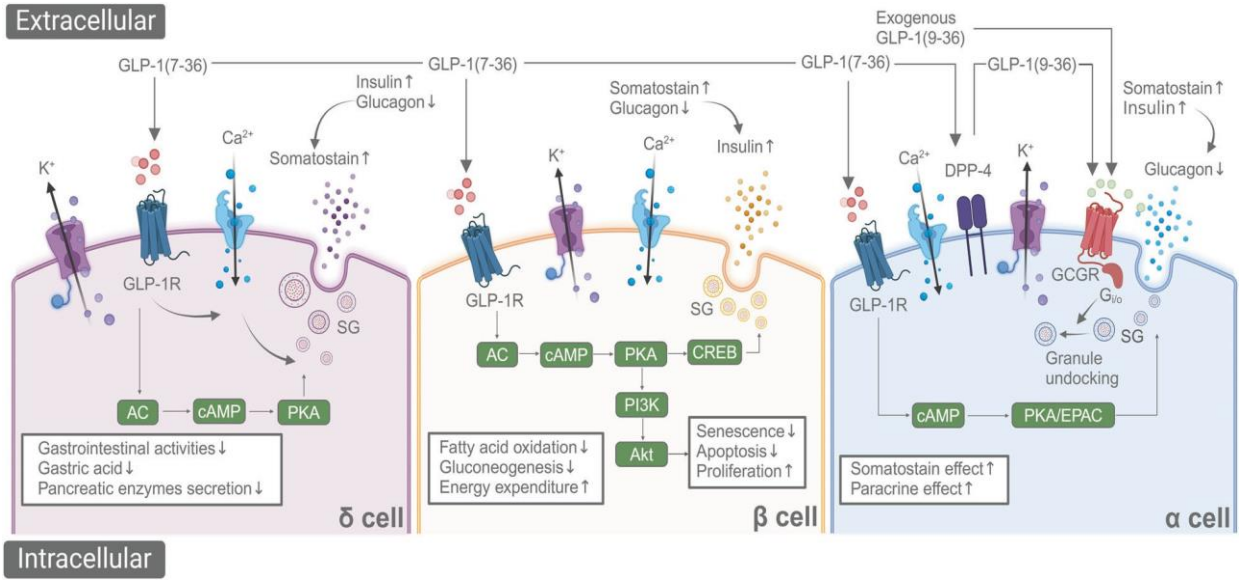
**Therapeutic Applications of GLP-1 Receptor Agonists Beyond Diabetes**

Glucagon-like peptide-1 receptor agonists (GLP-1RAs) have been developed to treat type 2 diabetes mellitus but there is growing evidence of their therapeutic effects that go beyond glycemic management. Given GLP-1 receptors' ubiquitous presence in tissues, the agents have multiple physiological effects such as anti-inflammatory, cardioprotective, neuroprotective and metabolic. In the context of obesity, GLP-1RAs have shown promising results, with their ability to induce satiety and decrease energy intake leading to long-term weight loss. Besides, they have been demonstrated to have beneficial impacts in cardiovascular ailments by enhancing endothelial function, blood pressure regulation, and lessening major adverse cardiovascular events. Recent research has also indicated potential applications in neurodegenerative diseases like Alzheimer's disease and Parkinson's disease, where they could help limit neuroinflammation and promote the survival of neurons. In addition, there is ongoing research into the therapeutic uses of GLP-1RAs in musculoskeletal conditions, non-alcoholic fatty liver disease, and some forms of cancer. The biological effects of these distinct types of drugs reinforce the growing clinical relevance of using GLP-1RAs as therapeutic agents and their potential as multi-functional drugs.

**A GLP-1RA and joint disorder:**

GLP-1 receptor agonists have been shown to have anti-inflammatory activity that could be useful in musculoskeletal and joint disorders. GLP-1 receptor activation can inhibit the release of pro-inflammatory cytokines and the inflammation of synovial tissues, and limit tissue damage. Studies have been conducted that indicate that GLP-1RAs might help to reduce inflammation from some diseases, including arthritis and osteoarthritis, improving joint function and slowing the progression of the disease. Although current evidence is largely derived from preclinical investigations, these findings indicate a promising role for GLP-1RAs as adjunctive therapies in inflammatory joint diseases. The major effect of GLP-1R expression is to inhibit the release of cytokines into synovial fluid which results in less inflammation.[52]

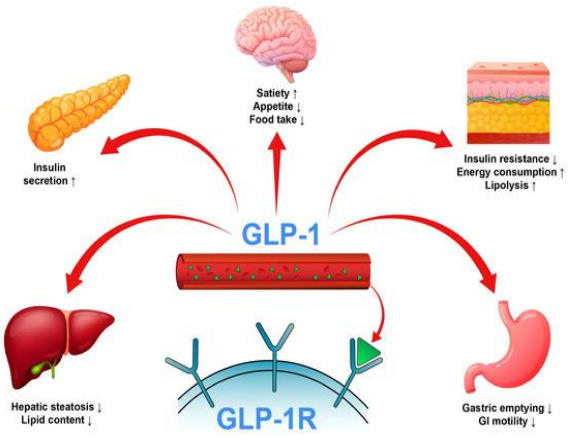
**Mechanisms of Blood Glucose Reduction by GLP-1 in Pancreatic α, β, and δ Cells:**

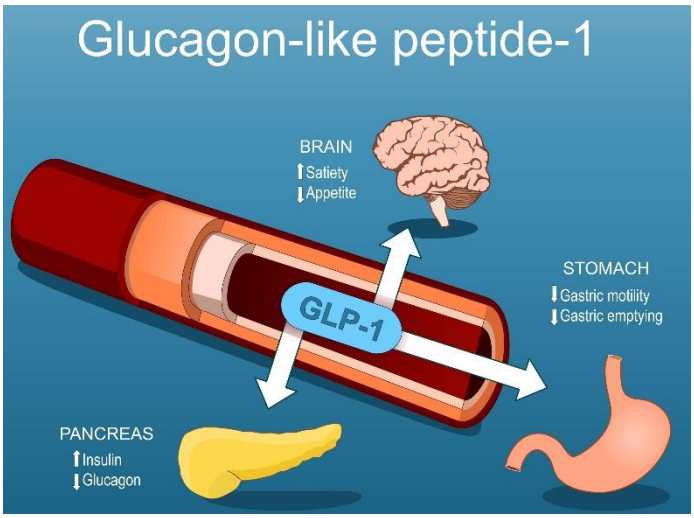



**GLP-1RAs in Enhancing Exercise Endurance Studies:**

Acute exercise and short-term endurance training greatly stimulate GLP-1 secretion in mice as indicated by s. In endurance-trained men, GLP-1 plasma concentrations are elevated immediately at 30 and 45 minutes after exercise. To confirm the role of GLP-1 in enhancing physical endurance and the possible mechanisms involved, an in vivo AAV-mediated GLP-1 overexpression model and an in vitro siRNA-mediated AMPK knockdown model were generated. We showed that GLP increases physical endurance by skeletal muscle remodeling, which might be mediated by GLP-1R/AMPK signaling.[53]

**GLP-1RAs and fat metabolism:** GLP-1RAs work via numerous mechanisms that contribute to weight loss, one of the most well known of which is the gut-brain axis. [42,43,54] Within this axis, GLP-1 functions by acting on both the gut and the brain.[55] Furthermore, the combination of GLP-1-mediated signaling and the adipocyte hormone leptin has recently garnered increased interest. Of particular note, leptin could also be an important biological signal for GLP-1, when acting together, these two hormones could help to reduce body weight and food intake.[56] The effects of the leptin-GLP-1 interaction could be regulated by intracellular signaling pathways such as that involving phosphorylated STAT3




**GLP-1RAs in nervous system:**

GLP-1 can attenuate oxidative stress and inflammatory responses in the nervous system, possibly via a reduction in the production of ROS and inflammatory cytokines. Activation of its receptor by GLP-1 can stimulate the phosphorylation of CREB, which in turn can lead to increased expression of neuronal survival and regeneration-related genes.[57,58]

**The SGLT2 family of drugs includes GLP-1RAs and certain nerves:**

Scientists have found that GLP-1RAs show a significant rise in the amount of phosphorylated ERK1/2 in the sciatic nerve of diabetic rats. This led them to believe that GLP-1 analogs may have unique neurotrophic properties and specifically protect the nerve.[59,60-62]

**The relationship of inflammatory response and neurodegenerative disease:**

The researchers started by inducing inflammation in mice using different Toll-like receptor (TLR) agonists and then measured the level of inflammation by measuring levels of plasma tumor necrosis factor-alpha (TNF-α).[63] They found that the GLP-1RA, exendin-4, had a significant anti-inflammatory effect on plasma TNF-α levels induced by multiple TLR agonists, suggesting that exendin-4 has anti-inflammatory properties on plasma TNF-α levels caused by various TLR agonists.

**GLP-1RAs and AD:**

In AD, anti-inflammatory effects of GLP-1(7-36) amide prevent the transcription of IL-1β, amyloid precursor protein production and cell death, all of which are processes associated with cognitive dysfunction. It enhances learning and memory by the process of longterm potentiation (LTP) as well. [64,65]

**GLP-1RAs and PD:**

Excessive dopaminergic degradation is key to the pathophysiology of PD and is the reason why GLP-1RAs are promising pharmacological agents for the treatment of PD, as they help preserve the integrity and function of the dopaminergic neurons in the CNS. When GLP 1 is synthesized within the brain, it has neuroprotective properties, in addition to its effects on metabolic regulation. [66,67,68] GLP-1RAs have been demonstrated to have a positive effect on endothelial integrity. GLP-1RAs have been proposed to have direct endothelial protective effects, mediated by the GLP-1R-dependent AMPK/Akt/eNOS pathway. This pathway allows NO formation which helps to maintain vascular health and function. Furthermore, GLP-1RAs contribute to maintaining the integrity of the endothelial barrier, which is very important in preventing vascular leakage.

**GLP-1RAs in the cardiovascular system:**

In the cardiovascular system, GLP-1 might also protect against cardiac ischemia reperfusion injury by stimulating specific signaling pathways, including the PI3K/Akt pathway, which would involve modulation of the process of cell apoptosis through, for example, decreased Bax/Bcl-2 ratio in cardiomyocytes, reduction in cytochrome C release, and activation of caspases.[69,70] GLP-1 may also improv,e endothelial function by increasing the production of NO, possibly by activating eNOS, and that would also involve its anti-inflammatory and anti-atherosclerosis effects, associated with decreased vasoconstriction.[69,71,72]

**GLP-1RAs and AS:**

Drugs belonging to the GLP-1RAs like liraglutide and semaglutide have shown remarkable cardiovascular protective properties. Liraglutide and semaglutide have been proven to be effective in lowering blood pressure and lipids levels in several scientific studies which helps in reducing AS and cardiovascular diseases.[73] Atherosclerosis is a chronic inflammatory disorder characterized by lipid accumulation, endothelial dysfunction, and plaque formation within arterial walls. Growing evidence suggests that GLP-1 receptor agonists (GLP-1RAs) exert protective effects against the development and progression of atherosclerosis. These agents improve cardiovascular health by enhancing endothelial function, reducing oxidative stress, suppressing inflammatory responses, and improving lipid metabolism. Clinical and experimental studies have demonstrated that GLP-1RAs, particularly liraglutide and semaglutide, can reduce cardiovascular risk factors such as hypertension, dyslipidemia, obesity, and insulin resistance. Furthermore, GLP-1RAs may stabilize atherosclerotic plaques and decrease vascular inflammation, thereby lowering the risk of major adverse

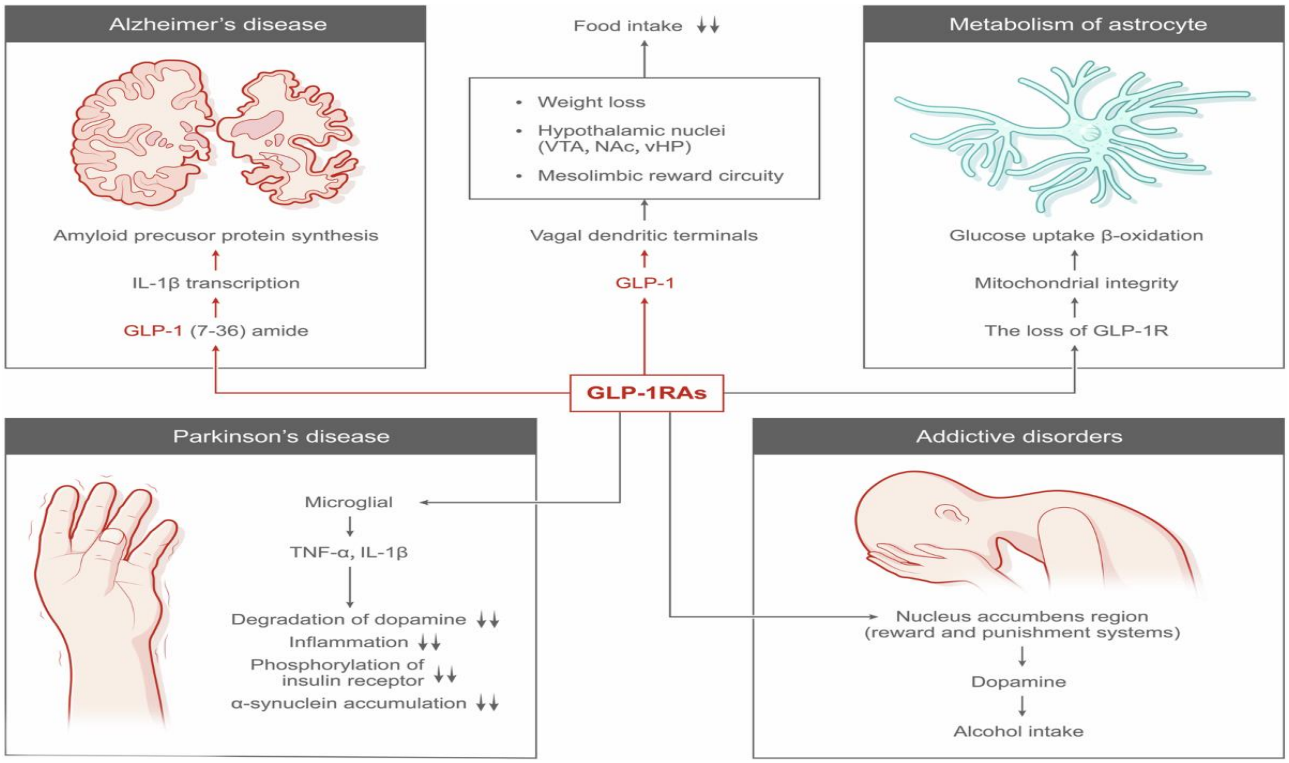
cardiovascular events. These findings highlight the potential of GLP-1RAs as valuable therapeutic agents in the prevention and management of atherosclerotic cardiovascular disease.

**GLP-1RAs and hypertension:**

Interestingly, the carotid body is also the site of GLP-1R, which is linked to the co-regulation of blood pressure and blood glucose.[74]

**The use of GLP-1RAs in the treatment of heart failure**:

LV ejection fraction (LVEF) preserved heart failure (HF) still continues to rise. Symptoms of patients are more pronounced and functional impairments are also common, particularly in the obese population. Heart failure with preserved ejection fraction (HFpEF) is a form of heart failure that represents about 50% of all HF cases, and patients experience a high burden of symptoms and functional limitations that affect their daily lives. These restrictions are tiredness, breathlessness, loss of exercise tolerance, and puffiness of legs. Currently,




there are no approved targeted therapies for LVEF-preserved heart failure associated with obesity. Further, no GLP-1R has been found on human myocardial cells, which invalidates potential direct effects of GLP-1RAs on myocardial cells.[75] Early models have demonstrated efficacy, but the use of GLP-1RAs in cancer therapy is not yet established and must be further investigated in clinical trials.[76]

**Hepatocellular carcinoma (HCC):**

Originally designed for diabetes treatment, GLP-1 receptor agonists (GLP-1RAs) have shown potential benefits for the management of non-alcoholic steatohepatitis (NASH), a condition highly associated with HCC.[77,78] Research has shown that the anti-inflammatory and metabolic effects of GLP-1RAs may influence the progression of liver diseases, including HCC.[80,81] These agents can modulate cellular proliferation, inflammation and oxidative stress in hepatocytes that are involved in the initiation and progression of HCC.[79] Liraglutide, a GLP-1RA, was effective in preventing the progression of hepatocellular carcinoma in a mouse model of NASH-associated HCC.[81] This protective effect was expressed by better glycaemic control, fewer liver tumours, and better liver histology compared with untreated controls.[81] Liraglutide may inhibit liver carcinogenesis via its metabolic actions, evidence suggests stressing the potential role of GLP-1RAs in the

prevention or treatment of HCC in patients with NASH. Besides hepatocellular carcinoma, GLP-1 has shown therapeutic potential in other gastrointestinal malignancies.

**Pancreatic cancer:** Investigators initially examined GLP-1 receptor (GLP-1R) expression in human pancreatic cancer tissues and adjacent non-cancerous pancreatic tissues, reporting reduced or absent GLP-1R expression in most pancreatic tumor samples.[82] Further in vitro and in vivo studies demonstrated that liraglutide inhibited pancreatic cancer cell growth and metastasis by activating GLP-1R.[82] The anti-cancer effects of liraglutide are linked to suppression of the PI3K/Akt signaling pathway, as Akt activation is a key driver of cell survival and proliferation, and liraglutide inhibits this pathway in a dose-dependent manner.[82] In the setting of type 2 diabetes mellitus (T2DM), liraglutide effectively limits the proliferation and dissemination of pancreatic cancer cells through GLP-1R activation and modulation of the PI3K/Akt pathway.[82]

**Colorectal cancer:** The therapeutic potential of GLP-1RAs in colorectal cancer (CRC) is primarily attributed to their ability to modulate Bone Morphogenetic Protein 4 (BMP4).[83] Aberrant BMP4 expression is a common feature of both T2DM and CRC and is an important research direction.[83] High glucose and insulin resistance in CRC cells upregulate BMP4 expression, which activates BMP4-Smad1/5/8 signalling pathway.[83] Activation of this pathway is involved in the promotion of epithelial-mesenchymal transition (EMT) which increases cellular proliferation, invasiveness and metastatic potential.[83] The exogenous administration of GLP-1RAs has been shown to reduce the expression of BMP4 . Reduced BMP4 also causes insulin resistance that leads to reduced proliferation of CRC cells treated with GLP-1RAs. BMP4 has thus emerged as a possible therapeutic target in CRC especially in diabetic patients as hyperglycemia plays a major role in cancer progression via BMP4 mediated mechanisms.[83] GLP-1RAs could be a promising therapeutic strategy by modifying BMP4 signalling and downstream effects on tumour growth and metastasis.[83] These findings highlight not only the significance of GLP-1RAs in diabetes management but also their potential use in integrated diabetes and cancer therapy.[82] Furthermore, they emphasise the significance of considering metabolic status in cancer treatment and advocate the need for further exploration in this area.[83] Although preliminary experimental models have shown promising results, the role of GLP-1RAs in the treatment of cancer has not been established yet and more clinical investigation and trials are required.[84]

## 2.CONCLUSION AND FUTURE PERSPECTIVES

The use of glucagon-like peptide-1 receptor agonists (GLP-1RAs) has revolutionized the care of T2DM, with proven impact on glycemic control combined with other beneficial effects like weight loss and cardiovascular protection. In addition to their accepted metabolic disorder indications, there is emerging evidence for the use of GLP-1RAs in a variety of disorders such as obesity, cardiovascular diseases, neurodegenerative disorders, non-alcoholic fatty liver disease, and some malignancies. There are a variety of these effects, which act through several molecular mechanisms related to glucose regulation, inflammation, oxidative stress, and cellular survival. Greater understanding of the benefits of GLP-1-based therapies, with the introduction of long-acting GLP-1s, oral GLP-1s, and multi-receptor GLP-1s, has enhanced their clinical use and increased patient adherence. New combinations and precision medicine strategies are likely to further improve clinical benefit and unmet clinical needs. Although notable advances have been accomplished, there is still a need for more research to better understand the long-term safety, efficacy and mechanism of action of GLP-1RAs in non-diabetic settings. As more studies and innovations continue, they are likely to expand their therapeutic uses and make GLP-1 receptor-targeted therapies a vital part of future disease management strategies. In summary, GLP-1RAs are a promising and versatile family of drugs that could be used to benefit many chronic conditions.

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