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## Glucagon-like Peptide-1 (GLP-1) Agonists: A Review



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### ABSTRACT

Diabetes mellitus (DM) is defined as a metabolic disease and is characterized by persistent elevation of blood glucose levels (Hyperglycemia). It is linked with abnormalities in the metabolism of carbohydrates, fats and proteins and if this illness is untreated over period it results in chronic complications which include Microvascular Complications (retinopathy, nephropathy and neuropathy) and Macrovascular complications (Coronary artery disease, Peripheral arterial disease and stroke). These complications can be prevented by optimal management of patient with diabetes mellitus and thereby improves quality of life. Valuable information that was obtained from research and drug development efforts over the past several decades has been applied directly for improving outcomes in Diabetes mellitus patients and this broaden the therapeutic repository. In recent years incretin has become an important target in the treatment of Type-2 Diabetes mellitus and Glucagon like peptide-1 receptor agonists (GLP-1 RA) are known for their role in glucose lowering effects. Glucagon like peptide-1 receptor agonists (GLP-1 RA) are evolving as a crucial therapy to consider in Type-2 Diabetes mellitus patients and this class drugs are given because of their ability to lower glycated haemoglobin and their associated weight loss and low risk for hypoglycemia. In this article we review GLP-1 agonists as a treatment of type 2 diabetes, their chemistry other effects will also be discussed.

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### 1. Introduction

Diabetes mellitus is a spectrum of metabolic disorders arising from diverse pathogenic mechanisms all resulting in hyperglycemia. Pathogenesis of this illness include both genetic and environmental factors, which involves inadequate insulin secretion, decreased responsiveness to endogenous or exogenous insulin, increased glucose production, or abnormalities in fat and protein metabolism. The resulting hyperglycemia may lead to both acute symptoms and metabolic abnormalities. Major causes of the morbidity of diabetes are the chronic complications that arise from prolonged hyperglycemia, including retinopathy, neuropathy nephropathy, and cardiovascular disease. These chronic complications can be alleviated in many patients by sustained control of the blood glucose and treatment of comorbidities such as hypertension and dyslipidemia [1]. There are now a wide variety of treatment options for hyperglycemia that target different processes involved in glucose regulation or dysregulation [2].

### 2. GLP-1 Agonists

Incretins are metabolic GI hormones that are secreted after nutrient intake and stimulate insulin secretion. The best-known incretins are

GLP-1 and GIP. GIP has reduced efficacy to stimulate insulin release and lower blood glucose in patients with type 2 diabetes, whereas GLP-1 is effective, and the GLP-1 signaling system has been a successful drug target. In recent years in the treatment of type-2 diabetes incretin system has become an important target and these peptides are known for its glucose-lowering effects.

Both GLP-1 and glucagon are derived from proglucagon, a 180 amino acid precursor with five separately processed domains. An amino-terminal signal peptide is followed by glycinin-related pancreatic peptide, glucagon, GLP-1, and GLP-2. Protein processing is chronological and takes place in a tissue-specific fashion. Pancreatic a cells cleave proglucagon into glucagon and a large C-terminal peptide that includes both of the GLPs. Intestinal L cells and specific hindbrain neurons process proglucagon into a large N-terminal peptide that includes glucagon or GLP-1 and GLP-2. GLP 2 affects the proliferation of epithelial cells lining the GI tract.

Apart from its primary function of GLP-1 to affect insulin release although it also effects in glucose metabolism and GLP-1 is secreted from the distal ileum and colon after nutrient intake and it also enhances glucose-dependent production and secretion of insulin it has also been shown to decrease glucagon secretion, increase glucose uptake and glycogen synthesis in peripheral tissues, delay gastric emptying and increase satiety, making it an ideal target for diabetes therapy [3].

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Given intravenously to diabetic subjects in higher amounts than normal, GLP-1 stimulates insulin secretion, inhibits glucagon release, reduces food intake, delays gastric emptying, and normalizes fasting and postprandial insulin secretion. The insulinotropic effect of GLP-1 is glucose dependent at insulin secretion at fasting glucose concentrations, even with high level of circulating GLP-1, is minimal. GLP-1 is rapidly inactivated by the enzyme DPP-4, yielding a plasma half-life of 1-2 min; thus, the natural peptide, itself, is not a useful therapeutic agent. Two broad strategies have been taken to applying GLP-1 to therapeutics: the development of injectable, DPP-4-resistant peptide agonists of the GLP-1 receptor and the creation of small-molecule inhibitors of DPP-4.

Exenatide was the first GLP-1 receptor agonist (GLP-1 RA) was approved by the US Food and Drug Administration (FDA) for the treatment of T2DM in April 2005 and since that time period onwards several other GLP-1 RAs have been added to the drug class and they possess characteristics such as improved weight loss, low risk for hypoglycemia and reduction in glycated haemoglobin (HbA1c) [4]. However, microvascular complications of diabetes can be reduced by improved glycaemic control but its effect on macrovascular complications is least and cardiovascular complications is one of the leading cause of death in type-2 Diabetes patient [5].

Many new diabetic drugs came to the market and clinical trials are mostly concerned regarding these drugs effect on cardiovascular risk and mostly with the drug Rosiglitazone linked with a significant increase in the risk of Myocardial infarction. Keeping these concerns in 2008 FDA came out with a initiative that anti diabetic drugs shown not to increase Cardiovascular risk. This recommendation led to initiation of prospective long term cardiovascular outcomes (CVOTS) for newly available diabetic drugs. This trial revealed that several drugs within the GLP-1 receptor agonists they have not only shown non inferiority but have also shown superiority in terms of cardiovascular Outcomes studies begin to show important cardiovascular benefits among certain drug classes, the American Diabetes Association (ADA) has now incorporated this consideration into its 2019 guidelines on diabetes treatment [6-8].

Since the approval of exenatide which is the first agent in the class there was number of GLP-1 receptor agonists have become available in United states. These include following medications:

1. Short-acting agents exenatide is administered twice daily (BID)
2. Intermediate-acting liraglutide which is administered once daily (OD)
3. Long-acting agents administered once weekly (QW), including exenatide QW, albiglutide, and dulaglutide. Lixisenatide (administered once daily) has also recently been approved in the United States [9].

### 3. Clinical Effects of GLP-1 Receptor Agonists

The primary goal of Antihyperglycaemic therapy is glycaemic control. GLP-1 receptor agonists is associated with A1C reductions from baseline during monotherapy and A1C reduction is more in dual and triple therapy [9].

The importance of weight management in Type- 2 diabetes patients was noted in the 2015 American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) clinical practice guidelines and recommend the use of antihyperglycemic agents that are associated with weight loss or at least have a neutral effect on body weight [10]. In Clinical trials while evaluating GLP-1 receptor agonists in type-2 diabetes they observed body weight reduction is the most common effect [9]. Weight loss in patients receiving GLP-1 receptor agonists is known to arise as a result of decreased gastric emptying and increased satiety.

In number of findings shown that GLP-1 receptor agonists do not aggravate CVD and may have wide potential cardiovascular benefits in type 2 diabetes patients. In recent report, liraglutide reduced the risk of cardiovascular death, non fatal myocardial infarction, or non fatal stroke in patients with type 2 diabetes and established cardiovascular disease [11]. Similar positive effects on cardiovascular risk have also been demonstrated in a trial of Semaglutide, a compound in development with similarities to liraglutide other GLP-1 receptor agonists (Exenatide and lixisenatide) are neutral with regards to cardiovascular risk in trials

completed to date. Moreover cardiovascular outcomes trials for other GLP-1 receptor agonists are in headway and results are expected in the forthcoming.

GLP-1 receptor agonists shows significant effects on blood pressure by decreasing systolic blood pressure (SBP) and, to a minor extent, diastolic blood pressure (DBP) [9].

Improvements in lipid levels also have been observed during treatment with GLP-1 receptor agonists [9].

### 4. Mechanism of Action

All GLP-1 RA share a common mechanism, activation of the GLP-1 receptor, a member of glucagon receptor family of GPCRs (class B GPCRs). GLP-1 receptors are expressed by beta cells, cells in the peripheral and central nervous systems, the heart and vasculature, kidney lung and GI mucosa. Binding of agonists to the GLP-1 receptor activates the CAMP-PKA pathway and several GEFs. The activity of several ion channels are altered by initiation of signalling via PKC and P13K by GLP-1 receptor activation, Increased biosynthesis of insulin and exocytosis in a glucose-dependent manner is attributed to end result of these actions in beta cells. Activation of GLP-1 receptors in the CNS accounts for the effects of receptor agonists on food intake and gastric emptying and for side effects such as nausea.

### 5. Adverse Effects

GLP-1 receptor agonists are associated with nausea and vomiting when they are administered through subcutaneous or intravenous route and this nausea and vomiting is attributed to neural activation of specific neurons in CNS that are activated only after following peripheral dosing of GLP-1 receptor agonist. The doses above which GLP-1 cause GI side effects are higher than those needed to regulate blood glucose. Nonetheless, up to 30%-50% of subjects report nausea at the initiation of therapy with any of the GLP-1 agonists, although the GI side effects of these drugs wane over time. Hypoglycemia associated with GLP-1 agonist treatment is rare. Based on surveillance data, there is a possible association of pancreatitis with exenatide treatment; therefore, these drugs should not be used in persons with a history of predisposition to pancreatitis. The GLP-1 is expressed by thyroid C cells. Although there is not an established clinical association with medullary carcinoma of the thyroid, GLP-1 agonists should not be given to these patients

### 6. Drug Interactions

Activation of GLP-1 receptors in the CNS mediates the typical delay of gastric emptying, and GLP-1 agonists may alter the pharmacokinetics of drugs that require rapid GI absorption such as oral contraceptives and antibiotics. In the absence of other diabetes drugs that cause low blood glucose, hypoglycemia associated with GLP-1 agonist treatment is rare, but the combination of GLP-1 agonist with sulfonylurea drugs which causes an increased propensity of hypoglycemia compared to sulfonylurea treatment alone.

### 7. Place in Therapy

While all of the GLP-1 receptor agonists have demonstrated efficacy as monotherapy, none is considered as a first-line agent. In people who do not achieve their HB A1C target after using metformin for 3 months then GLP-1 receptor agonists are suggested as add-on therapy. In patients who are contraindicated for Metformin then GLP-1 receptor agonists are advocated as first line therapy as an alternative to Metformin. GLP-1 receptor agonists are recommended for early use in type 2 diabetes because they suppress glucagon release and stimulate release of insulin only when blood glucose levels are raised thus, the risk of hypoglycemia is low [12].

In patients who do not achieve target HB A1C levels after using only Metformin then in those patients as dual therapy, GLP-1 receptor agonists are given in combination with metformin. In patients who are with persistent hyperglycemia and requiring triple therapy in those patients GLP-1 receptor agonists can be given in combination with metformin and a sodium-glucose co-transporter 2 inhibitor. This triple combination is particularly suggested for obese patients who are trying to control their weight. In addition use of in cretin with basal insulin may results in delay the use of bolus (mealtime) insulin with decreased risk of

hypoglycemia. This simplified regimen reduces the need for matching mealtime insulin to specific carbohydrate ratios and also helps reduce the weight gain often seen with insulin use [13].

### 8. Dosing in Renal Impairment

Exenatide BID and once weekly regimen should not be used in patients with severe renal impairment (creatinine clearance <30 mL/min) or end-stage renal disease (ESRD) and should be used with caution in patients with moderate renal impairment (creatinine clearance 30-50 mL/min) or with a history of renal transplantation [14].

There are limited data on the use of liraglutide in patients with renal impairment; thus, liraglutide should be used with caution in this population [15].

Albiglutide, lixisenatide, and dulaglutide may be used without dose adjustment in patients with mild, moderate, or severe renal impairment (estimated glomerular filtration rate 15–89 mL/min/1.73 m<sup>2</sup>), and dulaglutide may be used without dose adjustment in patients with ESRD. However, renal function must be monitored in patients with renal impairment who experience severe gastrointestinal adverse effects during treatment with albiglutide, lixisenatide, or dulaglutide because of the potential for dehydration [15-17].

### 9. Patient Education

Successful diabetes management includes educating patients regarding their specific treatment plan so that they know what to expect from the treatment and how to use it correctly.

Patients being prescribed a GLP-1 receptor agonist should be educated regarding proper storage and mixing (if needed) of the medication before injection, correct dosage, administration sites, and administration technique. Medication storage and injection preparation and use requirements may differ by product; thus, directions should be reviewed not only with patients receiving a first GLP-1 receptor agonist prescription, but also for those changing medications. Patients should be counseled that GLP-1 receptor agonists are not insulin, but some patients may need both a GLP-1 receptor agonist and insulin.

### 10. Conclusion

Agents in the GLP-1 receptor agonist class are successful treatment choices for patients with type 2 diabetes, promoting reductions in A1C, cardiovascular risk and body weight as monotherapy or as an add-on to other antihyperglycemic treatments, including insulin. Helping patients establish realistic expectations and providing instructions about how the medication works are important to help ensure desired outcomes.

### Conflict of Interest

Nil

### Ethical Consideration

None

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