

## Development of therapeutic options on type 2 diabetes in years: Glucagon-like peptide-1 receptor agonist's role in treatment; from the past to future

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### Abstract

Diabetes mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia. Type 2 diabetes (T2DM) accounting for 90% of cases globally. The worldwide prevalence of DM is rising dramatically over the last decades, from 30 million cases in 1985 to 382 million cases in 2013. It's estimated that 451 million people had diabetes in 2017. As the pathophysiology was understood over the years, treatment options for diabetes increased. Incretin-based therapy is one of them. Glucagon-like peptide-1 receptor agonist (GLP-1 RA) not only significantly lower glucose level with minimal risk of hypoglycemia but also, they have an important advantage in the management of cardiovascular risk and obesity. Thus, we will review here GLP-1 RA's role in the treatment of diabetes.

**Key words:** Incretin-based therapy; Incretin mimetics; Glucagon-like peptide-1 receptor agonist; Dipeptidyl peptidase-4 inhibitor

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**Core tip:** The prevalence of type 2 diabetes and its complications rising dramatically over the last years. It is well known that diabetes and its complications; especially cardiovascular complications lead to increased morbidity and mortality. Treatment options for diabetes have increased as the pathophysiology was understood. We discuss the incretin-based therapy, especially Glucagon-like peptide-1 receptor agonists and the beneficial effects on comorbidities besides glucose lowering effect.

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## INTRODUCTION

Diabetes Mellitus (DM) is a chronic metabolic disease characterized by hyperglycemia. Depending on etiology; decreased insulin secretion, decreased glucose utilization and increased glucose production contribute to hyperglycemia<sup>[1]</sup>. There are several distinct types of DM. Type 2 DM (T2DM) accounting for 90% of cases globally<sup>[2]</sup>. T2DM demonstrate insulin resistance in peripheral tissues, defective insulin secretion particularly in response to glucose stimuli and increased glucose production by the liver as three cardinal abnormalities<sup>[2]</sup>. Increased lipolysis in fat tissue, increased production of glucagon, incretin hormone deficiency and resistance, increased renal tubular glucose reabsorption and central nervous system role in metabolic regulation also contribute to the pathophysiology of T2DM<sup>[3]</sup>. The worldwide prevalence of DM is rising dramatically over the last decades, from 30 million cases in 1985 to 382 million cases in 2013<sup>[4]</sup>. It's estimated that 451 million people had diabetes in 2017<sup>[4]</sup>. As the pathophysiology was understood over the years, treatment options for diabetes increased. Thus, we will review here Glucagon-like peptide-1 receptor agonist (GLP-1 RAs) role in the treatment of diabetes. We aimed to summarize not only their glucose lowering effect but also their efficacy on the comorbidities come along with diabetes, such as obesity and cardiovascular disease (CVD).

We selected the articles by searching an electronic database (PubMed) with the following terms; glucagon-like peptide 1 agonists, glucagon-like peptide 1 agonists and CVD, glucagon-like peptide 1 agonists and obesity, dipeptidyl peptidase-4 (DPP-4) inhibitors. The articles not related to diabetes, the case reports, abstract only, comments and conference papers were excluded. Only studies in English language were included. Cardiovascular safety trial of each molecule (GLP-1 RA and DPP-4 inhibitor) were also included. All the included articles reviewed for full text.

## ROLE OF INCRETINS IN GLUCOSE HOMEOSTASIS

Glucose is the most important physiologic substance involved in the regulation of insulin secretion from the pancreas<sup>[5-7]</sup>. Glucose has a dose-dependent effect on the beta cells. It's well known that oral glucose administration has a greater effect on insulin release than intravenous glucose administration<sup>[8-10]</sup>. Known as the incretin effect. In a study, insulin secretion was detected 26% lower in response to IV administration than oral administration<sup>[10]</sup>. This increased response to oral glucose shows that glucose absorption from the gastrointestinal tract may cause secretion of some hormones which have an effect on B-cell sensitivity<sup>[5-10]</sup>. GLP-1 and glucose-dependent insulintropic polypeptide (GIP) are the major incretin hormones in humans<sup>[11]</sup>. GIP is produced in the K-cells and these cells are located predominantly in the proximal parts of the intestine, especially in the duodenum. GLP-1 is produced by the L-cells which distally situated especially in the ileum. L-cells also found in the colon in high density<sup>[12]</sup>. Both K-cells and L-cells can be situated throughout all parts of the intestine. It's also detected that there is a population of cells which contain both GLP-1 and GIP<sup>[13]</sup>. Secretion of incretin hormones is correlated with food intake and the driving factor is the presence of nutrients in the lumen, not distension since loading of water does not cause a significant increase in GLP-1 and GIP concentrations<sup>[14-16]</sup>. The incretins are cleaved by the enzyme DPP-4 and lose their biologic activity<sup>[1,2]</sup>.

## INCRETIN EFFECT IN DIABETES MELLITUS

The incretin effect found substantially reduced or even absent in patients who have T2DM and hyperglycemia<sup>[17-19]</sup>. As the fasting plasma glucose level increases above the level defining diabetic state (126 mg/dL), incretin effect seems to start to reduce<sup>[20]</sup>.

This reduced effect is universal with the possible exception of East Asians<sup>[21]</sup>.

T2DM patients almost completely lost response to GIP<sup>[22]</sup>. Because much of the incretin effect in healthy individuals is mediated by GIP, lack of activity may explain the reduced incretin effect in T2DM patients<sup>[20]</sup>. Besides this; the substantial insulinotropic activity of GLP-1 retains in these patients and GLP-1 activity related to dose and concentration, linearly<sup>[23-25]</sup>. However, GLP-1 insulinotropic effect is reduced compared with healthy individuals; a result of reduced B-cell mass, most likely<sup>[25,26]</sup>. The effects of GLP-1 on appetite, gastrointestinal motility, food intake, and suppression glucagon secretion are retained<sup>[23,27]</sup>. Parenterally given GLP-1 significantly increase insulin secretion, suppress glucagon secretion and normalize glucose concentration<sup>[22]</sup>.

## INCRETIN-BASED THERAPY IN T2DM

As the research in the field of diabetes progressed and the pathophysiologic processes were understood, new therapeutic options were invented. Incretin-based treatment is one of them. Practically, DPP-4 inhibitors or GLP-1 RAs can be used for this therapeutic approach. Besides that, GLP-1 gene transferring has studied in animal models and it was showed that GLP-1 gene transfer may be an alternative to GLP-1 infusion or multiple daily or weekly injections, in the future<sup>[28,29]</sup>.

There are several GLP-1 agonists used in daily clinical practice. Some of them are listed below in Table 1<sup>[30]</sup>. All of the GLP-1 agonists administered by subcutaneous injection but semaglutide also has an oral form<sup>[31]</sup>. On the other site, all of the DPP-4 inhibitors are given orally. Alogliptin (25 mg, once daily), linagliptin (5 mg, once daily), saxagliptin (5 mg once daily), sitagliptin (100 mg, once daily) and vildagliptin (50 mg, twice daily) are the DPP-4 inhibitors used in daily clinical practice<sup>[32]</sup>.

GLP-1 RA and DPP-4 inhibitors are important therapeutic options for patients with T2DM<sup>[33]</sup>. European Association for the Study of Diabetes and the American Diabetes Association recommend these agents as the second line for the treatment of T2DM<sup>[34]</sup>. The glucose-lowering effect of these agents with minimal risk of hypoglycemia is well studied. They also have a favorable effect on body weight and blood pressure<sup>[35-43]</sup>. The efficacy of GLP-1 RAs is greater than DPP-4 inhibitors, in general<sup>[44]</sup>. While patients who receive GLP-1 RA experience significant weight loss, the effect of DPP-4 inhibitors on body weight is neutral<sup>[44,45]</sup>. In a systematic review of comparative effectiveness of GLP-1 RAs, it was concluded that GLP-1 RAs are similar or more effective than oral glucose-lowering agents in improving glycemic parameters. In the same review, GLP-1 RAs found to provide similar or less decrease in HbA1c level compared with insulin therapy, with less hypoglycemia<sup>[46]</sup>.

## CARDIOVASCULAR OUTCOMES OF INCRETIN-BASED THERAPY IN T2DM

After the meta-analysis, published by Nissen and colleagues in 2007, suggesting that rosiglitazone (an anti-diabetic agent) was associated with increased risk of myocardial infarction (MI) among T2DM patients, United States Food and Drug Administration (FDA) mandated the conduct of large, randomized, placebo-controlled cardiovascular safety trials for all new anti-diabetic agents<sup>[47,48]</sup>. FDA defined the standards of these studies<sup>[48]</sup>. Several large randomized controlled trials (RCT) have been completed since that time. The RCT examined saxagliptin for cardiovascular safety established an unexpected increased risk of hospitalization for heart failure among patients randomized to saxagliptin<sup>[49,50]</sup>. The RCT's examined other DPP-4 inhibitors didn't establish such results<sup>[51-59]</sup>. Vildagliptin haven't been studied in RCT for examining cardiovascular safety.

Because the GLP-1 RAs promote weight loss, reduce blood pressure, decrease myocardial and vascular inflammation and decrease platelet aggregation behind their effect on blood glucose level, they thought to reduce cardiovascular risk<sup>[60,61]</sup>. Cardiovascular safety was established for the whole class in the RCTs of cardiovascular outcomes with GLP-1 RAs (liraglutide, semaglutide, lixisenatide, and extended-release exenatide). Besides that, the results for cardiovascular efficacy was mixed<sup>[62-65]</sup>. Among these RCTs in two studies (SUSTAIN 6 and LEADER) a significant reduction in three-point major adverse cardiovascular events (non-fatal stroke, non-fatal MI and cardiovascular mortality) was shown<sup>[63,64]</sup>. Questions emerged after these varying findings about the generalizability of the trials to the drug class. The data available from the RCTs of cardiovascular outcomes with GLP-1 RAs was synthesized in a meta-analysis to examine the overall effect on cardiovascular efficacy and

**Table 1** Glucagon-like peptide-1 receptor agonist

Drug	Administration	Phase 3 clinical trial
Exenatide	Twice daily (5 µg or 10 µg)	Amigo
Liraglutide	Daily (0.6 mg or 0.8 mg or 1.2 mg)	Leader
Exenatide ER	Weekly (2 mg)	Duration
Lixisenatide	Daily (10 µg or 20 µg)	Getgoal
Dulaglutide	Weekly (0.75 mg or 1.5 mg)	Award
Semaglutide	Weekly (0.5 mg or 1.5 mg)	Sustain
Albiglutide	Weekly (30 mg or 50 mg)	Harmony

safety<sup>[66]</sup>. According to this meta-analysis; cardiovascular safety appointed for all GLP-1 RAs, use of GLP-1 RAs was associated with a significant 10% relative risk reduction for the three-point major adverse cardiovascular events, also associated with risk reduction in cardiovascular mortality of 13% and all-cause mortality of 12% compared with placebo<sup>[66]</sup>. Likewise, it was determined in a retrospective epidemiological study that patients who treated with exenatide were less likely to have CVD, CVD related and all-cause hospitalizations<sup>[67]</sup>. The trial of cardiovascular outcomes in patients with T2DM on albiglutide was completed in 2018 and it was shown that albiglutide was both as safe as placebo in terms of cardiovascular outcomes and superior to placebo in efficacy even in short period of time (1.6 years)<sup>[68]</sup>.

The effect of incretin-based therapy on atherosclerosis was examined in a meta-analysis of RCTs. Incretin-based therapy showed significant improvement of carotid intima media thickness in the long term (2 years) but it has failed to show this effect in 1 year follow up<sup>[69]</sup>.

Certain experimental studies examined incretin receptors on vascular smooth muscle cells and showed their role in causing atherosclerosis<sup>[70,71]</sup>. Also, the efficacy of DPP-4 inhibitors on improvement of endothelial function was shown<sup>[72]</sup>.

It was generally shown in observational studies that there is a relationship between hyperglycemia and CVD but reduced CVD by reducing hyperglycemia haven't confirmed in clinical trials<sup>[73-78]</sup>. Moreover, one trial terminated early because in the intensive glycemic treatment arm, all-cause mortality was increased and, in each subgroup, it was associated with hypoglycemia<sup>[74,79]</sup>. It's an important point that GLP-1 RAs and DPP-4 inhibitors have a glucose lowering effect with less hypoglycemia (GLP-1 RAs are more potent than DPP-4 inhibitors)<sup>[35-44]</sup>.

According to the recent meta-analysis, GLP-1 RAs are seemed to be cardio-protective as a whole class<sup>[80]</sup>. They have pleiotropic actions on cardiovascular risk factors with a direct effect on the cardiovascular system (Table 2)<sup>[69,80,81]</sup>.

A recently published review in which several preclinical studies were examined, it was concluded that using GLP-1 agonists improve functional outcome after ischemic stroke. It's unknown whether these results are valid for humans in clinical practice<sup>[82]</sup>.

## THE EFFECT OF INCRETIN-BASED THERAPY ON BODY WEIGHT

Obesity is an important risk factor and comorbidity of T2DM, and it also elevates cardiovascular risk. Obesity must also be managed for effective treatment of T2DM. GLP-1 RAs were studied in several trials and it was established that GLP-1 RAs cause significant weight loss in T2DM patients with obesity<sup>[46,83,84]</sup>. The effect of DPP-4 inhibitors on weight in neutral<sup>[44,45,83]</sup>. Although GLP-1 RA's cost and administration route may be limitations for generalized acceptance, they may also offer a reasonable alternative choice for obese patients (liraglutide 3 mgr.) without diabetes who don't achieve weight-loss goals with lifestyle modification alone<sup>[84]</sup>.

## CONCLUSION

T2DM is a chronic disorder which comes along with several comorbidities like obesity, CVD, kidney disease, hypertension, *etc.* As long as the pathophysiologic process of DM was understood over the years, several new therapeutic options emerged. Individualizing care gained importance in the last years for the management of DM. It's important to manage obesity, hypertension, hyperlipidemia

**Table 2 Cardiovascular effect of glucagon like peptide-1 receptor agonists**

Anti-atherosclerotic effect	Decrease matrix metalloproteinase 2; decrease vascular smooth muscle cell proliferation
Improves endothelial function	Increase nitric oxide-induced vasodilation; decrease oxidative stress
Anti-inflammatory effect	Suppress human macrophages by inhibition of protein kinase C
Decrease infarct/injury size	Decrease glucose-induced apoptosis; decrease intracellular calcium overload
Modifies risk factors	Improve glycemic control; decrease body weight; decrease blood pressure; decrease low-density lipoprotein

and total cardiovascular risk together with lowering glucose level with minimal risk of hypoglycemia. GLP-1 RAs not only significantly lower glucose level with minimal risk of hypoglycemia but also, they have an important advantage in the management of cardiovascular risk and obesity.

All GLP-1 RAs are administered parenterally but semaglutide also can be given orally by now. Besides that, it was showed that GLP-1 gene transfer may be an alternative to GLP-1 injections, in the future.

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