The role of glucagon-like petide-1 receptor agonists in the treatment of type 2 diabetes

Forst, Laura Helene

Master's thesis / Diplomski rad

2023

Degree Grantor / Ustanova koja je dodijelila akademski / stručni stupanj: **University of Rijeka, Faculty of Medicine / Sveučilište u Rijeci, Medicinski fakultet**

Permanent link / Trajna poveznica: https://urn.nsk.hr/urn:nbn:hr:184:159016

UNIVERSITY OF RIJEKA
FACULTY OF MEDICINE

INTEGRATED UNDERGRADUATE AND GRADUATE UNIVERSITY STUDY OF

MEDICINE IN ENGLISH

Laura Helene Forst

THE ROLE OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS IN THE TREATMENT OF TYPE 2 DIABETES

GRADUATION THESIS

Rijeka, 2023

UNIVERSITY OF RIJEKA
FACULTY OF MEDICINE

INTEGRATED UNDERGRADUATE AND GRADUATE UNIVERSITY STUDY OF

MEDICINE IN ENGLISH

Laura Helene Forst

THE ROLE OF GLUCAGON-LIKE PEPTIDE-1 RECEPTOR AGONISTS IN THE TREATMENT OF TYPE 2 DIABETES

GRADUATION THESIS

Rijeka, 2023

Thesis mentor: Assoc. Prof. Sanja Klobučar, MD, PhD

The graduation thesis was graded on _____ in _____, before the Committee composed of the following members:

1. Assist. Prof. Duška Petranović, MD, PhD
2. Assist. Prof. Vanja Licul, MD, PhD
3. Prof. Ines Mrakovčić Šutić, MD, PhD

The graduation thesis contains 24 pages, 0 figures, 4 tables, 22 references.

Table of Content

List of abbreviations and acronyms

(GIP) ..... *Gastric inhibitory polypeptide*

BMI ..... *Body mass index*

DPP-4 ..... *Dipeptidyl peptidase-4*

GLP-1 ..... *Glucagon-like-peptide-1*

GLP-1-RA ..... *Glucagon-like-peptide-1 receptor agonist*

IL-6 ..... *Interleukin-6*

NEP 24.11 ..... *Neutral Endopeptidase 24.11*

SGLT-2 ..... *Sodium/glucose cotransporter 2*

T1DM ..... *Type 1 diabetes mellitus*

T2DM ..... *Type 2 diabetes mellitus*

TNF- alpha ..... *Tumor necrosis factor-alpha*

1. Introduction

1.1 Diabetes mellitus

Diabetes mellitus is a disease characterized by deteriorated blood glucose control. Diabetes can be differentiated in Type 1 (T1DM), Type 2 diabetes (T2DM), gestational diabetes and other specific types due to genetic defects, diseases of the exocrine pancreas, endocrinopathies, infections and side effects of drugs. T1DM is an autoimmune disease in which beta cells located in the islets of Langerhans of the pancreas are destroyed by autoantibodies, resulting in absolute insulin deficiency after approximately 90 percent of beta cells have been destroyed. Although T1DM can occur at older ages, most patients with T1DM manifest in childhood or adolescence. The patient is dependent on lifelong substitution therapy with insulin. The main symptoms of elevated glucose levels are polydipsia, polyuria, polyphagia, weakness, lethargy, fatigue, and decreased performance. In severe cases, patients may develop life-threatening ketoacidosis.
Type 2 diabetes is driven by insulin resistance and progressive loss of pancreatic beta cell function. The majority of patients are asymptomatic at the time of diagnosis. Overweight and obesity are believed to account for 85% of the risk of developing type 2 diabetes, particularly if the excess weight accumulates in the abdomen.
Visceral deposition of adipose tissue leads to a shift in the synthesis of several adipocytokines such as adiponectin, IL -6, and TNF- alpha, which promote oxidative stress and inflammation. These changes in visceral adipose tissue homeostasis promote the development of hypertension, dyslipidemia, insulin resistance, and atherogenesis. T2DM is a multifactorial process leading to an increased risk of a plethora of vascular and organ complications. We distinguish between microvascular complications and macrovascular complications.

1.2 Macrovascular complications

Macrovascular complications include atherosclerotic cardiovascular disease, stroke, and peripheral artery disease. While cardiovascular disease is three times more common in patients with diabetes compared to nondiabetic subjects, ischemic stroke is as many as five times more common in diabetics. Three out of four patients with type 2 diabetes die from cardiovascular disease or stroke. The mechanism of how diabetes affects the heart, brain and peripheral vessels is due to atherosclerosis. Atherosclerosis is the accumulation of lipids and increased

inflammation in the vessel wall. In addition to worsened glycemic control, dyslipidemia, hypertension, and activated inflammation are important drivers of atherosclerosis in patients with diabetes mellitus. Besides these cardiovascular atherosclerotic complications, heart failure is a common cardiac complication of T2DM.

1.3 Microvascular complications

Microvascular complications occur in the kidney as diabetic nephropathy, in the eyes as diabetic retinopathy, and in the nervous system as diabetic neuropathy. Nowadays, diabetic nephropathy, also known as diabetic kidney disease, has become the most common cause of chronic kidney disease and kidney failure. Furthermore, diabetic retinal disease is the most common cause of blindness in the western world. Peripheral diabetic neuropathy mainly affects sensory, motor and autonomic nerve fibers in the lower leg and is the main cause of diabetic foot ulcers. The impairment of autonomic nerve fibers throughout the body can lead to a plethora of symptoms such as silent myocardial infarction, sexual dysfunction, gastroparesis, impaired pupillomotor reflexes and many others.

1.4 Therapy

While insulin treatment is mandatory in patients with type 1 diabetes, most patients with type 2 diabetes do not require insulin in the early stages of the disease. Basic measures in the treatment of type 2 diabetes are lifestyle modification with a healthy diet and an increase in physical activity. If blood glucose levels are still inadequately controlled, first line treatment is based on metformin in order to improve hepatic insulin sensitivity. If metformin is not tolerated or if treatment goals are still not met, other blood glucose-lowering medications are required. While in the past, sulfonylureas, glinides, and insulin were the only available additional drugs to lower glucose levels in T2DM patients, incretin-based treatments (DPP-4 inhibitors, GLP-1 receptor agonists) or SGLT-2 inhibitors have expanded the pharmacological armamentarium in the treatment of T2DM.

2. Aims and objectives

The aim of this thesis is to illustrate the potential of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in the treatment of type 2 diabetes with regard to metabolic and pleiotropic effects such as cardio- and nephroprotection.

Several studies have shown that GLP-1 RAs such as liraglutide, semaglutide, or dulaglutide reduce body weight and should be used especially in T2DM when body weight reduction is a treatment goal. This is not only for cosmetic reasons, but could also help reduce obesity-related conditions such as dyslipidemia, inflammation, insulin resistance, or elevated blood pressure. Overall, the organ-protective effects demonstrated in several studies with GLP-1 RAs are promoted. The objective of this work is to provide an overview of the mode of action, metabolic, pleiotropic and organ protective effects of GLP-1 RAs in the treatment of T2DM.

3. Literature review

3.1 General Information

Incretins are a group of gut hormones that are released from intestinal cells after food intake. They function to regulate glucose and lipid metabolism as well as energy homeostasis, especially in postprandial metabolic control.

Gastric inhibitory polypeptide (GIP) and glucagon-like peptide-1 (GLP-1) both belong to the incretin family, which have an important role in the regulation of postprandial glucose and lipid homeostasis.

GIP and GLP-1 increase postprandial insulin release from beta cells. While in non-diabetic subjects, GIP has been found to have stronger insulin releasing effect compared to GLP-1, in patients with T2DM this effect has been found to be impaired. In contrast, GLP-1 has been found to maintain its metabolic effects in patients with T2DM, and to evolve potential beneficial effects in heart, stomach, brain and kidney function (1).

After post- transitional processing of proglucagon peptide, GLP-1 is obtained. There are two bioactive forms of GLP-1 derived from the inactivated form GLP-1 (1-37.) Through amidation and proteolytic cleavage of GLP-1 (1-37) the activated forms GLP-1 (7-36) and GLP-1 (7-37) are formed (2).

The structure is based on a 30- or 31- amino acid long peptide hormone sequence.

After food ingestion, enteroendocrine L- cells, located in the intestine, with particularly high density in the distal ileum and colon, release GLP-1 into the bloodstream (2).

3.2 Function

First studies with native GLP-1 given as an infusion to patients with type 2 diabetes have shown that it increases the insulin release and decreases the glucagon release in a strongly glucose-dependent manner.

The hormone binds to receptors for glucagon-like peptides located on pancreatic beta cells and coupled to G proteins. These activate the enzyme adenylate cyclase, which increases the cycle AMP. This in turn acts on PKA and Epac2, leading to a change in the activity of specific ion channels. Activation of this cascade results in an increase in cytosolic calcium levels, which triggers insulin release as glucose levels rise, eventually leading to exocytosis of insulin stored in the granules of pancreatic beta cells (2).

GLP-1 stimulates enzymes that convert proinsulin to insulin and C-peptide. Additionally, GLP-1 prevents beta cell exhaustion during secretion by providing for the synthesis and replenishment of insulin stores.

It is also able to promote proliferation and neogenesis to increase beta cell mass, while inhibiting apoptosis (2). Glucagon-like peptide-1 acts only in a glucose-dependent manner, which distinguishes it from drugs such as sulfonylureas. In addition to its effects on beta cells, GLP-1 inhibits glucagon release from alpha cells during postprandial glucose elevation without affecting glucagon release at low glucose levels.

GLP-1 has a variety of actions that include not only effects on the pancreas, but also stimulation of receptors in the kidney, heart, lung, adipose tissue, smooth muscle, and nuclei in the central nervous system (2).

3.3 Degradation

The degradation of glucagon-like peptide-1 can take place through three different mechanisms. Dipeptidyl peptidase-4 (DPP-4), an enzyme with catalytic and proteolytic functions, degrades GLP-1 within very short time. This enzyme is predominantly located in endothelial cells adjacent to cells which secrete GLP-1 and also in hepatocytes. The degradation amounts an approximate half- life of 2 minutes. Due to its rapid degradation, only 10-15% of GLP-1 is released into the bloodstream, and fasting plasma levels reach a rate of only 0-15 pmol/L (2).

Another way of how GLP-1 is removed from the body is by an enzyme called neutral endopeptidase 24.11, short NEP 24.11. This enzyme is a membrane bound zinc metallopeptidase which is found in multiple tissues, with a high expression especially in renal tissue. Degradation of GLP-1 by NEP 24.11 might raise up to 50%, in case degradation by DPP-4 is incomplete.

If GLP-1 is successfully splitted and inactivated by either DPP-4 or NEP 24.11 it will be eliminated by renal clearance (2).

3.4 Gene expression

Glucagon-like peptide-1 is a hormone originally derived from the proglucagon gene. This gene is expressed mainly in the alpha cells of the islets of Langerhans in the pancreas, the enteroendocrine L cells in the intestine, and in the caudal brainstem and hypothalamus of the brain. Proglucagon gene expression is promoted by low fasting glucose levels, whereas insulin secretion would result in inhibition of proglucagon gene expression (3).

3.5 Secretion

GLP-1 is a hormone which is stored in secretory granules in the L cells of the intestine. The release into the hepatic portal system takes place after ingestion of food. These intestinal L cells are located in the distal part of the ileum, colon, jejunum and duodenum.
The release of GLP-1 can be further characterized by a biphasic pattern, which differentiate into an early phase after 10-15 min and into a longer second phase after 30-60 min. The early phase taking place 10-15 minutes upon meal ingestion is mostly explained by mechanisms controlled by neural signaling, gut peptides or neurotransmitter release. A different theory assumes that direct contact between luminal nutrients and intestinal L cells, located in the proximal jejunum, triggers early phase secretion.
The second longer phase taking place after 30-60 minutes upon food ingestion is initiated through direct stimulation of intestinal L cell by ingested nutrients (3).

3.9 GLP-1 analogues

As presented, natural human GLP-1 is an endogenously produced incretin with important activities in glucose control and energy homeostasis. The extremely short half-life of 2 minutes makes human GLP-1 very problematic for its clinical use as a drug for the treatment of T2DM. A pharmacological approach is looking for peptides that activate the GLP-1 receptor and have a longer half-life.
A first so-called GLP-1 receptor agonist was realized with a peptide isolated from the saliva of a lizard called Heloderma suspectum. This peptide was named exendin 4 and was the first GLP-1 receptor agonist approved for the treatment of type 2 diabetes mellitus. It only corresponded 53% with the structural homology of native GLP-1 but showed the same efficacy in activating

GLP-1 R. Its resistance to degradation by the enzyme DPP-4 prolonged the half-life time to 3.3 to 4 hours, making the drug suitable for twice-daily subcutaneous injection (1).

Other GLP-1 receptor agonists are based on the amino acid sequence of human GLP-1 but are modified at some amino acid sequences to make the peptide resistant to DPP-4 degradation.

Nowadays seven different GLP1 RA have been introduced into the market for the treatment of T2DM. As shown in Table 1, these medications can be differentiated in short-acting GLP-1 RA and long-acting GLP-1 RA.

Short-acting GLP-1 RA include exenatide (administered twice daily) and lixisenatide (administered once daily), which have been shown to be highly resistant to DPP-4. Unfortunately, their half-life is still only 2 to 3 hours maximum due to renal excretion. Moreover, plasma concentrations show a strong fluctuation with intermittent activation of GLP1 RA due to the short half-life and once- or twice-daily injection.

Long-acting GLP-1RAs have been modified in a way to be bound to albumin and have prolonged renal elimination. They are characterized by longer half-lives and much less plasma fluctuation, resulting in continuous activation of GLP-1 R for over twenty-four hours. Long-acting GLP-1 RA include liraglutide, albiglutide, dulaglutide, exenatide once weekly, and semaglutide (1,4).

3.9.1 Short-acting GLP-1 RAs

The two short-acting GLP1 RAs are exenatide and lixisenatide. Exenatide, taken twice daily, and lixisenatide, taken once daily, are both drugs based on the structure of exendin 4. Their half-life is 2 to 4 hours (1,4).

As with all GLP-1 RA, both drugs enhance insulin biosynthesis and processing, thereby increasing insulin release from beta cells as blood glucose levels rise. In parallel, GLP-1 RA inhibit the release of glucagon from alpha cells during postprandial glucose elevations. (20,21). The inferred postprandial increase in the portal insulin/glucagon ratio suppresses hepatic glucose output, and reduces postprandial glucose excursions. In the stomach, GLP-1 RAs have an inhibitory effect on gastric motility and delay gastric emptying, further slowing the rise in glucose concentration after ingestion of a meal. This effect on gastric emptying is most apparent during treatment with short-acting GLP-1 RA and appears to diminish over time with long-acting GLP-1 RA due to steady stimulation of GLP-1-R and the development of tachyphylaxis (5).

Activation of GLP-1 receptors in hypothalamic regions of the central nervous system might drive the anorectic effects observed during treatment with GLP-1 RA. While both effects of GLP-1 RAs on gastric motility and in the central nervous system might support weight loss, they are also held responsible for the frequent gastrointestinal side effects such as nausea and vomiting.

3.9.2 Long-acting GLP-1 RA

Long-acting GLP-1 RA include liraglutide, semaglutide, dulaglutide, albiglutide and exenatide once weekly. With the exception of exenatide once weekly which is based on the similar peptide sequence as short-acting exenatide, all other long-acting GLP-1-RA are based on the synthetic version of native GLP-1.

Liraglutide is the only long-acting GLP-1-RA which is injected once daily, whereas all other medications should be administered once weekly. Due to the addition of a fatty acid chain, liraglutide works with delayed absorption from the subcutaneous tissue into the bloodstream after injection and its non-covalent albumin binding reduces renal clearance.

Even though liraglutide is injected once daily, its half-life of approximately 13 hours results in activation of the GLP-1 receptor that persists for more than 24 hours and is therefore classified as long-acting GLP-1 RA (1,4). Dulaglutide and albiglutide are protected from DPP-4 degradation by amino acid sequence modification at positions 8 and 9 of the amino acid chain. In addition, protein binding to albumin prolongs renal excretion of albiglutide. In dulaglutide, the GLP-1- RA is bound to an IgG-Fc fragment to slow renal clearance of this molecule (6). The half-life of liraglutide accounts for 13 hours whereas dulaglutide, albiglutide and exenatide have a half- life of approximately five days in the human body.

In terms of reduction of HbA1c long-acting GLP-1 RA were found to be more effective than exenatide twice daily or lixisenatide once daily. Reduction in body weight was best achieved with liraglutide or semaglutide compared with exenatide once weekly, dulaglutide, or albiglutide.

Albiglutide was discontinued in 2017 due to its weak effects on HbA1c and body weight. This was attributed to the molecule size being too large to cross the blood-brain barrier and therefore not showing central anorectic effects (1,4).

Semaglutide differs from liraglutide by binding to a different free fatty acid, that further increases binding to albumin. It has been shown to be more successful than dulaglutide and exenatide once weekly in decreasing HbA1c levels, fasting plasma glucose and body weight.

Gastrointestinal upsetting although, was more often seen with semaglutide than exenatide once weekly.

In addition to the subcutaneous formulation, an oral form of semaglutide has been developed that has been shown to have similar effects on lowering HbA1c levels, fasting plasma glucose levels, and body weight (7).

The most common adverse symptoms observed in patients taking long-acting GLP-1 RAs are gastrointestinal side effects, particularly nausea and vomiting.

Within the group of long-acting GLP-1 RAs, dulaglutide and liraglutide have been shown to have the highest incidence of nausea, whereas exenatide once weekly and albiglutide had fewer symptoms of nausea. In a study comparing dulaglutide and semaglutide, gastrointestinal side effects appeared to be comparable between these two once-weekly GLP-1 RAs (8)

Exenatide once weekly is the GLP-1 RA with the strongest antibody development compared with liraglutide, dulaglutide, or albiglutide (1).

Table 1. Overview of GLP–1 RAs

GLP-1 RA	Amino acid sequence	Elimination half- life	Administration
For subcutaneous injection - Short acting compound			
Exenatide	Exendin-4	3.3 - 4.0 h	Twice daily
Lixisenatide	Exendin-4	2.6 h	Once daily
- Long acting compounds			
Liragultide	Mammalian GLP-1	13 h	Once daily
Once weekly exenatide	Exendin-4	3.3 – 4.0 h	Once weekly
Dulaglutide	Mammalian GLP-1	4.7 – 5.5 d	Once weekly

Albiglutide	Mammalian GLP-1	5.7 – 6.7 d	Once weekly
Semaglutide	Mammalian GLP-1	5.7 – 6.7 d	Once weekly
For oral administration			
Semaglutide	Mammalian GLP-1	5.7 – 6.7 d	Once daily

3.10 Metabolic properties

For the treatment of T2DM, GLP-1 receptor agonism is highly relevant when it comes to the effect on the Langerhans islet of the pancreas. The main glucose lowering mechanism of action is to enhance insulin release from the beta cell in a glucose dependent matter. The exact way of how this happens is by a specific intracellular cascade which is described above.

GLP-1 RAs not only enhance insulin release from beta cells but also decrease glucagon release from alpha cells when postprandial glucose increases. In numerous studies, treatment with GLP-1 RAs has been shown to lower blood glucose levels without increasing the risk of hypoglycemia.

The importance of GLP-1 RA for metabolism is to improve glucose control and thereby prevent microvascular and macrovascular complications. By improving glucose control, the risk of developing strokes, heart attacks, peripheral arterial disease, nephropathies, and neuropathies is reduced in the long term, and eventually eye disease can be prevented (1–4).

3.11 Cardioprotective properties

Glucagon-like peptide-1 receptor agonists were shown to be protective of the cardiovascular system. The mechanisms and pathways behind these cardiovascular protective effects are not yet fully understood. Most likely, this cardiovascular protection can be explained by direct effects on the heart and blood vessels or by indirect effects such as correction of glycemia, reduction in blood pressure, postprandial increase in triglycerides, and reduction in markers of

oxidative stress and systemic inflammation. The reduction in adverse cardiovascular events is explained by anti-atherosclerotic components (9).

3.11.1 Cardiovascular outcome studies

In 2008, the FDA decided that antidiabetic drugs must undergo cardiovascular outcome trials to receive marketing approval (1). The baseline characteristics of these cardiovascular safety studies are shown in Table 2.

Table 2 . Baseline characteristic of cardiovascular outcome trials with GLP-1 RAs

Trial	Mean duration of diabetes	Mean HbA1c	Mean eGFR	Mean follow- up
ELIXA lixisenatide	9,2 years	7,7%	76,7 ml/min per 1,73 m^2	2,1 years
LEADER liraglutide	12,8 years	8,7%	-	3,8 years
SUSTAIN-6 semaglutide	13,9 years	8,7%	-	2,1 years
EXSCEL exenatide	12 years	8,0%	-	3,2 years
REWIND dulaglutide	9,5 years	7,2%	74,9 ml/min per 1,73 m^2	5,4 years
HARMONY albiglutide	14,1 years	8,7%	79 ml/min per 1,73 m^2	1,6 years

ELIXA

Lixisenatide was one of the first GLP-1 RA to demonstrate cardiovascular safety. This was demonstrated in a study including 6068 patients with type 2 diabetes and acute coronary syndrome, which concluded that there was no cardiovascular risk compared with the placebo. In this study, HbA1c at baseline was 7.7%, diabetes duration was 9.2 years, and median eGFR was 76.7 ml/min per 1.73 m^2. The median follow-up time was 2.1 years. In the lixisenatide group, HbA1c decreased by -0.6% compared with -0.2% in the placebo group.

No significant difference was found for the primary composite endpoint of cardiovascular mortality, non-fatal myocardial infarction, non-fatal stroke, or hospitalization for unstable angina compared to placebo with a hazard ratio (HR) of 1.02 (0.89-1.17) (95% Confidence interval).

No significant differences compared to placebo were found for cardiovascular death HR 0.98 (0.78-1.22), non-fatal myocardial infarction HR 1.03 (0.87-1.22), or non-fatal stroke HR 1.12 (0.79-1.58) (10).

LEADER

LEADER focused on the GLP-1 receptor agonist liraglutide and included 9 340 patients. Patients enrolled in this study had an average duration of diabetes of 12.8 years, an average HbA1c of 8.7, and an average follow-up of 3.8 years.

In the liraglutide group, HbA1c decreased by -0.45% compared to -0.34% in the placebo group. The study showed significantly better results for the primary composite endpoint of cardiovascular mortality, non-fatal myocardial infarction and non-fatal stroke compared with placebo, with a hazard ratio (HR) of 0.87 (0.78-0.97).

No significant differences compared with placebo were observed for non-fatal myocardial infarction HR 0.86 (0.73-1.00) or non-fatal stroke HR 0.86 (0.71-1.06). In contrast, significantly better results were obtained for cardiovascular death compared with placebo, HR 0.78 (0.66-0.93) (11).

SUSTAIN 6

This study included 3 297 patients and focused on the GLP-1 RA semaglutide. The mean duration of diabetes was 13.9 years, with a mean HbA1c of 8.7%. The mean follow-up time

was 3.2 years. In the semaglutide group, HbA1c decreased by -1.4% compared with -0.4% in the placebo group. The study showed significantly better results for the primary composite endpoint of cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke for semaglutide compared with placebo, with a hazard ratio (HR) of 0.74 (0.58-0.95). No significant differences were observed for cardiovascular death HR 0.98 (0.65-1.48) and non-fatal myocardial infarction HR 0.74 (0.51-1.08) compared with placebo. For non-fatal stroke, semaglutide showed significantly better results compared with placebo, with a HR of 0.61 (0.38-0.99) (12).

EXSCEL

The properties of exenatide were evaluated in the EXSCEL study of 14,752 patients followed over 7.5 years. Patients had diabetes for a median of 12 years. The median HbA1c level was 8.0% and the median follow-up time was 3.2 years. The HbA1c level at the end of the study was -0.53% lower in the exenatide group than in the placebo group.
The hazard ratio (HR) for the primary composite end point of cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke was 0.91 (0.83-1.00) compared with placebo. No significant differences were observed for cardiovascular death HR 0.98 (0.78-1.22), non-fatal myocardial infarction HR 1.03 (0.87-1.22), or non-fatal stroke HR 1.12 (0.79-1.58) compared with placebo (13).

REWIND

The REWIND study of 9 901 patients focused on the GLP-1 RA dulaglutide. Patients enrolled in this study had a median diabetes duration of 9.5 years with a median HbA1c of 7.2% and a median eGFR of 74.9 ml/min per 1.73 m^2. The median follow-up time was 5.4 years.
In the dulaglutide group, HbA1c decreased by -0.46% compared with an increase of 0.16% in the placebo group. The study showed significantly better results for the primary composite endpoint of cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke compared with placebo, with a hazard ratio (HR) of 0.88 (0.79-0.99).
No significant differences were observed for cardiovascular death HR 0.91 (0.78-1.06) and non-fatal myocardial infarction HR 0.96 (0.79-1.16) compared with placebo. For non-fatal stroke, significantly better results were obtained compared with placebo HR 0.76 (0.62-0.94) (14).

HARMONY

This study focused on the GLP-1 RA albiglutide and included a number of 9463 patients with a mean duration of diabetes of 14.1 years. The mean HbA1c was 8.7%, the mean eGFR was 79 ml/min per 1.73 m^2, and the mean follow-up was 1.6 years.

A greater decrease in HbA1c was observed in the albiglutide group (-0.52%) compared with the placebo group. The study showed significantly better results for the primary composite endpoint of cardiovascular mortality, non-fatal myocardial infarction, and non-fatal stroke compared with placebo, with a hazard ratio (HR) of 0.78 (0.68-0.90).

No significant differences were observed for cardiovascular death HR 0.93 (0.73-1.19) and non-fatal stroke HR 0.86 (0.66-1.14) compared with placebo. For non-fatal myocardial infarctions, significantly better results were obtained compared with placebo with a HR of 0.75 (0.61-0.90) (15).

Table 3. Primary composite outcome

Study	Drug/comparator	HR (95% Cl)
ELIXA	lixisenatide/placebo	1.02 (0.89-1.17)
LEADER	liraglutide/placebo	0.87 (0.78-0.97)
SUSTAIN-6	semaglutide/placebo	0.74 (0.58-0.95)
EXSCEL	exenatide/placebo	0.91 (0.83-1.00)
REWIND	dulaglutide/placebo	0.88 (0.79-0.99)
HARMONY	albiglutide/placebo	0.78 (0.68-0.90)

Table 4. Secondary Outcomes			
Trial	Cardiovascular death (HR)	Non-fatal myocardial infarction (HR)	Non-fatal stroke (HR)
ELIXA lixisenatide	0.98 (0.78-1.22)	1.03 (0.87-1.22)	1.12 (0.79-1.58)
LEADER liraglutide	0.78 (0.66-0.93)	0.86 (0.73-1.00)	0.86 (0.71-1.06)
SUSTAIN-6 semaglutide	0.98 (0.65-1.48)	0.74 (0,51-1.08)	0.61 (0.38-0.99)
EXSCEL exenatide	0.98 (0.78-1.22)	1.03 (0.87-1.22)	1.12 (0.79-1.58)
REWIND dulaglutide	0.91 (0.78-1.06)	0.96 (0.79-1.16)	0.76 (0.62-0.94)
HARMONY albiglutide	0.93 (0.73-1.19)	0.75 (0.61-0.90)	0.86 (0.66-1.14)

All studies were designed and powered to examinate the combined three-point MACE including cardiovascular death, non-fatal cardiovascular infarction and non-fatal cardiovascular stroke. None of the studies were powered to confirm a significant difference in the composites of the combined end point.

3.12 Nephroprotective properties

Diabetes mellitus is a major driver for the development of chronic kidney disease and deteriorating kidney function. Patients suffering from chronic diabetic kidney disease have a higher risk of mortality, and especially cardiovascular complications.

GLP-1 RAs have been shown to reduce the development of new-onset macroalbuminuria, urinary albumin excretion and to slow the decline in estimated glomerular filtration rate (eGFR) (16). The exact mechanism of how these renal benefits take place remains unknown.

Anatomically, the location of GLP-1 receptors in the kidney has not been fully elucidated; they have been found in the afferent renal arterioles, but their existence in the renal glomeruli and proximal tubules is still controversial (16,17).

The effect of GLP-1 RAs on renal hemodynamics and improvement of glomerular hyperfiltration was found with chronic administration of GLP-1 RAs. In addition to these hemodynamic effects, GLP-1 RAs have been shown to reduce oxidative stress and inflammation with potentially nephroprotective consequences.

Conclusive data on the effect of GLP-1 RAs on renal outcomes are still lacking. This may be due to the fact that previous studies were not designed to investigate this as a primary endpoint and that patients with advanced renal disease were excluded from these studies.

The study, FLOW, is an ongoing trial evaluating the benefit of 1.0 mg s.c. semaglutide on renal outcomes in patients with type 2 diabetes. Overall, 3 500 patients at very high risk for progression to chronic kidney disease are enrolled in this study. Results of the study are expected in mid-2024 and will focus on delaying the progression of renal impairment and the risk of death from renal failure or cardiovascular disease in patients with type 2 diabetes and chronic kidney disease (16,17).

3.13 Neuroprotective factors

GLP-1 acts on receptors located in the caudal brainstem and hypothalamus of the brain. Activation of these specific receptors is associated with neurogenesis and neuroprotective effects that include a reduction in necrotic and apoptotic signaling, cell death, and dysfunction. Experimental disease models have shown that there is a correlation between GLP-1 receptor agonism and amelioration of neurological diseases such as Parkinson's disease, Alzheimer's disease, stroke, traumatic brain injury, and multiple sclerosis (4).

Activation of receptors in the brainstem and hypothalamus further induces satiety and reduces the amount of food and water intake of an individual.

3.14 Adverse effects

As mentioned in earlier sections, GLP-1 RAs affect the gastrointestinal system, causing nausea and diarrhea. Several studies addressed different agonists, their dosages, and the resulting side

effects. Nausea and vomiting were by far the most commonly described symptoms, but patients also complained of diarrhea, constipation, dyspepsia, and dehydration.

Another concern with the use of incretin mimetics was the development of pancreatic inflammation and pancreatitis. However, the harmful effects have been observed only in animal studies. The FDA and the European Medicines Agency reviewed studies involving 18 000 healthy animals and 28 000 patients taking GLP-1 RAs and concluded that the data on pancreatic inflammation or pancreatitis were inconsistent (18).

Another negative consequence of GLP-1 RAs is the development of gallstones, which is indirectly associated with the medication. The occurrence of gallstones is related to short-term weight loss in patients. The rapid breakdown of adipose tissue leads to biliary congestion, which is triggered by the reduced caloric intake. In addition, cholesterol saturation increases, which can be explained by increased mobilization of cholesterol and increased nucleation due to changes in arachidonate and glycoprotein concentrations in bile (19).

Despite the cardioprotective properties seen with GLP-1 RAs treatment, these drugs show an increase in heart rate. The most likely reason for this is the location of GLP-1 R in the sinoatrial node of the heart. Administration of this drug activates the sympathetic nervous system, resulting in an increase in heart rate (20).

An increased risk of thyroid C-cell carcinoma has been suggested with the use of GLP-1 RAs. Several studies in rodents showed an increase in C-cell carcinomas compared to the placebo group. However, this was not the case in human clinical trials (21).

3.15 Future incretin treatments

GLP-1 RAs have been very successfully introduced in the treatment of T2DM with reliable effects on glucose control and body weight. In a couple of studies treatment with GLP-1 RAs has been shown to improve cardiovascular endpoints in T2DM, with a reduction in cardiovascular mortality, non-fatal myocardial infarction or non-fatal stroke. Beyond GLP-1, other intestinal hormone signaling pathways appear to play a substantial role in the regulation of postprandial metabolism, food intake and energy homeostasis. Therefore, multimodal interventions are thought to have an even stronger impact on metabolic pathways and might provide even more powerful body weight reduction. The future of incretin receptor agonists might be in the development of dual or triple agonists including the opportunity to act not only on GLP-1 R but also additional incretin receptors like the GIP or the glucagon receptor. This

might further improve efficacy with regard to metabolic control and especially weight reduction.

Tirzepatide, a first dual GIP/GLP-1 receptor agonist has already been approved in Europe and the United States for the treatment of T2DM. Compared with GLP-1 RA semaglutide, tirzepatide was shown to be more effective with regard to glucose control and body weight reduction in patients with T2DM (22).

4. Discussion

This review summarizes the various properties of GLP-1 RA and their positive and negative effects. Incretin mimetics are extremely successful in the treatment of patients with type 2 diabetes. They are able to control blood glucose levels by regulating insulin secretion in a glucose-dependent manner and inhibiting glucagon secretion during the postprandial rise in glucose. They help patients reduce their body weight, thus preventing hypertension, dyslipidemia, insulin resistance, and atherogenesis (4).

Additionally, these medications have been shown to be beneficial in preventing cardiovascular complications by reducing the risk of cardiovascular death, non-fatal myocardial infarction and non-fatal stroke (9).

GLP-1 RAs have been shown to reduce the development of new-onset macroalbuminuria, urinary albumin excretion and to slow the decline in estimated glomerular filtration rate (eGFR). In addition to these hemodynamic effects, GLP-1 RAs have been found to reduce oxidative stress and inflammation with potentially nephroprotective consequences.

The most common side effects of GLP-1 RAs are gastrointestinal disorders. These range from nausea, vomiting, diarrhea, abdominal pain, constipation to dyspepsia or even dehydration. The reason for the symptoms affecting the GI tract is highly associated with delayed gastric emptying.

The occurrence of these symptoms is generally seen at the beginning of GLP-1 RA administration and is usually dose-dependent and disappears with long-term treatment (18). Previously, pancreatic inflammation, pancreatitis, and pancreatic cancer were considered side effects of incretin mimetics. However, several studies refuted these claims and showed no risk for these conditions (21).

The formation of gallstones was observed in patients who lost weight in a short period of time, which can only be indirectly related to the use of GLP-1 RA. The formation of gallstones is due to accelerated fat breakdown and not to the administration of incretin mimetics (19).

5. Conclusion

Current guidelines advocate a personalized approach to the treatment of type 2 diabetes. The choice of drug must be tailored to the patient's needs, cardiovascular risk, and personal preferences.

Choosing GLP-1 RAs not only gives patients the opportunity to regulate their glucose metabolism, but also prevents the overall consequences of type 2 diabetes.

This includes regulating body weight, which is one of the main problems in patients with type 2 diabetes, as well as achieving normal blood pressure and blood lipid levels.

Although many adverse effects such as pancreatitis and pancreatic cancer have been attributed to GLP-1 RAs, recent studies refute these claims. With the exception of gastrointestinal symptoms, it can be concluded that GLP-1 RAs are safe and very effective drugs.

The option of once daily, once weekly or even oral administration makes the drug not only safe but also convenient for the patient.

6. Summary

The aim of this review was to highlight the potential of glucagon-like peptide-1 receptor agonists (GLP-1RAs) in the treatment of type 2 diabetes with regard to metabolic and pleiotropic effects such as cardio- and nephroprotection.

GLP-1 RAs exert their main action by stimulating glucose-dependent insulin release from beta cells and inhibiting glucagon secretion from alpha cells. They have also been shown to slow gastric emptying and reduce food intake. Ultimately, this leads to a reduction in HbA1c levels and body weight. These features make GLP-1 RAs a unique treatment option.

In addition, GLP-1 RAs act on the heart and show outstanding cardioprotective properties, including an increase in glucose utilization, left ventricular function and myocyte survival. Cardiovascular outcome studies have confirmed that GLP-1 RAs reduce the risk of cardiovascular death, non-fatal myocardial infarction, and non-fatal stroke. The antiatherosclerotic effects of GLP-1 RAs are associated with the action of GLP-1 on blood vessels, leading to increases in vasodilation, blood flow, plaque stability, and endothelial function, as well as decreases in smooth muscle cell proliferation, blood pressure, and platelet aggregation. Furthermore, GLP-1 RAs have been shown to reduce the development of new-onset macroalbuminuria, urinary albumin excretion and to slow the decline in estimated glomerular filtration rate.

Nevertheless, GLP-1 RAs also have some disadvantages, mostly associated with gastrointestinal symptoms such as nausea and vomiting. An increase in heart rate has also been noted in several studies.

The future of incretin therapy is very promising, with triple agonists being developed that will provide even more effective glycemic control and body weight reduction in patients with type 2 diabetes.

7. Literature

1. Andersen A, Lund A, Knop FK, Vilsbøll T. Glucagon-like peptide 1 in health and disease. Nat Rev Endocrinol. 2018;14(7):390–403.
2. Glucagon-like peptide-1. In: Wikipedia [Internet]. 2022 [accessed 2. Mai 2023]. Available online: https://en.wikipedia.org/w/index.php?title=Glucagon-like_peptide-1&oldid=1109579436
3. Vila G, Riedl M. A hormon introduces itself: „Glucagon-like Peptide 1".
4. Andreasen CR, Andersen A, Knop FK, Vilsbøll T. How glucagon-like peptide 1 receptor agonists work. Endocr Connect. 2021;10(7):R200–12.
5. Tong J, D'Alessio D. Give the receptor a brake: slowing gastric emptying by GLP-1. Diabetes. 2014;63(2):407–9.
6. Scheen AJ. Dulaglutide for the treatment of type 2 diabetes. Expert Opin Biol Ther. 2017;17(4):485–96.
7. Rubino D, Abrahamsson N, Davies M, Hesse D, Greenway FL, Jensen C, u. a. Effect of Continued Weekly Subcutaneous Semaglutide vs Placebo on Weight Loss Maintenance in Adults With Overweight or Obesity: The STEP 4 Randomized Clinical Trial. JAMA. 2021;325(14):1414–25.
8. Dungan KM, Povedano ST, Forst T, González JGG, Atisso C, Sealls W, u. a. Once-weekly dulaglutide versus once-daily liraglutide in metformin-treated patients with type 2 diabetes (AWARD-6): a randomised, open-label, phase 3, non-inferiority trial. Lancet Lond Engl. 2014;384(9951):1349–57.
9. Ma X, Liu Z, Ilyas I, Little PJ, Kamato D, Sahebka A, u. a. GLP-1 receptor agonists (GLP-1RAs): cardiovascular actions and therapeutic potential. Int J Biol Sci. 2021;17(8):2050–68.
10. Pfeffer MA, Claggett B, Diaz R, Dickstein K, Gerstein HC, Køber LV, u. a. Lixisenatide in Patients with Type 2 Diabetes and Acute Coronary Syndrome. N Engl J Med. 2015;373(23):2247–57.
11. Marso SP, Daniels GH, Brown-Frandsen K, Kristensen P, Mann JFE, Nauck MA, u. a. Liraglutide and Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2016;375(4):311–22.
12. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, u. a. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016;375(19):1834–44.

13. Holman RR, Bethel MA, Mentz RJ, Thompson VP, Lokhnygina Y, Buse JB, u. a. Effects of Once-Weekly Exenatide on Cardiovascular Outcomes in Type 2 Diabetes. N Engl J Med. 2017;377(13):1228–39.
14. Gerstein HC, Colhoun HM, Dagenais GR, Diaz R, Lakshmanan M, Pais P, u. a. Dulaglutide and cardiovascular outcomes in type 2 diabetes (REWIND): a double-blind, randomised placebo-controlled trial. The Lancet. 2019;394(10193):121–30.
15. Hernandez AF, Green JB, Janmohamed S, D'Agostino RB, Granger CB, Jones NP, u. a. Albiglutide and cardiovascular outcomes in patients with type 2 diabetes and cardiovascular disease (Harmony Outcomes): a double-blind, randomised placebo-controlled trial. The Lancet. 2018;392(10157):1519–29.
16. Greco EV, Russo G, Giandalia A, Viazzi F, Pontremoli R, De Cosmo S. GLP-1 Receptor Agonists and Kidney Protection. Med Kaunas Lith. 2019;55(6):233.
17. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. Mol Metab. 2021;46:101102.
18. Filippatos TD, Panagiotopoulou TV, Elisaf MS. Adverse Effects of GLP-1 Receptor Agonists. Rev Diabet Stud RDS. 2014;11(3–4):202–30.
19. Weinsier RL, Ullmann DO. Gallstone formation and weight loss. Obes Res. 1993;1(1):51–6.
20. Russell And C, Petrie J. GLP-1 Receptor Agonists. In: Fisher M, Mckay GA, Llano A, Publisher . Diabetes Drug Notes [Internet]. 1. Aufl. Wiley; 2022 [accessed 2. Mai 2023]. S. 130–60. Available online: https://onlinelibrary.wiley.com/doi/10.1002/9781119785033.ch6
21. Hu W, Song R, Cheng R, Liu C, Guo R, Tang W, u. a. Use of GLP-1 Receptor Agonists and Occurrence of Thyroid Disorders: a Meta-Analysis of Randomized Controlled Trials. Front Endocrinol. 2022;13:927859.
22. Frías JP, Davies MJ, Rosenstock J, Pérez Manghi FC, Fernández Landó L, Bergman BK, u. a. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes. N Engl J Med. 2021;385(6):503–15.

8. CV

Laura Helene Forst was born in January 1998 in Mainz, Germany. She is the first child of Mr. Prof. Dr. med. Thomas Andreas Forst and Mrs. Senait Forst. Her sister Xenia Forst was born in 2002 and is currently studying at the Faculty of Medicine Rijeka in her second year.

Mr. Prof. Dr. med. Thomas Forst is working as a specialist in the field of endocrinology and diabetology. Mrs. Senait Forst worked as a nurse and continued with supervising of several pharmaceutical studies.

After finishing elementary school in 2008, Laura continued her education at IGS Mainz – Bretzenheim until 2017. During this time, she went on an exchange year in 2014 to Idaho, United States of America. After graduation with a high school diploma, in the same year, Laura enrolled into medical school at the Faculty of Medicine in Rijeka.

During her six years of medical school Laura completed several internships in the field of Infectiology, Endocrinology and Dermatology.