Review Article

Pharmacogenetics of Glucagon-like-peptide-1 receptor in diabetes management

Mariya Kalinkova[1], Tanya Kadiyska[2], Teodora Handjieva-Darlenska[1]

1 *Department of pharmacology and toxicology, Medical faculty, Medical University, Sofia, Bulgaria*

2 *Department of physiology and pathophysiology, Medical faculty, Medical University, Sofia, Bulgaria*

Corresponding author: Mariya Kalinkova (maria_kalinkova@abv.bg)

Citation: Kalinkova M, Kadiyska T, Handjieva-Darlenska T (2023) Pharmacogenetics of Glucagon-like-peptide-1 receptor in diabetes management. Pharmacia 70(2): 383–390. https://doi.org/10.3897/pharmacia.70.e104481

Abstract

Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder, primarily characterized by a decrease in insulin secretion and typically accompanied by insulin resistance. When untreated, T2DM is leading to an inevitable long-term complication. However, the novel treatment of T2DM like for example Glucagon-like Peptide-1 receptor agonists (GLP-1 RAs) give new perspectives for the patients to achieve a better glycemic control and additional metabolic improvements. Pharmacogenetics is a field in pharmacotherapy, which investigates the individual response to the medical treatment, according to polymorphic variations in the receptors of the drugs. This review aims to summarize current scientific evidence on the pharmacogenetics of the GLP-1 RA /liraglutide/ and the possible implementation in the treatment of T2D.

Keywords

GLP1RA, pharmacogenetics, precision medicine, T2DM

Introduction

More than 400 million people throughout the world are suffering from diabetes and more than 90% are diagnosed with T2DM (Saeedi et al. 2019). Type 2 diabetes mellitus (T2DM) is a complex metabolic disorder, primarily characterized by a decrease in insulin secretion and characterized by the inability of the body to carry out the typical role of the insulin, accompanied by insulin resistance. When untreated, T2DM is leading to multiple vascular complications, resulting in blindness, kidney failure, heart attacks, stroke and lower-limb amputation and can result in lower life expectancy by 5–10 years (Rathmann and Bongaerts 2021).

During the last decade, some new drug groups have been added in the American and European guidelines for diabetes treatment. These include the classes of dipeptidyl peptidase-4 (DPP-4) inhibitors, glucagon-like peptide-1 (GLP-1) receptor agonists (GLP-1RAs) and sodium-glucose linked transporter-2 (SGLT-2) inhibitors (Miller et al. 2000).

The GLP-1 receptor agonist are glucose-lowering medications, approved of treatment of diabetes. The American Diabetes Association (ADA), European Association for the Study of Diabetes (EASD), American Association of Clinical Endocrinologists (AACE) and American College of Endocrinology (ACE) recommend GLP-1RAs as a class of agents that improve the glycemic control and lower the risk of cardiovascular complications in patients with T2DM (van Schaik et al. 2020).

Pharmacogenetics is a part of the pharmacology, focused on the variation in human genome and how it influences the individual response of treatment, efficacy, and toxicity. Moreover, the difference in genetics modulates

the mechanism action of the drugs and changes the approach in which these patients are treated.

The aim of this article is to review the mechanism of action and clinical profile of GLP-1RAs regarding the individual polymorphisms in the receptors of GLP1RA.

Pharmacogenetics in type 2 diabetes

T2DM is a chronic metabolic disease characterized with insulin resistance and progressively reduced insulin secretion, which leads to impaired glucose utilization, dyslipidemia and hyperinsulinemia and progressive pancreatic beta cell dysfunction (Petersen and Shulman 2018). The etiology of T2D is known to have a significant genetic component, confirmed by family based studies (Ali 2013). The development of genotyping technologies and statistical tools combined with computational software have achieved a remarkable progress in the research of genetic associations in recent years (Daly and Hovorka 2021). Since the first genome-wide association study (GWAS) for T2DM identified novel susceptibility loci in 2007, more than 100 T2DM susceptibility loci have been discovered (Marullo et al. 2014; Caparrotta et al. 2021).

Over the last decade there has been an excessive development of antidiabetic agents. One of the main strategies aimed to improve the outcome of the therapy might be an individualized approach which is facilitated by pharmacogenetic studies. Establishing the mechanism of drug-gene interactions may give an attractive perspective for treatment in the clinical practice—stratifying the patient groups, decision-making on the therapeutic approach,

reducing the rates of side effects and thereby improving the outcome of T2D. All these take part of the so-called precision medicine.

What is glucagon-like peptide-1 (GLP-1) and their role in the glucose metabolism?

It was well known that an oral food intake leads to a greater insulin response compared to the intravenous glucose application (Nicolaidis and Rowland 1976). This response is provoked by the effect of incretins. These are peptides that are secreted in the small intestine. Some of them are Glucose-dependent insulinotropic polypeptide (GIP) and GLP-1 (Nauck and Meier 2018). They are produced by the K cells and L cells in the distal ileum and colon and influence the b-cells in the pancreas through connecting with GLP-1 and GIP receptors (Nauck et al. 2021). This connection activates b-cells, which leads to a glucose-dependent insulin secretion (Fig. 1). More than a half of the insulin secretion is in response to the secretion of incretins from the gastrointestinal tract (Vilsboll and Holst 2004). However, only GLP-1 exerts further glucose lowering actions via slowing gastric emptying and inhibition of glucagon secretion (Maselli and Camilleri 2021).

The half-life of the autonomic incretins is limited and their effects are decreased in patients with T2D (Holst 2019). Additionally, there is a pancreatic resistance to the effects of GLP-1 regarding the insulin secretion, resulting in decreased the secretion of GLP-1 by L cells (Lim et al. 2009). All these processes lead to developing a glucose intolerance (Akerstrom et al. 2022). The impaired incretin effect of GLP-1 occurs early in the natural history of
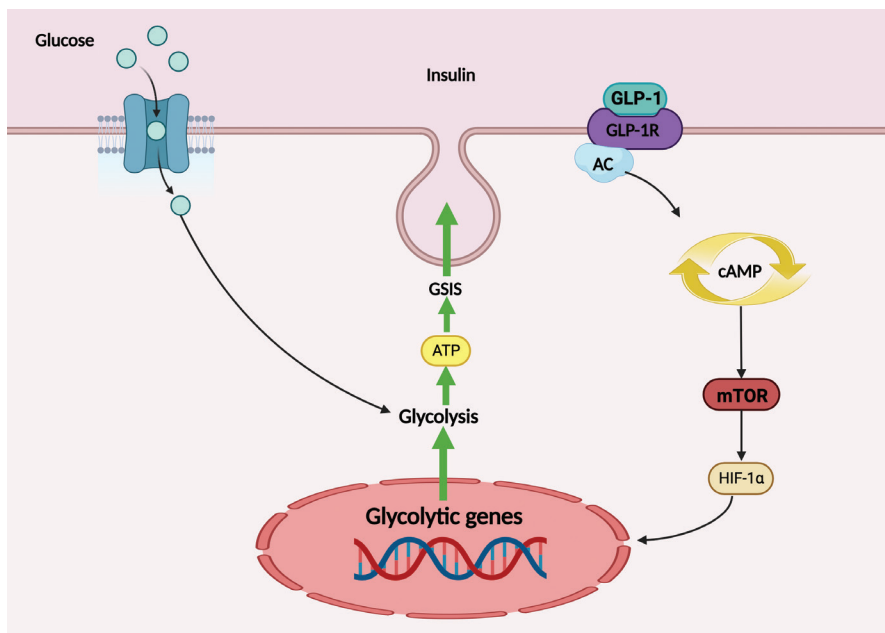
Figure 1. Via mTOR-dependent HIF-1 alfa activation, GLP-1R signaling impacts glucose metabolism in beta cells. When GLP-1 binds with its receptor GLP-1R (G-protein receptor), adenylyl cyclase (AC) is activated. The cyclic ATP is increased, which promotes the mTOR pathway in beta cells, HIF-1 alfa upregulates the transcription of glycolic genes. The increased glycolic enzymes lead to elevated glycolytic flux and capacity, these increase the ATP and results in GSIS (glucose stimulated insulin secretion).

T2DM, which makes the replacement therapy with GLP-1 agonists a logical choice to improve the insulin response in patients with T2DM (Meloni et al. 2013).

What is GLP1RA?

The GLP-1RA are designed to imitate GLP-1 activity, but to resist the quick metabolic degradation (Hinnen 2017). Nowadays, there are several GLP-1RA used in clinical practice with subcutaneous and oral formulations. GLP-1RA are considered as safe antidiabetic drugs, which have a positive impact on reducing the cardiovascular complications and as a second line therapy when metformin is insufficient or inappropriate (Trujillo et al. 2015).

It is nowadays estimated that some subtypes of GLP1RA have shown cardioprotective benefits (Ravassa et al. 2012). These are long-acting liraglutide and semaglutide. Moreover, several studies have shown a positive role of GLP1Rs in treatment of fatty liver disease, which also has an impact on glucose homeostasis (Mantovani et al. 2021). The positive effect of liraglutide, a short acting GLP-1RA, was reported in patients with NASH in Western countries (LEAN study) and Japanese studies (LEAN-J study) (Zhu et al. 2021). Semaglutide, a novel GLP-1 RA, is the newest and most popular labeled drug for diabetes (Andreadis et al. 2018). To investigate the effect of semaglutide on NASH, a phase 2 RDBPCT comparing the efficacy and safety of three different doses of once-daily subcutaneous semaglutide versus placebo in 372 participants with NASH is now ongoing Newsome et al. 2021).

The mechanism of action of GLP-1-receptor agonists

Glucagon-like peptide 1 is a peptide hormone secreted by the small intestine (Muller et al. 2019). It increases insulin secretion and decreases glucagon secretion from the pancreas in a glucose-dependent manner (Nadkarni et al. 2014). GLP-1 RAs act in reducing glucose levels and weight by increasing glucose-dependent insulin secretion and decreasing glucagon secretion. They also delay gastric emptying and increase satiety (MacDonald et al. 2002). Moreover, GLP-1 RA are highly efficacious weight loss drugs (Aroda 2018). Most of the GLP-1 RA agents are applied as subcutaneous (SC) injections, but there are also oral forms (Cho et al. 2013). The adverse effects differ between specific agents, the main adverse effects with the GLP-1 RA class are gastrointestinal (GI) related (nausea, vomiting, and diarrhea). In Europe there are five approved for use exenatide, liraglutide, albiglutide, lixisenatide, dulaglutide and semaglutide (Fig. 2) (Trujillo et al. 2015).

Pharmacokinetics of GLP-1Ras

GLP-1 RAs are administered via subcutaneous injections, which has an impact on the efficient absorption into the bloodstream. Additionally, semaglutide is available also for oral application. The absorption process varies depending on the specific GLP-1 RA (Table 1).

The difference in the effects of GLP-1 RAs is analyzed in the third phase of clinical studies such as the AMIGO
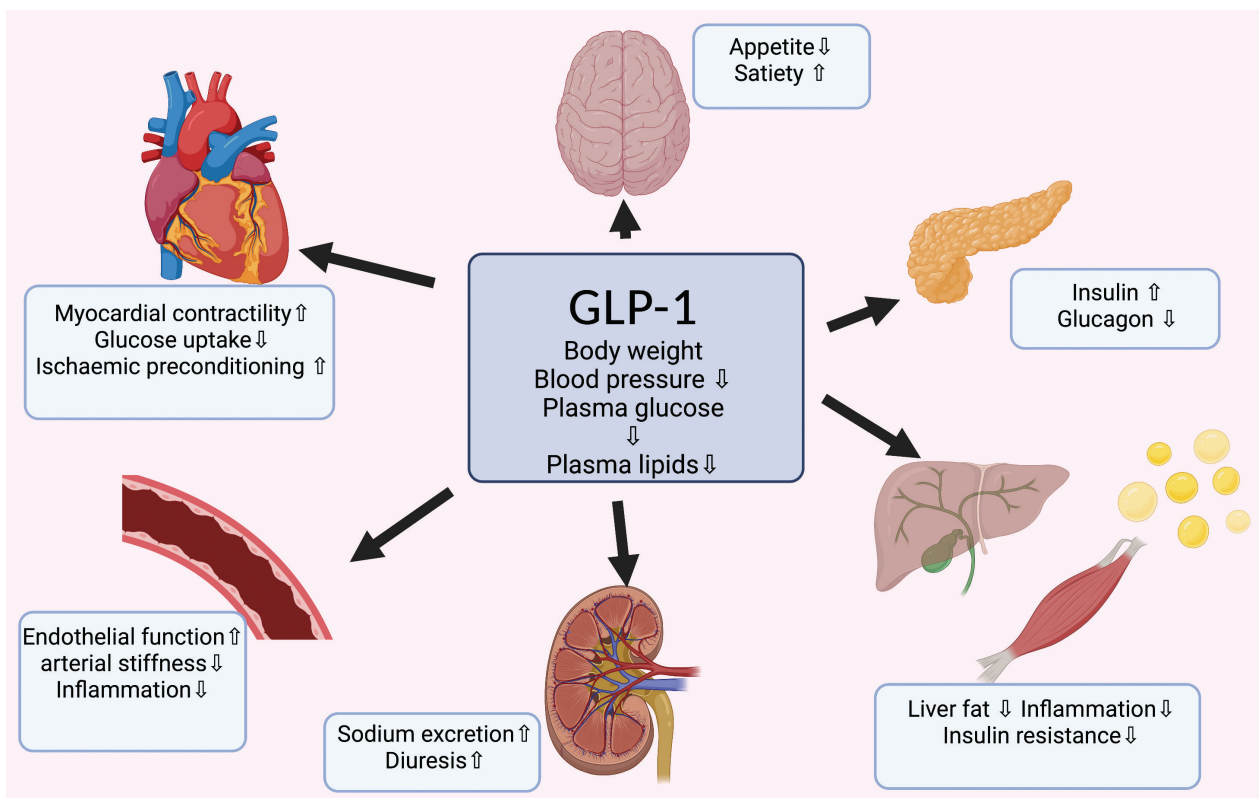

Figure 2. Mechanisms of action of GLP-1RA.

Table 1. Pharmacokinetics of GLP-1Ras. A comparison between the dosage, administration, half-life and side effects of the different GLP-1Ras.

Generic name	Trade name	Dosage	Administration	Half-life	Side Effects
Exenatide	Byetta, Bydureon	5–10 µg, Twice daily	subcutaneously	2.4 h	nausea, vomiting, diarrhea, and injection-site reactions.
Liraglutide	Victoza, Saxenda	0.6–1.8 mg /daily 3 mg / daily	subcutaneously	13 h	nausea, vomiting, diarrhea, and headache.
Albiglutide	Eperzan, Tanzeum	30–50 mg per week	subcutaneously	5 days	nausea, diarrhea, injection-site reactions, and upper respiratory tract infections.
Dulaglutide	Trulicity	0.75–1.5 mg per week	subcutaneously	4.7 days	nausea, diarrhea, abdominal pain, and injection-site reactions.
Lixisenatide	Lyxumia, Adluxin	10–20 µg / daily	subcutaneously	3 h	nausea, vomiting, diarrhea, and headache
Semaglutide	Ozempic, Wegovy	0.5–1 mg / per week 2.4 mg / Per week	subcutaneously	160 h	nausea, vomiting, diarrhea, and injection-site reactions.
Semaglutide	Rybelsus	3–14 mg	orally	7 days	nausea, vomiting, diarrhea, and injection-site reactions.

(exenatide), DURATION (exenatide extended-release), Get Goal (lixisenatide), LEAD (liraglutide), HARMONY (albiglutide), AWARD (dulaglutide), and SUSTAIN (semaglutide) trials.

Exenatide

Exenatide is a GLP-1 RA with a short action. It has a 53% homology to native GLP-1 and originally was isolated from the venom of the gila monster (Heloderma suspectum). Exenatide consists of 39 aminoacids with a glycine instead of alanine in the second position of the polypeptide chain, which results a longer half-life of 2.4 h. It is applied subcutaneously, twice-daily, in a dose of 5–10 µg and has an effect on HbA1c, fasting plasma glucose, and body weight according to the three 30-week AMIGO trials.

Liraglutide

Liraglutide is available as Victoza 0.6 to 1.8 mg. It is applied once per day subcutaneously for the T2D treatment. The other indication of liraglutide is as a therapy for overweight and obese patients, with or without diabetes. It is available also as Saxena (up to 3.0 mg daily). In Europe liraglutide 3.0 mg is the only GLP-1 RA approved for the treatment of obesity and is indicated for patients with a body mass index (BMI) over 30 kg/m2 or for the patients with BMI over 27 kg/m2 and some other comorbidity such as hypertension, dyslipidemia, or type 2 DM.

Liraglutide was developed by using a GLP-1 (7–37) back-bone in which on the 34 position lysine is replaced with arginine, and it is also added a palmitoyl (C16) fatty acid at position 26 The pharmacokinetic profile enables liraglutide to be applied for once-daily. The half-life of liraglutide is 13 h.

The effects of liraglutide have been studied in the 6 phase III LEAD (Liraglutide Effect and Action in Diabetes) trials as part of monotherapy or in combination with other antidiabetic drugs.

The Satiety and Clinical Adiposity-Liraglutide Evidence in individuals with and without diabetes (SCALE) clinical trial program investigated.

Albiglutide

Albiglutide, which in Europe is available as Eperzan and in the USA as Tanzeum, is a long-acting GLP-1 RA, a subcu-

taneous injection and the recommended dose is 30–50 mg per week. Albiglutide is produced by recombinant DNA technology from the yeast species Saccharomyces cerevisiae. Two sequential copies of the human GLP-1 (de Luis et al. 2015; Daly and Hovorka 2021) are merged with the human albumin, which leads to an increased half-life of 5 days. Albiglutide has been studied in the HARMONY clinical trial program (32-weeks, open-label, non-inferiority, randomized-controlled trial) which compares albiglutide 50 mg weekly to liraglutide 1.8 mg daily in patients with type 2 DM inadequately controlled on oral antidiabetic drugs. Patients who were treated with liraglutide had greater reductions in HbA1c than those on albiglutide, while gastrointestinal side effects were less frequent in the albiglutide group.

Dulaglutide

Dulaglutide, administered as Trulicity, is a long-acting GLP-1 RA, which is subcutaneous injection in a dose of 0.75 or 1.5 mg. The modified GLP-1 [7–37] peptide contains 3 amino acids. In the second position alanine is substituted with valine, which results in DPP-4 resistance. The fusion protein leads to a decreased clearance and an extended half-life of 4.7 days, allowing for weekly administration.

The effect of dulaglutide has been examined in the AWARD (Assessment of Weekly Administration of dulaglutide in Diabetes) clinical trials. The AWARD-3 52-week, clinical trial compared the efficacy and safety of monotherapy with dulaglutide to metformin-treated patients with type 2 DM.

Lixisenatide

Lixisenatide is a GLP-1 RA, which is applied once daily, with short action, marketed as Lyxumia in Europe and as Adlyxin in the USA. Lixisenatide consists of 44 aminoacids, amidated at the C-terminal amino acid. The addition of 6 lysine and deletion of a proline in lixisenatide increases the binding activity to the GLP-1 receptor and increases the half-life to 3 h. The starting dose of lisixenatide is 10 µg applied subcutaneously once-daily and the maximum dose is 20 µg once-daily. Lixisenatide has been studied in phase III Get Goal trials in patients with type 2 diabetes for Glycemic control and safety evaluation.

Semaglutide

Semaglutide, a long-acting, once-weekly GLP-1 RA, was approved under the name Ozempic. It is administrated by subcutaneous injection at the doses of 0.5 and 1.0 mg, applied subcutaneously. The start dose is 0.5 mg/weekly and it is titrated according to the needs of the patient. Semaglutide structure is based on liraglutide with the replacement of glycine by α-aminoisobutyric acid (Aib 8) and lysine on 26th position by acylated with a stearic diacid instead of palmitate. The GLP-1 receptor affinity of semaglutide is 3-fold decreased compared with liraglutide, but the albumin affinity is increased. It has a half-life of 160 h, allowing for weekly application. Moreover, semaglutide is also administrated orally, once-daily with a starting dose of 3 mg/daily with a titration up to 14 mg/daily for the treatement of T2D.

The higher dose of semaglutide 2.4 mg/weekly, under the name of Wegovy (semaglutide) injection is approved in USA by FDA for the treatment of overweight and obesity.

The SUSTAIN-1 to 6 clinical trials assessed the efficacy and safety of subcutaneously injected semaglutide (0.5 mg or 1.0 mg) vs placebo in drug naive patients with type 2 DM for a 30-week period.

Pharmacogenetics of GLP1RA

Pharmacogenetics explores the role of human genome in the effect of the treatment with pharmacological agents (Fig. 3) (Imamovic Kadric et al. 2021). According to a large cohort study, rs10305492 variant in the GLP1R gene is associated with a lower risk of heart disease, lower fasting glucose and reduced T2D risk (Scott et al. 2016). Several other studies explored the pharmacogenetics of GLP-1RA (Table 2).

For example, a study with 285 overweight Chinese patients with T2D, genotyped for the two common variants rs3765467 C>T and rs10305420 (C>T; p. Pro7Leu), was examining the effects of exenatide after 6 months of treatment, the results showed that the minor allele of rs10305420 was associated with a decreased reduction in body weight and HbA1c, which means that this variant is a potentially good pharmacogenetic marker especially in overweight diabetic patients (Yu et al. 2019).

A GWAS identified a variant rs57922 (C/C genotype) linked to a higher GLP-1 secretion and cardio-vascular benefits from intensive hypoglycemic treatment (Hayes 2013).

Another study was conducted with 36 patients with uncontrolled T2D, who were treated with exenatide for 3 days after 6 days of subcutaneous insulin infusions. The authors found a significant change in the levels of the plasma glucose during the treatment with exenatide associated with the variants rs3765467 C>T and rs761386 C>T. However, after multivariate analysis the data became insignificant (Lin et al. 2015). In a similar study with 90 overweight patients with T2D, treated with liraglutide for 14 weeks, was concluded that patients carrying variant A allele of rs6923761 had greater reductions in BMI (−0.59±2.5 kg/m2 vs. −1.69±3.9 kg/m2; p<0.05), weight (−2.78±2.8 kg vs. −4.52±4.6 kg; p<0.05) and fat mass (−0.59±2.5 kg vs. −1.69±3.9 kg; p<0.05) after liraglutide treatment (de Luis et al. 2015). Moreover, another study with 60 obese patients, has examined the effect of liraglutide and exenatide on the gastric emptying and weight loss. The result after 5 weeks of treatment with liraglutide 3 mg/daily and exenatide 10 mkgr/daily for the period of 30 days was that patients carrying the A allele of rs6923761 had a decrease in gastric emptying after treatment with either liraglutide or exenatide (117.9±27.5 minutes and 128.9±38.3 minutes, respectively) compared to the GG carriers (95.8±30.4 minutes and 61.4±21.4 minutes, respectively) (p = 0.11). The genotypes did not affect weight loss (Chedid et al. 2018).

Additionally, according to a study examining the effect of incretins' therapy in a total of 176 subjects (mean age 50.9 ± 12.7 years, 111 men), treated for 12 weeks with either exenatide (20 µg/day) or liraglutide (1.2 mg/day), the reduction in HbA1c levels was more significant in subjects carrying the rs3765467 GG genotype vs. GA + AA genotypes (1.7% ± 2.4% vs. 0.8% ± 1.8%; P = 0.002). Moreover, the target of 7.0% for the HbA1c was more significant in subjects carrying the rs3765467 GG genotype vs. GA + AA genotypes (50.9% vs. 23.8%; P = 0.002). Gastrointestinal adverse reactions did not differ significantly among different genotypes. They concluded that GLP1R rs3765467 polymorphism is associated with therapeutic response to GLP1RAs in Chinese T2DM patients. HbA1c reduction was larger in subjects with the GG genotype (Long et al. 2022).

In their study Long et al. described the effect of rs3765467 and rs2254336 in the GLP-1 R gene on adverse reactions in the gastrointestinal system in patients with T2DM treated with liraglutide. According to the study, the females are more susceptible to gastrointestinal adverse

Table 2. Genetic variations, which affect the response to GLP-1 RAs.

Study	Drug	Gene	Location	SNPs	Amino-acid change	Impact
Yu M et al. (2019)	Exenatide	GLP-1	6p21	rs3765467C > T; rs10305420C > T	Missense Variant-Impair.	A 0.4% reduction in HbA1C and a 1.27 kg less weight loss
Lin et al. 2015	Exenatide	GLP-1	6p21	rs3765467C >T; rs761386C > T	Missense Variant-Impair. Intron variant	Effect on plasma glucose levels
Chedid et al. (2018)	Exenatide Liraglutide	GLP-1	6p21	rs3765467C > T; rs10305492	Missense variants-Impair receptor function	Impaired β cell secretion of insulin and β cell viability
Guan et al. (2022)	Exenatide Liraglutide	GLP-1	6p21	rs3765467C > T	Missense variants-Impair receptor function	Larger reduction of HbA1C
Long et al. (2022)	Liraglutide	GLP-1	6p21	rs3765467C>T. rs2254336 A > T	Missense Variant-Impair receptor function; Intron variant	Associated with gastrointestinal adverse reaction
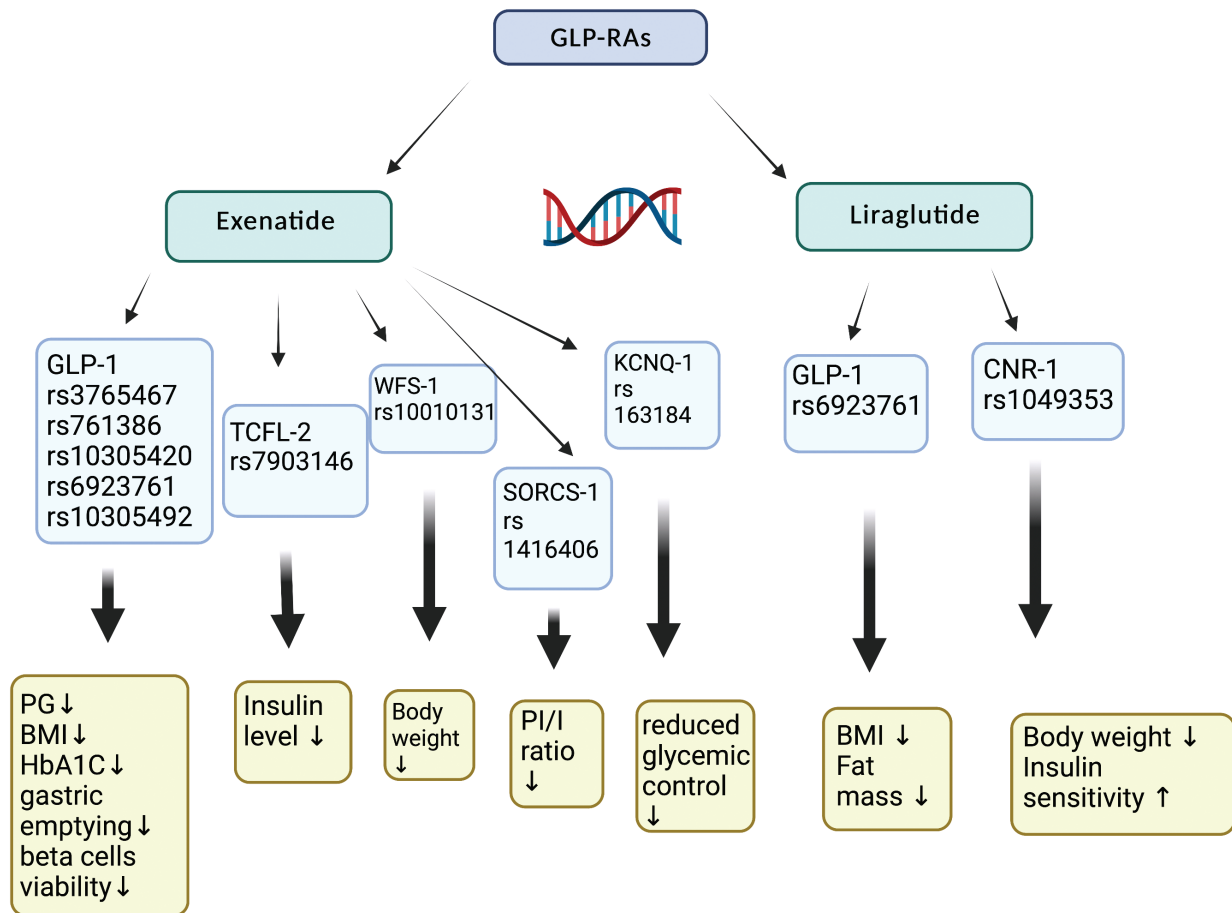
Figure 3. Representation of genetic variants affecting pharmacokinetics and pharmacodynamics of GLP-1 Ras. PG: plasma glucose; BMI: body mass index; HbA1C: glycemic hemoglobin, PI/I: proinsulin/insulin ratio.

reactions compared to males. Furthermore, this adverse effect was associated with the T allele of rs2254336 and the A allele of rs3765467 respectively (Pearson et al. 2019).

Another study is genome-wide pharmacogenomic study of GLP-1 receptor agonists conducted with 4571 adults from different nations (3339 (73%) were White European, 449 (10%) Hispanic, 312 (7%) American Indian or Alaskan Native, and 471 (10%) were other, and 47% of all participants were women.

Discussion

According to a recent studies and practical guidelines when the therapy is started early and patients are well-controlled, the rate of the late diabetes complications is decreased. Nowadays with the progression of technologies, increased information and digitalization, the rate of mortality and morbidity associated with type 2 diabetes is significantly reduced (Davies et al. 2022). It is not fully estimated whether genetic information can be constantly implicated in the prevention and treatment of diabetes. This is still the beginning of the usage of genetic information for stratification individuals for their individual response to the treatment. This information needs to be considered together with the clinical status for everyone

along to their disease progression path. The increasing availability and decreasing cost of human genetic analysis can be implicated in clinical medicine and used for diagnostic and therapeutic recommendations in different fields beyond the diabetology (Gonzaga-Jauregui et al. 2012). Algorithms incorporating predictive genetic variation and biomarkers for drug response and complications, validated by clinical trials, should enhance our ability to transform diabetes care (Dennis 2020).

A precision medicine approach requires attention to the gaps in our current knowledge base, which include the clinical guideline for a treatment in adolescents, the elderly, and during pregnancy. The available outcomes data for recommending type 2 diabetes therapy that is directed at primary prevention of macrovascular complications in young, healthier individuals are insufficient (Davies et al. 2022).

Nevertheless, given the staggering numbers of patients with type 2 diabetes, critical evaluation of the cost versus benefit of the use of genomics, biomarkers, new technologies, and specific medications will be needed to support recommendations for clinical use in specific populations. Given the tremendous progress made over the past decade, it is reasonable to predict greater adoption of precision medicine approaches in the type 2 diabetes clinic in the years to come (Gloyn and Drucker 2018).

Conclusion

T2D is a pandemic disease rapidly spreading all over the world. According to the prognosis the number of people suffering from diabetes has been expected to rise from 366 to 522 million by 2030. The major factor, contributing to this is that it goes undiagnosed in many individuals. More than 183 million individuals have been still undiagnosed with diabetes worldwide. The current therapeutic approaches for the treatment of diabetes include various drug categories according to the overall state of the patients. GLP-1 receptor agonists are one of the sec-

ond-line oral anti-diabetic drugs prescribed by clinicians and administrated as a therapy for overweight and obese patients. They influence both insulin secretion and glucagon-suppression.

Pharmacogenetic studies are focusing on T2DM therapies. Unravelling the pharmacogenetics of T2DM is an approach towards individualized therapy. Although the research in the field of pharmacogenetics/ pharmacogenomic in T2DM is not still a part of the clinical practice, the genetic basis of personalized medicine is growing with solid evidence indicating its importance in future clinical practice.

Reference

Akerstrom T, Stolpe MN, Widmer R, Dejgaard TF, Hojberg JM, Moller K, Hansen JS, Trinh B, Holst JJ, Thomsen C, Pedersen BK, Ellingsgaard H (2022) Endurance training improves GLP-1 Sensitivity and glucose tolerance in overweight women. Journal of the Endocrine Society 6(9): bvac111. https://doi.org/10.1210/jendso/bvac111

Ali O (2013) Genetics of type 2 diabetes. World Journal of Diabetes 4(4): 114–123. https://doi.org/10.4239/wjd.v4.i4.114

Andreadis P, Karagiannis T, Malandris K, Avgerinos I, Liakos A, Manolopoulos A, Bekiari E, Matthews DR, Tsapas A (2018) Semaglutide for type 2 diabetes mellitus: A systematic review and meta-analysis. Diabetes, Obesity and Metabolism 20(9): 2255–2263. https://doi.org/10.1111/dom.13361

Aroda VR (2018) A review of GLP-1 receptor agonists: Evolution and advancement, through the lens of randomised controlled trials. Diabetes, Obesity and Metabolism 20(Suppl 1): 22–33. https://doi.org/10.1111/dom.13162

Caparrotta TM, Templeton JB, Clay TA, Wild SH, Reynolds RM, Webb DJ, Colhoun HM (2021) Glucagon-like peptide 1 receptor agonist (GLP1RA) exposure and outcomes in type 2 diabetes: A systematic review of population-based observational studies. Diabetes Therapy 12(4): 969–989. https://doi.org/10.1007/s13300-021-01021-1

Chedid V, Vijayvargiya P, Carlson P, Van Malderen K, Acosta A, Zinsmeister A, et al. (2018) Allelic variant in the glucagon-like peptide 1 receptor gene associated with greater effect of liraglutide and exenatide on gastric emptying: A pilot pharmacogenetics study. Neurogastroenterology and Motility 30(7): e13313. https://doi.org/10.1111/nmo.13313

Cho YM, Wideman RD, Kieffer TJ (2013) Clinical application of glucagon-like Peptide 1 receptor agonists for the treatment of type 2 diabetes mellitus. Endocrinol Metab (Seoul) 28(4): 262–274. https://doi.org/10.3803/EnM.2013.28.4.262

Daly A, Hovorka R (2021) Technology in the management of type 2 diabetes: Present status and future prospects. Diabetes, Obesity and Metabolism 23(8): 1722–1732. https://doi.org/10.1111/dom.14418

Davies MJ, Aroda VR, Collins BS, Gabbay RA, Green J, Maruthur NM, Rosas SE, Del Prato S, Mathieu C, Mingrone G, Rossing P, Tankova T, Tsapas A, Buse JB (2022) Management of hyperglycaemia in type 2 diabetes, 2022. A consensus report by the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetologia 65(12): 1925–1966. https://doi.org/10.1007/s00125-022-05787-2

de Luis DA, Diaz Soto G, Izaola O, Romero E (2015) Evaluation of weight loss and metabolic changes in diabetic patients treated with liraglutide, effect of RS 6923761 gene variant of glucagon-like peptide

1 receptor. Journal of Diabetes and its Complications 29(4): 595–598. https://doi.org/10.1016/j.jdiacomp.2015.02.010

Dennis JM (2020) Precision medicine in type 2 diabetes: Using individualized prediction models to optimize selection of treatment. Diabetes 69(10): 2075–2085. https://doi.org/10.2337/dbi20-0002

Gloyn AL, Drucker DJ (2018) Precision medicine in the management of type 2 diabetes. Lancet Diabetes & Endocrinology 6(11): 891–900. https://doi.org/10.1016/S2213-8587(18)30052-4

Gonzaga-Jauregui C, Lupski JR, Gibbs RA (2012) Human genome sequencing in health and disease. Annual Review of Medicine 63: 35–61. https://doi.org/10.1146/annurev-med-051010-162644

Hayes B (2013) Overview of statistical methods for genome-wide association studies (GWAS). Methods In Molecular Biology 1019: 149–169. https://doi.org/10.1007/978-1-62703-447-0_6

Hinnen D (2017) Glucagon-Like Peptide 1 Receptor Agonists for Type 2 Diabetes. Diabetes Spectrum 30(3): 202–210. https://doi.org/10.2337/ds16-0026

Holst JJ (2019) The incretin system in healthy humans: The role of GIP and GLP-1. Metabolism 96: 46–55. https://doi.org/10.1016/j.metabol.2019.04.014

Imamovic Kadric S, Kulo Cesic A, Dujic T (2021) Pharmacogenetics of new classes of antidiabetic drugs. Bosnian Journal of Basic Medical Sciences 21(6): 659–671. https://doi.org/10.17305/bjbms.2021.5646

Lim GE, Huang GJ, Flora N, LeRoith D, Rhodes CJ, Brubaker PL (2009) Insulin regulates glucagon-like peptide-1 secretion from the enteroendocrine L cell. Endocrinology 150(2): 580–591. https://doi.org/10.1210/en.2008-0726

Lin CH, Lee YS, Huang YY, Hsieh SH, Chen ZS, Tsai CN (2015) Polymorphisms of GLP-1 receptor gene and response to GLP-1 analogue in patients with poorly controlled type 2 diabetes. J Diabetes Res. 2015: 176949. https://doi.org/10.1155/2015/176949

Long J, Liu Y, Duan Y, Li Y, Yang G, Ren Z, Tao W, Liu D (2022) Effect of GLP-1R rs2254336 and rs3765467 polymorphisms on gastrointestinal adverse reactions in type 2 diabetes patients treated with liraglutide. European Journal of Clinical Pharmacology 78(4): 589–596. https://doi.org/10.1007/s00228-021-03225-7

MacDonald PE, El-Kholy W, Riedel MJ, Salapatek AM, Light PE, Wheeler MB (2002) The multiple actions of GLP-1 on the process of glucose-stimulated insulin secretion. Diabetes 51(Suppl 3): S434–442. https://doi.org/10.2337/diabetes.51.2007.S434

Mantovani A, Petracca G, Beatrice G, Csermely A, Lonardo A, Targher G (2021) Glucagon-like peptide-1 receptor agonists for treatment of

nonalcoholic fatty liver disease and nonalcoholic steatohepatitis: An updated meta-analysis of randomized controlled trials. Metabolites 11(2): 73. https://doi.org/10.3390/metabo11020073

Miller CD, Phillips LS, Tate MK, Porwoll JM, Rossman SD, Cronmiller N, Gebhart SS (2000) Meeting American Diabetes Association guidelines in endocrinologist practice. Diabetes Care 23(4): 444–448. https://doi.org/10.2337/diacare.23.4.444

Marullo L, El-Sayed Moustafa JS, Prokopenko I (2014) Insights into the genetic susceptibility to type 2 diabetes from genome-wide association studies of glycaemic traits. Current Diabetes Reports 14(11): 551. https://doi.org/10.1007/s11892-014-0551-8

Maselli DB, Camilleri M (2021) Effects of GLP-1 and its analogs on gastric physiology in diabetes mellitus and obesity. Advances in Experimental Medicine and Biology 1307: 171–192. https://doi.org/10.1007/5584_2020_496

Meloni AR, DeYoung MB, Lowe C, Parkes DG (2013) GLP-1 receptor activated insulin secretion from pancreatic beta-cells: mechanism and glucose dependence. Diabetes, Obesity and Metabolism 15(1): 15–27. https://doi.org/10.1111/j.1463-1326.2012.01663.x

Muller TD, Finan B, Bloom SR, D'Alessio D, Drucker DJ, Flatt PR, et al. (2019) Glucagon-like peptide 1 (GLP-1). Molecular Metabolism 30: 72–130. https://doi.org/10.1016/j.molmet.2019.09.010

Nadkarni P, Chepurny OG, Holz GG (2014) Regulation of glucose homeostasis by GLP-1. Progress in Molecular Biology and Translational Science 121: 23–65. https://doi.org/10.1016/B978-0-12-800101-1.00002-8

Nauck MA, Meier JJ (2018) Incretin hormones: Their role in health and disease. Diabetes, Obesity and Metabolism 20(Suppl 1): 5–21. https://doi.org/10.1111/dom.13129

Nauck MA, Quast DR, Wefers J, Meier JJ (2021) GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. Molecular Metabolism 46: 101102. https://doi.org/10.1016/j.molmet.2020.101102

Newsome PN, Buchholtz K, Cusi K, Linder M, Okanoue T, Ratziu V, Sanyal AJ, Sejling A-S, Harrison SA (2021) A placebo-controlled trial of subcutaneous semaglutide in nonalcoholic steatohepatitis. The New England Journal of Medicine 384(12): 1113–1124. https://doi.org/10.1056/NEJMoa2028395

Nicolaidis S, Rowland N (1976) Metering of intravenous versus oral nutrients and regulation of energy balance. American Journal of Physiology 231(3): 661–668. https://doi.org/10.1152/ajplegacy.1976.231.3.661

Pearson S, Kietsiriroje N, Ajjan RA (2019) Oral semaglutide in the management of type 2 diabetes: A report on the evidence to date. Diabetes, Metabolic Syndrome and Obesity 12: 2515–2529. https://doi.org/10.2147/DMSO.S229802

Petersen MC, Shulman GI (2018) Mechanisms of insulin action and insulin resistance. Physiological Reviews 98(4): 2133–223. https://doi.org/10.1152/physrev.00063.2017

Rathmann W, Bongaerts B (2021) Pharmacogenetics of novel glucose-lowering drugs. Diabetologia 64(6): 1201–1212. https://doi.org/10.1007/s00125-021-05402-w

Ravassa S, Zudaire A, Diez J (2012) GLP-1 and cardioprotection: from bench to bedside. Cardiovascular Research 94(2): 316–323. https://doi.org/10.1093/cvr/cvs123

Saeedi P, Petersohn I, Salpea P, Malanda B, Karuranga S, Unwin N, Colagiuri S, Guariguata L, Motala AA, Ogurtsova K, Shaw JE, Bright D, Williams R, IDF Diabetes Atlas Committee (2019) Global and regional diabetes prevalence estimates for 2019 and projections for 2030 and 2045: Results from the International Diabetes Federation Diabetes Atlas, 9th edn. Diabetes Research and Clinical Practice 157: 107843. https://doi.org/10.1016/j.diabres.2019.107843

Scott RA, Freitag DF, Li L, Chu AY, Surendran P, Young R, et al. (2016) A genomic approach to therapeutic target validation identifies a glucose-lowering GLP1R variant protective for coronary heart disease. Science Translational Medicine 8(341): 341ra76. https://doi.org/10.1126/scitranslmed.aad3744

Trujillo JM, Nuffer W, Ellis SL (2015) GLP-1 receptor agonists: a review of head-to-head clinical studies. Therapeutic Advances in Endocrinology and Metabolism 6(1): 19–28. https://doi.org/10.1177/2042018814559725

van Schaik J, Begijn DGA, van Iersel L, Vergeer Y, Hoving EW, Peeters B, van Santen HM (2020) Experiences with glucagon-like peptide-1 receptor agonist in children with acquired hypothalamic obesity. Obesity Facts 13(4): 361–370. https://doi.org/10.1159/000509302

Vilsboll T, Holst JJ (2004) Incretins, insulin secretion and Type 2 diabetes mellitus. Diabetologia 47(3): 357–366. https://doi.org/10.1007/s00125-004-1342-6

Yu M, Wang K, Liu H, Cao R (2019) GLP1R variant is associated with response to exenatide in overweight Chinese Type 2 diabetes patients. Pharmacogenomics 20(4): 273–277. https://doi.org/10.2217/pgs-2018-0159

Zhu Y, Xu J, Zhang D, Mu X, Shi Y, Chen S, Wu Z, Li S (2021) Efficacy and safety of GLP-1 receptor agonists in patients with type 2 diabetes mellitus and non-alcoholic fatty liver disease: A systematic review and meta-analysis. Front Endocrinol (Lausanne) 12: 769069. https://doi.org/10.3389/fendo.2021.769069