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Pharmacogenetic Insights into Glucagon-Like Peptide-1 Receptor and Its Role in Diabetes Therapy

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ABSTRACT

Type 2 diabetes mellitus (T2DM) represents a multifactorial metabolic disorder primarily marked by impaired insulin secretion and the presence of insulin resistance. If left untreated, T2DM inevitably progresses to various long-term complications. The emergence of novel therapeutic agents, such as Glucagon-like Peptide-1 receptor agonists (GLP-1 RAs), has introduced new possibilities for improved glycemic regulation and additional metabolic advantages. Pharmacogenetics, a branch of pharmacotherapy, explores how genetic polymorphisms influence individual responses to specific medications. This review focuses on the current scientific understanding of the pharmacogenetics of GLP-1 receptor agonists—particularly liraglutide—and their potential role in the personalized management of T2DM.

Keywords: GLP1RA, Pharmacogenetics, T2DM, Precision medicine

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Introduction

Globally, over 400 million individuals are affected by diabetes, with approximately 90% diagnosed with T2DM [1]. This disorder is a multifaceted metabolic condition characterized by inadequate insulin secretion and an impaired physiological response to insulin, often accompanied by insulin resistance. If untreated, T2DM results in serious vascular complications, including retinopathy, nephropathy, cardiovascular disease, stroke, and limb amputations, which may shorten life expectancy by 5–10 years [2].

In recent years, several innovative drug classes have been incorporated into American and European diabetes treatment guidelines. These include dipeptidyl peptidase-4 (DPP-4) inhibitors, sodium-glucose cotransporter-2 (SGLT-2) inhibitors, and Glucagon-like Peptide-1 receptor agonists (GLP-1RAs) [3]. GLP-1RAs are glucose-lowering agents approved for diabetes management and are endorsed by major organizations such as 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). These bodies recommend GLP-1RAs due to their ability to enhance glycemic control while reducing cardiovascular risk in T2DM patients [4].

Pharmacogenetics, a subdiscipline of pharmacology, investigates genetic variability within the human genome and its impact on drug response, therapeutic efficacy, and toxicity. Genetic polymorphisms can significantly influence drug mechanisms and determine individualized treatment strategies.

Therefore, the present article aims to examine the mechanism of action and clinical profile of GLP-1 receptor agonists with a particular emphasis on receptor polymorphisms influencing therapeutic outcomes.

Pharmacogenetics in type 2 diabetes

T2DM is a chronic metabolic disorder characterized by progressive insulin resistance and diminished insulin secretion, leading to hyperglycemia, dyslipidemia, and pancreatic beta-cell deterioration [5]. Genetic

predisposition plays a crucial role in T2DM pathogenesis, as evidenced by familial aggregation studies [6]. The advancement of genotyping platforms, statistical modeling, and computational tools has significantly accelerated the identification of genetic factors associated with T2DM [7]. Since the first genome-wide association study (GWAS) in 2007, which revealed several susceptibility loci for T2DM, more than 100 genetic loci linked to disease risk have been reported [8, 9].

Over the past decade, antidiabetic drug development has progressed rapidly, emphasizing individualized therapeutic strategies. Pharmacogenetic research offers a promising avenue for tailoring treatments by elucidating drug-gene interactions. Such understanding enables clinicians to categorize patients more effectively, personalize treatment regimens, minimize adverse reactions, and enhance therapeutic outcomes. This individualized strategy aligns with the principles of precision medicine, aiming to optimize treatment efficacy based on genetic diversity among patients.

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

It has long been recognized that oral ingestion of nutrients triggers a stronger insulin response than the administration of glucose intravenously [10]. This enhanced response is mediated by incretins—hormonal peptides secreted from the small intestine. Among the most significant incretins are Glucose-dependent Insulinotropic Polypeptide (GIP) and Glucagon-like Peptide-1 (GLP-1) [11]. These hormones are synthesized by K cells and L cells located in the distal ileum and colon, respectively, and exert their effects on pancreatic β-cells through activation of GIP and GLP-1 receptors [12]. Binding to these receptors stimulates β-cell activity, resulting in glucose-dependent insulin release **(Figure 1).** It is estimated that more than half of postprandial insulin secretion originates from incretin stimulation in the gastrointestinal tract [13]. In addition to enhancing insulin secretion, GLP-1 uniquely contributes to glucose regulation by delaying gastric emptying and suppressing glucagon release [14].

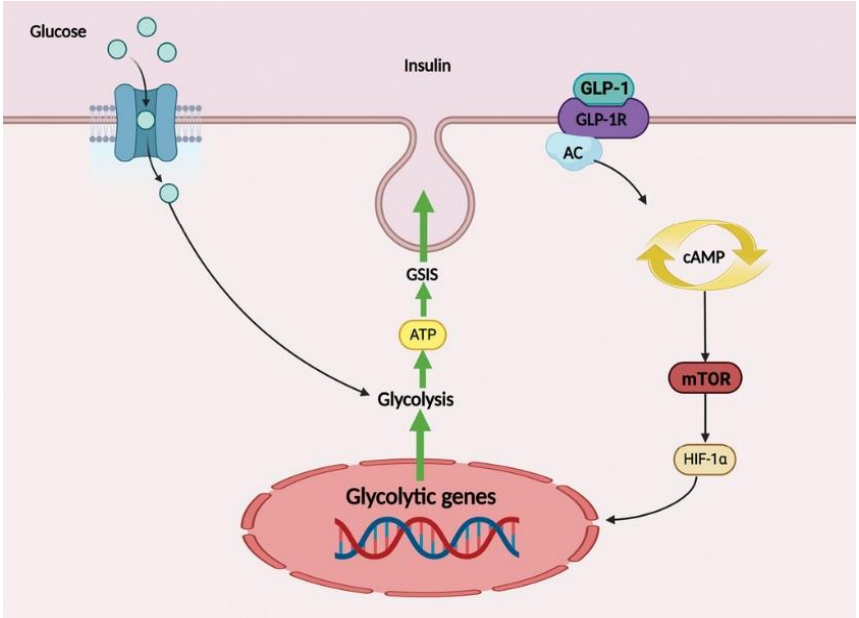

Figure 1. Through mTOR-dependent activation of HIF-1α, GLP-1R signaling regulates glucose metabolism in pancreatic β-cells. Upon binding of GLP-1 to its receptor, GLP-1R—a G protein-coupled receptor—adenylyl cyclase (AC) becomes activated, leading to an elevation in cyclic AMP levels. This, in turn, stimulates the mTOR signaling cascade in β-cells. The activated HIF-1α promotes transcription of glycolytic genes, increasing glycolytic enzyme production and thereby enhancing glycolytic flux and capacity. These processes elevate ATP generation, which subsequently triggers glucose-stimulated insulin secretion (GSIS).

The biological half-life of natural incretins is short, and their effectiveness is significantly reduced in individuals with T2DM [15]. Moreover, pancreatic β-cells in these patients exhibit reduced responsiveness to GLP-1, coupled with diminished GLP-1 secretion from intestinal L cells [16]. These alterations collectively contribute to glucose intolerance [17]. The early decline in GLP-1 activity during the progression of T2DM provides a rationale for utilizing GLP-1 receptor agonists (GLP-1RAs) as replacement therapy to enhance insulin secretion [18].

What is GLP-1RA?

GLP-1 receptor agonists (GLP-1RAs) are pharmacological agents engineered to replicate the physiological actions of endogenous GLP-1 while remaining resistant to rapid enzymatic degradation [19]. Multiple GLP-1RA formulations—administered either subcutaneously or orally—are currently available in clinical settings. These agents are recognized as effective and safe antidiabetic medications, particularly recommended as second-line therapies when metformin therapy alone fails to achieve adequate glycemic control or is contraindicated [20].

Certain long-acting GLP-1RAs, such as liraglutide and semaglutide, have demonstrated cardioprotective properties [21]. In addition, GLP-1R activation has been associated with beneficial outcomes in nonalcoholic fatty liver disease (NAFLD), contributing to improved glucose regulation [22]. Liraglutide, a short-acting GLP-1RA, showed favorable results in treating nonalcoholic steatohepatitis (NASH) in both Western (LEAN study) and Japanese populations (LEAN-J study) [23]. Semaglutide, a newer GLP-1RA, has emerged as one of the most widely used drugs for diabetes management [24]. A phase 2 randomized, double-blind, placebo-controlled trial is currently investigating the safety and efficacy of three daily subcutaneous doses of semaglutide in 372 participants with NASH [25].

Mechanism of action of GLP-1 receptor agonists

Glucagon-like peptide-1 is a gut-derived hormone secreted by intestinal L cells [26]. It facilitates glucose-dependent insulin secretion while suppressing glucagon release from pancreatic α-cells [27]. GLP-1 receptor agonists mimic these physiological actions, thereby lowering blood glucose and promoting weight loss through enhanced insulin release, reduced glucagon secretion, delayed gastric emptying, and increased satiety [28, 29]. Most GLP-1RAs are administered via subcutaneous injection, though oral formulations are also available [30].

While generally well tolerated, GLP-1RAs may cause gastrointestinal side effects such as nausea, vomiting, or diarrhea, with the intensity varying among agents. In Europe, six GLP-1 receptor agonists—exenatide, liraglutide, albiglutide, lixisenatide, dulaglutide, and semaglutide—are currently approved for clinical use **(Figure 2)** [20].

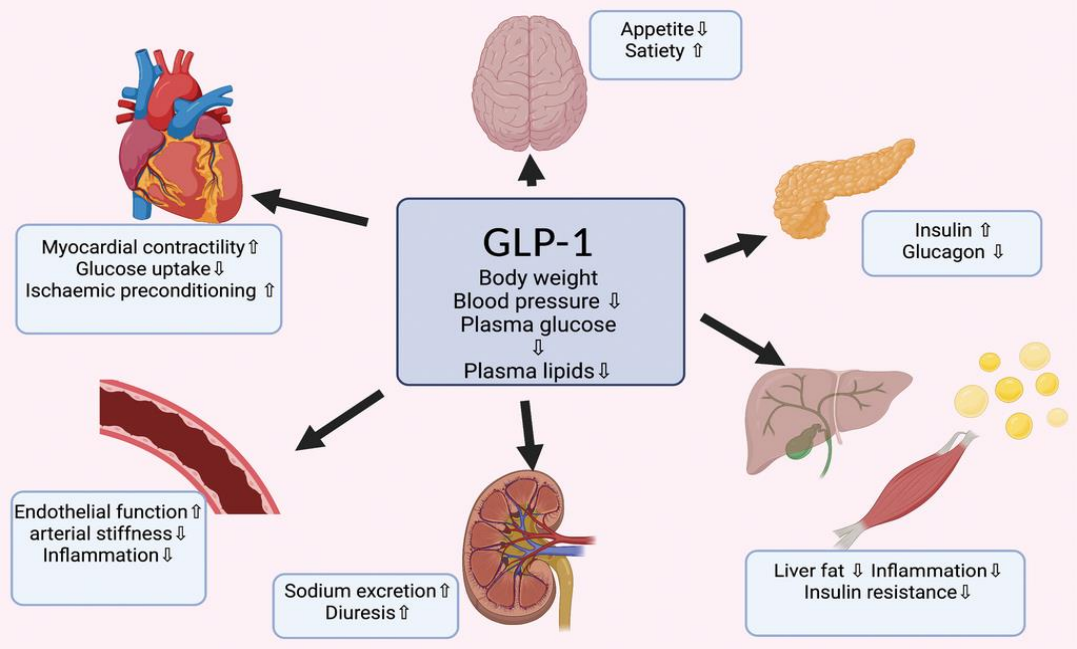

Figure 2. Mechanisms of action of GLP-1RA.

Pharmacokinetics of GLP-1RAs

GLP-1 receptor agonists are primarily administered through subcutaneous injection, which influences their rate and extent of absorption into systemic circulation. Among them, semaglutide is the only agent also available in an oral formulation. The absorption characteristics differ between various GLP-1RAs, depending on their molecular structure and formulation type **(Table 1).**

Table 1. Pharmacokinetics of GLP-1RAs. Comparison of the dosage, administration route, half-life, and common adverse effects among different GLP-1 receptor agonists.

Generic Name	Trade Name(s)	Dosage	Administration Route	Half-life	Common Side Effects
Exenatide	Byetta, Bydureon	5–10 μg twice daily	Subcutaneous injection	2.4 hours	Nausea, vomiting, diarrhea, and local injection-site reactions
Liraglutide	Victoza, Saxenda	0.6–1.8 mg daily; 3 mg daily (for weight management)	Subcutaneous injection	13 hours	Nausea, vomiting, diarrhea, and headache
Albiglutide	Eperzan, Tanzeum	30–50 mg once weekly	Subcutaneous injection	5 days	Nausea, diarrhea, injection-site reactions, and upper respiratory tract infections
Dulaglutide	Trulicity	0.75–1.5 mg once weekly	Subcutaneous injection	4.7 days	Nausea, diarrhea, abdominal discomfort, and injection-site irritation
Lixisenatide	Lyxumia, Adluxin	10–20 μg daily	Subcutaneous injection	3 hours	Nausea, vomiting, diarrhea, and headache
Semaglutide	Ozempic, Wegovy	0.5–1 mg per week; 2.4 mg per week (for obesity treatment)	Subcutaneous injection	160 hours	Nausea, vomiting, diarrhea, and injection-site reactions
Semaglutide	Rybelsus	3–14 mg daily	Oral tablet	7 days	Nausea, vomiting, diarrhea, and injection-site reactions

The differences in the pharmacological actions of GLP-1 receptor agonists (GLP-1RAs) have been evaluated in multiple phase III clinical studies, including the AMIGO trials (exenatide), DURATION studies (extended-release exenatide), GetGoal trials (lixisenatide), LEAD trials (liraglutide), HARMONY trials (albiglutide), AWARD trials (dulaglutide), and SUSTAIN trials (semaglutide).

Exenatide

Exenatide is a short-acting GLP-1 receptor agonist sharing approximately 53% sequence similarity with native GLP-1. It was initially isolated from the saliva of the Gila monster (Heloderma suspectum). The peptide is composed of 39 amino acids, with a substitution of glycine for alanine at the second position, which extends its half-life to about 2.4 hours. Administered subcutaneously at doses of 5–10 μg twice daily, exenatide has been shown in three 30-week AMIGO trials to significantly reduce HbA1c levels, fasting plasma glucose, and body weight in patients with T2DM.

Liraglutide

Liraglutide is marketed as Victoza (0.6–1.8 mg daily) for type 2 diabetes and as Saxenda (up to 3.0 mg daily) for weight management. It is given subcutaneously once daily. In Europe, the 3.0 mg formulation is the only GLP-1RA approved for treating obesity, indicated for individuals with a BMI ≥30 kg/m² or ≥27 kg/m² with comorbid conditions such as hypertension, dyslipidemia, or T2DM. Structurally, liraglutide is derived from the GLP-1 (7–37) backbone, where lysine at position 34 is replaced by arginine, and a C16 palmitic acid chain is attached at position 26. These modifications extend its half-life to approximately 13 hours, permitting once-daily administration. The drug's efficacy and safety have been extensively evaluated in six phase III LEAD (Liraglutide Effect and Action in Diabetes) trials, both as monotherapy and in combination with other antidiabetic agents. Its effects on body weight and appetite regulation were further investigated in the SCALE (Satiety and Clinical Adiposity–Liraglutide Evidence) trial series.

Albiglutide

Albiglutide, marketed as Eperzan in Europe and Tanzeum in the United States, is a long-acting GLP-1RA administered subcutaneously at 30–50 mg once weekly. It is synthesized using recombinant DNA technology in Saccharomyces cerevisiae and consists of two tandem human GLP-1 molecules fused to human albumin, which prolongs its half-life to approximately 5 days [7, 31]. The HARMONY clinical trial program—an open-label, 32-week, randomized, non-inferiority study—compared albiglutide 50 mg weekly with liraglutide 1.8 mg daily in

patients with T2DM inadequately controlled with oral hypoglycemics. Although liraglutide produced a greater reduction in HbA1c levels, albiglutide was associated with fewer gastrointestinal side effects.

Dulaglutide

Dulaglutide, marketed as Trulicity, is another long-acting GLP-1 receptor agonist administered subcutaneously at doses of 0.75 mg or 1.5 mg weekly. The molecule is a modified GLP-1 (7–37) peptide in which alanine is replaced by valine at position 2, conferring resistance to degradation by DPP-4. It is fused to an Fc fragment, which slows systemic clearance and extends its half-life to approximately 4.7 days, allowing for once-weekly dosing. The AWARD (Assessment of Weekly Administration of Dulaglutide in Diabetes) clinical trials evaluated its therapeutic potential, with the AWARD-3 study—spanning 52 weeks—demonstrating that dulaglutide monotherapy achieved effective glycemic control comparable to metformin in patients with type 2 diabetes.

Lixisenatide

Lixisenatide is a short-acting GLP-1 receptor agonist administered once daily, marketed as Lyxumia in Europe and Adlyxin in the United States. The peptide comprises 44 amino acids with amidation at the C-terminal. Structural modifications, including the addition of six lysines and the deletion of a proline, enhance its binding affinity to the GLP-1 receptor and extend its half-life to approximately 3 hours. The recommended starting dose is 10 μg subcutaneously once daily, titrated up to a maximum of 20 μg daily. The efficacy and safety of lixisenatide have been evaluated in phase III GetGoal trials in patients with type 2 diabetes.

Semaglutide

Semaglutide is a long-acting GLP-1RA administered once weekly under the brand name Ozempic. It is given subcutaneously at 0.5 mg or 1.0 mg, starting at 0.5 mg per week and adjusted according to clinical response. Structurally, semaglutide is derived from liraglutide, with glycine at position 8 replaced by α-aminoisobutyric acid (Aib) and lysine at position 26 acylated with a stearic acid instead of palmitate. These modifications reduce its GLP-1 receptor affinity threefold compared to liraglutide while increasing albumin binding, resulting in an extended half-life of 160 hours, which permits weekly dosing. Semaglutide is also available as an oral formulation (Rybelsus), administered once daily, starting at 3 mg and titrated up to 14 mg for the treatment of T2DM. Additionally, a higher dose of 2.4 mg weekly (Wegovy) is FDA-approved in the United States for obesity management. The efficacy and safety of subcutaneous semaglutide (0.5 or 1.0 mg) were evaluated in the SUSTAIN-1 through SUSTAIN-6 trials over 30 weeks in drug-naive patients with type 2 diabetes.

Pharmacogenetics of GLP-1RA

Pharmacogenetics investigates how variations in the human genome influence responses to pharmacological treatments **(Figure 3)** [32]. For instance, a large cohort study identified the rs10305492 variant in the GLP1R gene as being associated with reduced risk of cardiovascular disease, lower fasting glucose levels, and decreased susceptibility to T2DM [33]. Multiple other studies have explored the pharmacogenetic aspects of GLP-1 receptor agonists, summarized in **Table 2.**

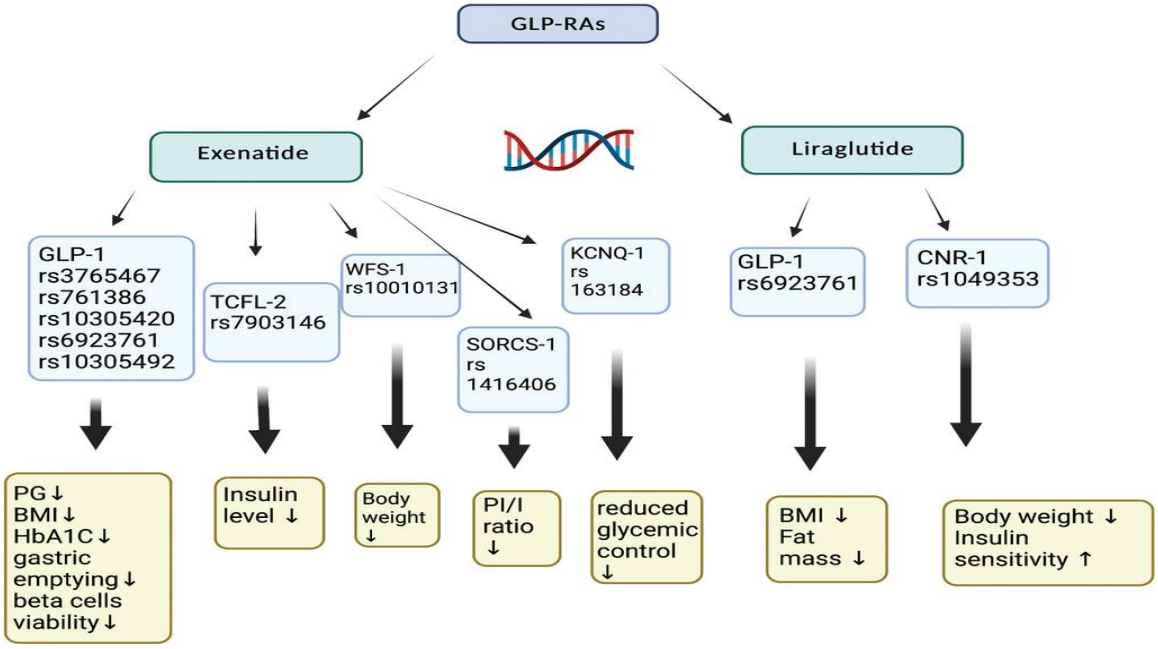

Figure 3. Illustration of genetic variants influencing the pharmacokinetics and pharmacodynamics of GLP-1 receptor agonists. Abbreviations: PG= plasma glucose; BMI= body mass index; HbA1c= glycated hemoglobin; PI/I= proinsulin-to-insulin ratio.

Table 2. Genetic variations affecting the response to GLP-1RAs

Study	Drug	Gene	Chromosomal Location	SNPs	Amino Acid Change / Variant Type	Observed Impact
Yu M *et al.* (2019)[34]	Exenatide	GLP-1R	6p21	rs3765467 C>T; rs10305420 C>T	Missense variant – Impaired function	0.4% smaller reduction in HbA1c and 1.27 kg less weight loss
Lin *et al.* (2015)[35]	Exenatide	GLP-1R	6p21	rs3765467 C>T; rs761386 C>T	Missense variant – Impaired; intron variant	Altered plasma glucose response
Chedid *et al.* (2018)[36]	Exenatide, Liraglutide	GLP-1R	6p21	rs3765467 C>T; rs10305492	Missense variants – Impaired receptor function	Reduced β-cell insulin secretion and compromised β-cell viability
Guan *et al.* (2022)	Exenatide, Liraglutide	GLP-1R	6p21	rs3765467 C>T	Missense variant – Impaired receptor function	Greater reduction in HbA1c
Long *et al.* (2022)[37]	Liraglutide	GLP-1R	6p21	rs3765467 C>T; rs2254336 A>T	Missense variant – Impaired receptor function; intron variant	Increased likelihood of gastrointestinal adverse effects

In one study, 285 overweight Chinese patients with T2DM were genotyped for the variants rs3765467 C>T and rs10305420 (C>T; p.Pro7Leu) and treated with exenatide for six months. The results indicated that carriers of the minor allele of rs10305420 experienced smaller decreases in body weight and HbA1c, suggesting that this variant may serve as a useful pharmacogenetic marker, particularly for overweight individuals with diabetes [34].

A genome-wide association study (GWAS) also identified the rs57922 C/C genotype as being linked to enhanced GLP-1 secretion and improved cardiovascular outcomes during intensive glycemic therapy [38].

In a separate trial, 36 patients with poorly controlled T2DM received exenatide for three days following six days of subcutaneous insulin infusion. Initial analysis showed plasma glucose changes associated with the rs3765467 C>T and rs761386 C>T variants; however, these associations lost significance after multivariate adjustment [35].

Another investigation of 90 overweight T2DM patients treated with liraglutide for 14 weeks found that individuals carrying the A allele of rs6923761 had greater reductions in BMI (−1.69 ± 3.9 vs. −0.59 ± 2.5 kg/m²; $p<0.05$), body weight (−4.52 ± 4.6 vs. −2.78 ± 2.8 kg; $p<0.05$), and fat mass (−1.69 ± 3.9 vs. −0.59 ± 2.5 kg; $p<0.05$) compared to non-carriers [31].

In a study of 60 obese participants assessing gastric emptying and weight loss with liraglutide 3 mg/day or exenatide 10 μg/day, carriers of the A allele of rs6923761 showed slower gastric emptying after 30 days of treatment (117.9 ± 27.5 min for liraglutide and 128.9 ± 38.3 min for exenatide) than GG carriers (95.8 ± 30.4 min and 61.4 ± 21.4 min, respectively; p = 0.11), although weight reduction was not influenced by genotype [36].
A separate study of 176 subjects (mean age 50.9 ± 12.7 years, 111 men) treated with either exenatide (20 μg/day) or liraglutide (1.2 mg/day) for 12 weeks found that patients with the rs3765467 GG genotype had a more substantial decrease in HbA1c compared to GA + AA genotypes (1.7% ± 2.4% vs. 0.8% ± 1.8%; P = 0.002). Achievement of the HbA1c target of 7% was also higher in GG carriers (50.9% vs. 23.8%; P = 0.002), while gastrointestinal adverse effects did not differ between genotypes, indicating that rs3765467 influences the glycemic response to GLP-1RAs in Chinese T2DM patients [37].
Further analysis by Long *et al*. [37]. examined rs3765467 and rs2254336 in the GLP-1R gene in relation to gastrointestinal side effects in liraglutide-treated T2DM patients. They found that women were more susceptible to these adverse events, and that the T allele of rs2254336 and the A allele of rs3765467 were linked to increased gastrointestinal reactions [39].
Finally, a genome-wide pharmacogenomic study involving 4,571 adults from diverse ethnic backgrounds (3,339 [73%] White European, 449 [10%] Hispanic, 312 [7%] American Indian or Alaskan Native, and 471 [10%] from other populations) included 47% women, investigating the genetic factors influencing responses to GLP-1 receptor agonists.

Results and Discussion

Recent studies and practical guidelines indicate that early initiation of therapy and effective patient management can reduce the risk of long-term diabetes complications. Advances in technology, information access, and digitalization have contributed to a notable decline in morbidity and mortality related to type 2 diabetes [40]. However, the integration of genetic information into routine diabetes prevention and treatment is still in its infancy. Genetic data could help stratify patients according to their likely response to therapy, but such information must be interpreted alongside individual clinical status and disease progression. The expanding accessibility and decreasing costs of genetic testing have the potential to influence diagnostic and therapeutic decisions across various medical fields beyond diabetology [41]. Predictive algorithms incorporating genetic variants and biomarkers for drug response and complications, once validated in clinical trials, could significantly enhance diabetes care [42].
Implementing a precision medicine approach also requires addressing current knowledge gaps, including clinical guidelines for treatment in adolescents, older adults, and pregnant patients. Evidence supporting therapies aimed at primary prevention of macrovascular complications in younger, healthier individuals with T2DM remains limited [40]. Given the vast number of patients affected by T2DM, careful evaluation of the cost-effectiveness of genomics, biomarkers, emerging technologies, and targeted therapies is essential before widespread clinical adoption. Considering the rapid advancements over the past decade, broader incorporation of precision medicine strategies in T2DM management is likely in the near future [43].

Conclusion

Type 2 diabetes is a global health challenge with a rapidly increasing prevalence. Estimates suggest that the number of individuals with diabetes will rise from 366 million to 522 million by 2030, with a significant contributor being undiagnosed cases, currently exceeding 183 million worldwide. Current treatment strategies encompass multiple drug classes tailored to patient condition, with GLP-1 receptor agonists serving as second-line therapies, particularly for overweight and obese patients, due to their dual effects on stimulating insulin secretion and suppressing glucagon.
Pharmacogenetic research in T2DM aims to support individualized treatment approaches. Although pharmacogenetic and pharmacogenomic applications are not yet routine in clinical practice, growing evidence underscores the importance of genetic insights for precision medicine, suggesting that their integration will play a key role in future T2DM management.

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