https://doi.org/10.31925/farmacia.2023.1.1 **REVIEW**

THE NEWEST THERAPEUTICALLY APPROACH OF "DIABESITY" USING GLP-1 RA MOLECULES: IMPACT OF THE ORAL FORMULATION

MARIANA CORNELIA TILINCA [1,2#], CSILLA ANTAL [2#], ALINA BALINT [3#], ANDREEA SĂLCUDEAN [4]*, ANDREEA VARGA [5]

[1]*Department of Internal Medicine I, "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology of Târgu Mureș, 540142, Romania*
[2]*Department of Diabetology, Emergency County Hospital of Târgu Mureș, 540042, Romania*
[3]*Department of Analytical Chemistry and Drug Analysis "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology of Târgu Mureș, 540142, Romania*
[4]*Department of Ethics and Social Sciences, "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology of Târgu Mureș, 540142, Romania*
[5]*Department of Family Medicine, "George Emil Palade" University of Medicine, Pharmacy, Science, and Technology of Târgu Mureș, 540142, Romania*

**corresponding author: andreea.salcudean@yahoo.com*
[#]Authors with equal contribution.

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Abstract

Co-existing diabetes and obesity, frequently described by the term "diabesity", is a major health problem associated with increased long-term complications and mortality. The management of "diabesity" could be challenging, because several anti-diabetic drugs cause weight gain. Glucagon-like peptide receptor agonists (GLP-1 RAs) have been demonstrated to be effective agents for achieving glycaemic control in addition to reducing body weight in patients with type 2 diabetes. Oral semaglutide, the first oral formulation of a GLP-1 RA, is an important therapeutic option for individuals with a preference for oral therapy. This medication was created by co-formulating the semaglutide molecule with an absorption enhancer (SNAC) to overcome the difficulties of oral peptide administration. The introduction of an oral GLP-1 RA broadens the therapeutic choices for patients and represents an important milestone in the management of "diabesity".

Rezumat

Coexistența obezității și a diabetului zaharat, descrise frecvent prin termenul „*diabesity*" sau „diabezitate", reprezintă o problemă majoră de sănătate asociată cu creșterea complicațiilor și a mortalității pe termen lung. Managementul „diabezității" ar putea fi o provocare, deoarece mai multe medicamente antidiabetice pot determina creștere în greutate. S-a demonstrat că agoniștii receptorilor *glucagon-like peptide-1* (GLP-1 RA) sunt eficienți pentru obținerea controlului glicemic pe lângă reducerea greutății corporale în cazul pacienților cu diabet zaharat tip 2. Semaglutida orală, prima formularea orală a GLP-1 RA, este o opțiune terapeutică importantă pentru persoanele cu preferință pentru terapia orală. Acest medicament a fost creat prin co-formularea moleculei de semaglutidă cu un amplificator de absorbție (SNAC) pentru a depăși dificultățile administrării orale a peptidelor. Introducerea unui agonist de receptor GLP-1 cu administrare orală, lărgește opțiunile terapeutice pentru pacienți și reprezintă un medicament cheie în tratamentul „diabezității".

Keywords: diabesity, obesity, diabetes mellitus, GLP-1, semaglutide

Introduction

Nowadays, we are dealing with a global epidemic of obesity and type 2 diabetes mellitus (DM), which are frequently linked together, described by the term "diabesity" [32, 53]. "Diabesity" represents the main risk factor for the development of other comorbidities, including dementia, cancer and cardiovascular diseases [58]. In 2016, the WHO estimated that 1.9 billion people aged 18 or older were overweight and over 650 million adults were obese [75]. It is estimated that DM affects 463 million adults globally and is presumed to increase to 592 million by 2035 and 700 million by 2045 [17, 24]. 90% of these cases are represented by type 2 DM, although more than 50% of them did not have access to early diagnosis and adequate treatment. Furthermore, 374 million people have insulin resistance (IR) which increases their chance of developing type 2 DM [18, 24].

Obesity is considered as a lifelong progressive disease with periods of remission and recurrences that plays a significant role in the evolution of DM and its clinical manifestations [54]. In type 2 DM, oxidative stress, chronic inflammation and lipid metabolism dysfunction as well as micro- and macro-vascular

complications are the leading causes of premature morbidity and mortality. Furthermore, research has shown that untreated obesity can rapidly progress to DM as a result of the excessive adipose tissue, which is linked with a long-term pro-inflammatory condition, leading to IR – a key pathogenic factor in the development of DM [33]. Existing therapeutic interventions for obesity have unfavourable benefit-to-risk rations, fail to achieve their long-term goals, and do not reach patients' expectations. Consequently, there is a need for a practical, efficient and secure therapy for obesity and associated metabolic disorders in order to reduce mortality and improve quality of life [70].

Since several commonly used antidiabetic drugs, including sulfonylureas and insulin, may cause weight gain and so create a vicious circle, managing "diabesity" can be difficult [71]. A highly effective class of medicaments for type 2 DM is represented by the Glucagon-Like Peptide-1 (GLP-1) receptor agonist (RA) [8]. Their influence on weight loss and vascular tone promotes cardiovascular safety which is one of the main advantages of this class [27]. Exenatide, the first GLP-1 RA received approval in June 2005. Since then there are several other injectable agents available in the treatment of DM and obesity such as the short-acting formulation lixisenatide and exenatide and the longer-acting-formulation liraglutide, once-weekly extended-release dulaglutide, semaglutide and exenatide [21, 71]. Tirzepatide is a novel and the first dual association between a GLP-1 and a Glucose-dependent Insulinotropic Peptide (GIP) RA recommended in obese patients, administered subcutaneously once weekly, which provides consistent and persistent reductions in body weight [25]. It is generally known that among patients with DM oral medications tend to have higher rates of therapy adherence than injectable ones, which could represent a limitation of GLP-1 RAs usage [19, 68]. The first oral formulation of the GLP-1 analogue, oral semaglutide has been developed for once-daily administration, in which a molecule called SNAC (sodium N-(8-[2-hydroxybenzoyl] amino) caprylate) enhances the absorption of the active ingredient through gastric mucosa [8, 21]. In this context, the invention of a semaglutide formulation for oral administration, represents a supplementary variant for patients with obesity and DM [68].

The pathophysiological mechanisms of "diabesity"

"Diabesity" or co-existing DM and obesity is responsible for several impaired metabolic cell signalling pathways associated with insulin dysfunction and it also has an influence on various metabolic cascades with a systemic effect [44]. There are several theories about the molecular disturbances in the pathogenesis of "diabesity" [17]. Chronic obesity (BMI > 30 kg/m^2) is a lifestyle disorder characterized by an excess accumulation of body fats due to increased calorie intake, insufficient physical activity, endocrine disorders, genetic factors and numerous medications [4, 39, 49]. Metabolic syndrome (MS), which includes hyper-tension, hyperglycaemia and dyslipidaemia, is frequently present in patients with central obesity. Obesity-related adipose tissue dysfunction results in a disruption in immune cell activity and distribution, which can cause both local and systemic low-grade inflammation. These significant alterations in the adipose tissue's immune cell composition stimulate inflammatory signalling pathways and enhance the expression of inflammatory receptors, which is linked to the development of IR [17, 39]. Furthermore, the adipose tissue is known as a metabolically active organ that produces adipokines such as leptin, resistin, adiponectin, interleukins (IL-6 and IL-1b) and tumour necrosis factor alpha (TNF-alpha), which play a significant role in obesity-related comorbidities and inflammation [11, 45, 72]. Serum leptin concentrations appear to be a reliable indicator of body fat composition and elevated levels of leptin increase Th-1 immune response, stimulate macrophage activity and result in the release of several cytokines. Resistin is described as a significant pro-inflammatory adipokine that is implicated in the evolution of metabolic syndrome and cardiovascular diseases. In contrast, adiponectine, which serum levels are decreased in obese individuals, has important anti-diabetic, anti-inflammatory and anti-atherogenic properties [35, 45]. Although there are a few uncommon monogenic types of obesity, in most cases numerous genes, gene polymorphisms and environmental conditions, like dietary habits and lifestyle play a role in the development of obesity, and these involved genes have not been yet entirely understood [10, 45, 49]. The ADIPOQ gene, which is only expressed in the human adipose tissue has a considerable number of single nucleotide polymorphism (SNP) and three of them (rs1501299, rs266729 and rs2241766) have been widely investigated in connection to the pathophysiology of DM and obesity [49, 66]. It has been proven that obesity may change the link between IL-1b genetic variation and C-reactive protein (CRP) level regulation. A frequent polymorphism in the TNF-alpha promoter region is thought to be associated with a high risk of IR in patients with obesity and plays a major role in the identification of obesity-associated hypertension. Finally, genetic variations at the resistin or RETN locus have also been associated with serum resistin levels and cardiovascular risk factors [45]. As for type 2 DM, it is a heterogeneous chronic clinical syndrome defined by high blood glucose levels as a result of insulin deficiency and/or impaired peripheral glucose uptake, which simultaneously affects the metabolism of glucose, proteins and lipids [73]. The development of DM is significantly influenced by genetic factors and there is consistent evidence that inflammation process plays a crucial role in the pathophysiology of DM. Hyper-

glycaemia also induces changes in the inflammatory signalling pathways of tissues, and it accelerates cellular ageing processes that may lead to increased secretion of further inflammatory cytokines, creating a vicious cycle [14, 65, 73]. CRP is secreted by the liver and constitutes an acute phase indicator, which is involved in the inflammatory pathways associated with the development and progression of DM. Multiple studies have demonstrated an association of SNPs in the CRP gene region with variation in plasma concentrations of CRP and with DM, MS and coronary heart disease. Additionally, it has been proven that blood CRP levels positively correlate with fasting and 2 hours glucose levels, the major clinical criteria used for the diagnosis of type 2 DM [41, 60, 65].

Incretin hormones involved in the regulation of metabolism

GLP-1 and GIP are two important endogenous gut or incretin hormones that stimulate the secretion of insulin [31]. GLP-1 is a 30 amino-acid peptide hormone secreted by the hindbrain neurons and specialized endocrine cells of the small intestine as a response to food intake. GLP-1 receptors are mainly distributed in the gastrointestinal tract, central nervous system and pancreas, but they can be found also in the kidney, lungs and vascular endothelium [34, 64]. Following oral nutrient intake, GLP-1 is physiologically secreted from intestinal L-cells and released into the circulation at concentrations of 5 to 15 pmol/L. These levels of GLP-1 can facilitate pancreatic beta-cells through their receptors, to increase glucose-stimulated insulin secretion [30]. Because of this selectivity of action, GLP-1 is often referred to as a member of the family of incretin hormones, which can enhance insulin secretion exclusively during periods of hyperglycaemia [16, 46]. Moreover, GLP-1 decreases the production of glucagon in a glucose-dependent way by inhibiting the pancreatic alpha-cells. It has also been proved to have pleiotropic effects which include reducing the appetite and food intake by delaying stomach emptying and slowing small intestinal movements [31, 64]. Gut hormones-based therapy has become an attractive treatment strategy for optimizing glycaemic control and reducing the accompanying comorbidities in type 2 DM which led to the development of GLP-1 RAs. GLP-1 RAs can reach higher concentrations than those seen under physiological conditions therefore they have a variety of effects in addition to reducing blood glucose levels such as the delayed gastric emptying and central anorexigenic effects. When administered to this group of patients, GLP-1 RAs has been demonstrated to provide considerable glycaemic and extra-glycaemic advantages [37, 50]. After the approval of the first GLP-1 RA, exenatide in the USA (2005) and Europe (2006), pharmaceutical companies began various development projects focused on GLP-1 receptor activation with increased potency and longer duration of action [46] (Table I).

Table I

Mechanism of action and types of GLP-1 RAs

Mechanism of action of GLP-1 RAs	GLP-1 binds to the GLP-1 receptor, stimulating glucose-dependent insulin secretion. GLP-1 RAs act by increasing insulin-, proinsulin- and somatostatin secretion while suppressing glucose-dependent glucagon secretion (except for hypoglycaemic episodes). GLP-1 RAs stimulate the proliferation and regeneration of islet cells and inhibit their apoptosis. The main target of GLP-1 is the pancreatic islet cell, but this type of receptors can be found in the kidneys, heart, lungs, stomach, central and peripheral nervous system too. GLP-1 RAs slow gastric emptying and induce gastric acid secretion; they suppress appetite through a neural mechanism, therefore producing weight loss; they have heart-protective effects.		
GLP-1 RAs molecules	Injectable form	Short-acting GLP-1RAs	Exenatide Lixisenatide Liraglutide
		Long-acting GLP-1RAs	Exenatide – extended release Semaglutide Dulaglutide Albiglutide
	Oral form		Semaglutide

Challenges of an oral peptide development

The concept of oral peptide therapies started from an older idea, and the challenges experienced are best demonstrated by the fact that despite many attempts, no commercially viable oral form of insulin has been developed since its discovery in 1921 [5]. Peptides are small, shorter than 100 amino-acid monomer chains which places them between proteins and tiny molecules. Potential benefits of using peptides as therapeutic drugs include their wide range of targets, low toxicity, increased potency and selectivity, safety and tolerability as well as their low tissue accumulation and good efficacy. On the other hand, specialists have to overcome several barriers of the oral delivery of peptides, such as different pH gradients in each region of the gastro-intestinal tract, various proteolytic enzymes, the mucus layer covering the different gastrointestinal regions, the epithelial barriers and inter-individual variability too [18, 47, 78]. Semaglutide (molecular formula $C_{187}H_{291}N_{45}O_{59}$) is a 31 amino-acid peptide that was

developed as a potent GLP-1 analogue that could be injected subcutaneously once weekly rather than once daily to improve treatment adherence. The structure of semaglutide is 94% identical to the native GLP-1 in order to prevent immunogenicity, but there are three major structural changes that ensure extended pharmacokinetics. Aib (2-aminoisobutyric acid) was used to replace the alanine residue at position 8 which prevents enzymatic degradation of the molecule by dipeptidyl peptidase-4 (DPP-4) inhibitor. In addition, lysine residue in position 34 was substituted by arginine and lysine residue at 26th position was acylated and attached through a linker with a C18 di-acid chain, which enhances stronger binding to albumin [26, 40]. Despite these changes, semaglutide is still exposed to rapid proteolytic degradation in the digestive tract, and oral administration could be difficult given to the acidic environment and low permeability of peptides through gastrointestinal epithelium [3, 52]. The most effective technique to improve drug absorption is to directly change the structure of the molecule and integrate an absorption enhancer, which in the case of semaglutide was SNAC (Sodium-N-[8-(2-hydroxy-benzoyl) amino] caprylate) [25]. SNAC is a low molecular weight fatty acid derivate developed by Emisphere (US) in the 1990s that facilitates absorption through the transcellular route and unlike the other carrier-based permeation enhancers does not need a protective enteric coating [3, 5]. SNAC and GLP-1 form a noncovalent bond in a concentration-dependent way, which increases semaglutide's lipophilicity and absorption through the gastric epithelium. Moreover, SNAC serves as a local pH buffer for the active ingredient in an acidic environment, protecting it from degradation and so improving its solubility. Once the medication enters the bloodstream, the enhancer molecule separates from it, since its activity is transient and reversible [31]. Even though oral bioavailability is limited to the range of 0.4 - 1%, this co-formulated tablet can achieve clinically meaningful drug exposure and strong activation of GLP-1 receptors. As food and liquids in the stomach have a major impact on drug absorption, the dosing regimen in case of oral semaglutide is quite restrictive for patients [30, 52].

Dosing conditions and oral formulation of semaglutide pharmacokinetics

According to the phase 3a clinical studies, particular dosing conditions play an important role in the clinically meaningful exposure of oral semaglutide [59]. Since oral semaglutide is almost entirely absorbed in the stomach it has a different pharmacokinetic profile from the majority of other medications absorbed in the intestine [31]. The presence of food in the abdomen interferes with drug absorption, therefore it is recommended for patients to take the oral semaglutide tablet during the fasting period, usually 30 minutes before any other food or medication [26, 31, 42]. Moreover, studies have examined the impact of water volume on pharmacokinetics when the pill is swallowed and patients should take the pill with approximately half a glass (120 mL) of water [3, 26]. In drug-drug interaction studies have demonstrated that neither subcutaneous nor oral semaglutide did not affect the exposure of other commonly used medications such as warfarin, digoxin, lisinopril, metformin, atorvastatin and combined oral contraceptives. There have been no clinically significant interactions between oral semaglutide and omeprazole, a proton pump inhibitor, which increases gastric pH gradient. On the other hand, levothyroxine exposure was raised by 33% when administered together with oral semaglutide, probably because of the delayed gastric emptying and prolonged levothyroxine absorption [20, 31]. Monitoring of thyroid function is necessary in the case of patients treated with levothyroxine and oral semaglutide at the same time [20]. Because of its complex pharmacokinetics, the therapeutic success of oral semaglutide depends on patient counselling and on adherence to the administration instructions [26].

Safety and tolerability

In general, the incidence of adverse effects was comparable between oral semaglutide and placebo or active comparators across any patient subgroups. As predicted, gastrointestinal symptoms such as nausea, vomiting, dyspepsia or diarrhoea were the most commonly observed side effects and they occurred more common with oral semaglutide and were mild to moderate in severity and transient [2, 7]. In the background medication subgroups, 3 - 17% of patients experienced serious adverse events, and up to 17% of patients quit their prescribed medicine permanently [57]. In case of oral semaglutide 3, 7 or 14 mg the number of subjects who experienced gastrointestinal adverse events (mostly during dose escalation in the first 8 - 16 weeks) and the number of subjects who discontinued the trial due to these symptoms, appeared to rise with the dose [3, 6, 63, 79]. Accordingly, to these observations, a dosage-escalation strategy is suggested, beginning with a low dose (3 mg) to prevent gastrointestinal adverse effects [67]. Despite patients receiving background basal/bolus insulin treatment in PIONEER 8 trial [79], oral semaglutide patients had a low frequency of symptomatic, blood glucose-confirmed hypoglycaemia, and its incidence did not surpass 8% in any treatment group [6, 10, 42, 55-63, 69]. As for special patient populations, individuals with an e-GFR lower than 60 mL/min/1.73 m^2 had a greater proportion of severe gastrointestinal adverse effects than those with e-GFR > 60 mL/min/1.73 m^2, although significant hypoglycaemic episodes were

rare [42]. Similar to changes found with liraglutide and other GLP-1 analogues, oral semaglutide generally elevated blood lipase and amylase levels when compared to placebo, however no increased incidence of acute pancreatitis was noted [6, 42, 55-57, 61, 69, 74]. Yet, GLP-1 RAs should be avoided in the case of patients diagnosed with pancreatitis or pancreatic neoplasm [79].

The impact of clinical trials outcomes in oral semaglutide therapy

The first GLP-1 RA in a tablet formulation developed for treatment of adults with type 2 DM is once-daily oral semaglutide [12]. The Peptide Innovation for Early Diabetes Treatment program or PIONEEER program was designed to evaluate the efficacy and safety of this formulation in a large and diverse group of patients with DM from early to late disease stage [12, 59]. This phase 3 clinical research program comprised 8 10 international studies (PIONEER 1-10) [6, 10, 42, 55, 61-63, 76-79]. In these trials, oral semaglutide in three different doses of 3, 7 and 14 mg were examined in comparison to placebo (PIONEER 1, 8, and 4 - 6), sitagliptin in dose of 100 mg (PIONEER 3 and 7), empagliflozin in dose of 25 mg (PIONEER 2), liraglutide (PIONEER 4, 9) and dulaglutide (PIONEER 10) [3, 68, 69] (Table II). Over the course of the program 9543 individuals were included with different background therapies, and in case of two studies, patients with cardiovascular disease or renal impairment were specifically recruited. The decrease in HbA1c at 26 weeks served as the primary endpoint for the majority of the trials, while for some studies the secondary endpoint was changed in body weight [59].

Table II

Overview of PIONEER trials

Name of the trial	Number included patients	Follow-up period (in weeks)	Background treatment	Dosage of oral semaglutide	Comparator drug	Stage of DM
PIONEER 1	703	26	diet and lifestyle	3, 7 or 14 mg	Placebo	early stage (mean 3.5 years)
PIONEER 2	822	52	metformin	14 mg	empagliflozine 25mg	established DM (7-9 years)
PIONEER 3	1864	78	metformin ± sulfonylureas	3, 7 or 14 mg	sitagliptin 100mg	established DM (7-9 years)
PIONEER 4	711	52	metformin ± SGLT-2i	up to 14 mg/day	liraglutide up to 1.8 mg/day	established DM (7-9 years)
PIONEER 5	324	26	metformin ± sulfonylureas or insulin ± metformin	up to 14 mg/day	Placebo	advanced DM (14-15 years)
PIONEER 6	3183	event-driven	any standard medication except for GLP-1 RAs and DPP-4i	up to 14 mg/day	Placebo	advanced DM (14-15 years)
PIONEER 7	504	52	1-2 oral antidiabetic drugs	flexible dose semaglutide 3, 7 or 14 mg	fixed-dose sitagliptin	established DM (7-9 years)
PIONEER 8	731	52	insulin ± metformin	3, 7 or 14 mg	Placebo	advanced DM (14-15 years)

These clinical studies achieved multiple benefits as follows:

Glycaemic effects on diabetes management

In the PIONEER 1 and 8 trials oral semaglutide was significantly more beneficial compared to placebo and reduced baseline HbA1c in a dose-dependent way with 0.7 - 1.4% and 0.5 - 1.2%, respectively [6, 76]. Oral semaglutide was more efficient than the active comparators in individuals with established type 2 DM (mean duration between 7.4 and 8.6 years) who were using other oral antidiabetics (PIONEER 2-4) [56, 57, 61, 63]. In the PIONEER 2 trial greater reduction in HbA1c were observed in case of 14 mg oral semaglutide at week 26 compared with 25 mg empagliflozine (1.3% *versus* 0.9% estimated treatment difference) and significant differences were observed at week 52 also. There was no considerable difference referring to the two studied groups in the reduction of fasting plasma glucose with either therapy [61]. Semaglutide at the dose of 7 and 14 mg/day seemed to be more effective in reducing HbA1c in the PIONEER 3 trial than the 100 mg sitagliptin (difference,

0.3 and 0.7%, respectively) [63, 68]. The first research, which compared the safety and effectiveness of another GLP-1 RA (subcutaneous liraglutide) to oral semaglutide was the PIONEER 4 trial [48]. The subcutaneous liraglutide group started therapy with 0.6 mg once daily and increased the dose to 1.2 mg after one week and 1.8 mg after two weeks, whereas oral semaglutide was started at 3 mg and advanced to 7 and 14 mg after 8 weeks. In terms of lowering HbA1c, oral semaglutide showed non-inferiority to subcutaneous liraglutide group and superiority to placebo group. Moreover, at week 52, oral semaglutide significantly reduced HbA1c in comparison with both liraglutide and placebo [48, 56]. The PIONEER 7 trial compared the fixed dose of sitagliptin (100 mg) to flexible dose-adjustment of oral semaglutide [62]. In the oral semaglutide group 58% achieved the HbA1c target of < 7%, at week 52, while in the fixed-dose sitagliptin group only 25% [55].

Anti-obesity consequences and benefits

Using the treatment policy estimand similarly to the trial product estimand, oral semaglutide was effective in lowering body weight across the continuum of subjects with type 2 DM [69]. Oral semaglutide monotherapy in case of patients controlled by life-style changes in early stages of disease (average duration 3.5 years) significantly reduced body weight from baseline with a 0.1 (3 mg semaglutide), to 2.3 kg (14 mg semaglutide) placebo adjusted treatment differences [6]. In case of patients with established type 2 DM (mean duration between 7 and 9 years) on Metformin treatment (PIONEER 2) the effect of 14 mg oral semaglutide was not significantly better than 25 mg empagliflozine at week 26, but was considered superior to empagliflozine at week 52 when evaluated by the trial product estimand (4.7 compared to 3.8 kg), as opposed to the treatment policy estimand [5, 61]. When associated to metformin with or without sulfonylureas, the effect of both 7 and 14 mg oral semaglutide was superior to sitagliptin and reduced body weight with –1.6 and –2.5 kg, respectively [5, 63]. At week 26, oral semaglutide was also more effective at reducing weight than liraglutide (estimated treatment difference ETD: –1.2 kg) and placebo (ETD: –3.8 kg) in patients treated with metformin with or without an SGLT2 inhibitor (PIONEER 4) [5, 56]. In the PIONEER 8 trial patients with advanced type 2 DM were included (mean duration 14-15 years) on insulin treatment with or without metformin, where oral semaglutide 3, 7 and 14 mg reduced body weight from baseline with –1.4, –2.4, –3.7 kg respectively, and placebo with –0.4 kg. These body weight reductions were superior to placebo for all oral semaglutide dosages, in both estimands [79]. Additionally, clinically significant weight loss improves glycaemic management and lowers cardiovascular risk factors, all of which are advantageous in a population where comorbid obesity is a common occurrence [63].

Cardiovascular outcomes

According to the most recent ADA guidelines, GLP-1 RAs can specifically be beneficial as a second treatment to metformin, particularly if patients have a predominance of atherosclerotic cardiovascular disease (ASCVD) independent of HbA1c. Moreover, the GLP-1 RAs could represent an alternative therapeutic option for patients with heart failure (HF) and chronic kidney disease (CKD) who are not eligible for SGLT-2 inhibitors [13]. The mechanism by which this class of drugs decreases cardiovascular risk, is not fully understood, however atherosclerosis and thrombosis may be prevented by their effect on adhesion molecules and endothelial function, according to in vitro investigations. The PIONEER 6 included two categories of patients with uncontrolled DM and high risk for cardiovascular events, patients >50 years old with CKD or established cardiovascular disease (and patients > 60 years old with cardiovascular risk factors only [9, 28]. PIONEER 6 was an event-driven experiment, with a median follow-up period of 16 months [9, 59]. A percentage of 3.8% of participants in the oral semaglutide group and 4.8% in the placebo group had the primary composite endpoint of major adverse cardiovascular events (MACE), respectively. These results demonstrated oral semaglutide's non-inferiority ($p < 0.001$) but not superiority ($p = 0.17$) to placebo in this trial [3, 9]. It is important to mention that PIONEER 6 was not powered to demonstrate superiority because it was intended to exclude a higher risk of cardiovascular events associated with oral semaglutide than with placebo. As a result, it included fewer patients and had a shorter duration than would have been necessary to demonstrate safety in a post-approval setting [5]. Besides, the cardiovascular safety of other GLP-1 RAs was investigated in comparison to placebo in large prospective, randomized clinical studies; and either neutral effects or decreases in cardiovascular events have been observed [46]. Liraglutide, semaglutide (subcutaneous or oral), or dulaglutide did not differ from placebo in their respective cardiovascular outcome trials when HF was taken into account as an endpoint in its own right [9, 22, 23, 36, 38].

Renal impairment impact

Renal impairment is frequently associated with type 2 DM, making treatment goals difficult to achieve and limiting the use of several antidiabetic drugs. All patients treated with insulin and/or sulfonylureas, but especially those with CKD have a higher risk of hypoglycaemia and weight gain [42]. The majority of SGLT2 inhibitors are contraindicated in individuals with clearance of creatinine less than 45 mL/min/1.73 m^2, while metformin can be administered with safety in individuals with an e-GFR of at least 30 mL/min/1.73 m^2 [15]. All stages of CKD, can be treated with DPP-4-inhibitors, although these medications (with the exception of linagliptin) must be administered at a

lower dose, based on the stage of CKD [15, 42]. On the other hand, GLP-1 RAs do not necessitate constrain dosage modification in patients with CKD stage 4 or above. It has been demonstrated, that renal impairment had no impact on the pharmacokinetics of oral formulation of semaglutide in individuals without DM [42]. Patients with type 2 DM and mild renal impairment (e-GFR between 30-59 mL/min/1.73 m^2) were included in the PIONEER 5 study to compare the safety and effectiveness of 14 mg oral semaglutide against placebo [42, 62]. Following the protocol study, at week 26, oral semaglutide was considered more efficient to placebo in lowering HbA1c and body weight with an estimated treatment difference of 0.8% and 2.5 kg, respectively [42, 59]. Among patients with stage 3 CKD, oral semaglutide was associated with a decrease in albuminuria correlated with a reduction of both systolic and diastolic blood pressure in comparison to the placebo group. These findings point to additional benefits of oral semaglutide in a specific patient category [13, 51].

Pleiotropic effects

An exploratory analysis which included phase 3 clinical trials evaluated the impact of semaglutide on hs-CRP levels in participants with various stages of type 2 DM, as well as its role in glucose management and weight reduction [43]. Although less consistently than with GLP-1 RAs, decreases in hs-CRP have also been seen with other kinds of oral antidiabetics such as metformin, DPP-4 inhibitors, and SGLT-2 inhibitors [29]. In subjects with type 2 DM, semaglutide seemed to reduce hs-CRP levels more than comparators, which were represented by another GLP-1 analog (exenatide ER in SUSTAIN 3), an SGLT-2 inhibitor (empaglifozin in PIONEER 2), and placebo (PIONEER 1) [1, 6, 43, 61]. That could be possibly mediated in part by its effect on body weight and HbA1c, but a direct semaglutide effect on hs-CRP levels could potentially exist [43].

Conclusions

Semaglutide is presently the first GLP-1 analogue to be licensed for use in an oral pharmaceutical conception, and it serves as a great example of how the absorption enhancer SNAC molecule may overcome the challenges associated with oral administration of peptides. With its tolerability and safety profile closely associated with the members of GLP-1 RA class, clinical studies have demonstrated that oral semaglutide is more effective in decreasing HbA1c and body weight than placebo and a variety of oral and injectable active comparators. Future research in certain subgroups, such as those with and without established cardio-vascular disease as well as microvascular complications, will also reveal new information on the function of this medication in the treatment of type 2 DM. Oral semaglutide has a potential future as an anti-obesity medication in patients with or without DM and it may improve treatment compliance and the quality of life.

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Conflict of interest

The authors declare no conflict of interest.

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