REVIEW ARTICLE

An Insight into the Treatment Strategies of Obesity using Semaglutide and its Competitive Analogues: A Review Article

Nahid Rao*, Reenoo Jauhari, Vaishali Sati, Pallavi Godiyal

Abstract

Obesity is a major public health problem in the world. This growing rate represents an epidemic that requires immediate attention. Oral Semaglutide is a semaglutide compound with an absorption enhancer, a sodium N- (8 - [2-hydroxybenzoyl] amino) caprylate (SNAC). The mechanism of action simply produces Glucagon-like peptide-1 (GLP-1) as a food-based digestive hormone that acts as an appetite signal, stimulates insulin release, inhibits glucagon production, and regulates diarrhea. This article shows the correlation of GLP-1 association with motivation to feed and Semaglutide's anorectic effect and relation to cravings. We have performed complete searches from PubMed, Cochrane, Scopus, Medline, Medscape, and Wiley online library from 2015 to 2022. The trial data (SUSTAIN, PIONEER, STEP) suggested a major decrease in weight and HbA 1c. SELECT trial data showed cardiovascular safety of semaglutide over other anti-diabetic drugs. This review article summarized semaglutide trial data as an anti-obesity drug and compared the effects of semaglutide (oral and subcutaneous) with other GLP-1 analogs.

Keywords: Bimagrumab, Clinical trials, Diabetes mellitus, GLP-1 analogues, Obesity, Pioneer trials, Select trial, Semaglutide, Setmelanotide, Step trials, Sustain Trials,Tirzepatide.

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INTRODUCTION

Obesity is a major public health problem in the world and it is growing rapidly in many industrialized nations around the world. This growing rate represents a pandemic that needs urgent attention if obesity's potential toll on morbidity, mortality, and economics is to be avoided. Research into the complex physiology of obesity may aid in avoiding this impact.[1]

According to a study, the annual cost of managing obesity in the United States alone amounts to approximately $190.2 billion per year or 20.6% of national health expenditures.[2] Compared to a non-obese person, an obese person spends $2741 more on medical per year. In addition, the annual cost of lost productivity due to obesity is approximately $73.1 billion,[3] and almost $121 billion is spent annually on weight-loss products and services.[4]

In a 2016 position statement, the American Association of Clinical Endocrinologists (AACE) and the American College of Endocrinology (ACE) have proposed a new term for obesity, an adiposity-based chronic illness (ABCD). AACE/ACE did not name it as a real substitute for the term obesity but instead as a way to help the medical community focus on the pathophysiologic impact of excess weight.[5]

As per WHO, approx. estimates of annual healthcare costs attributable to obesity are US $190 billion per year in the USA, approximately 21% of US healthcare expenditures. Given its complexity, the obesity epidemic requires high-quality and integrated solutions, from individual interventions to comprehensive food policy, industry, and agricultural systems.

As per the definition by WHO, Overweight and obesity are defined as abnormal or excessive fat accumulation that may impair health.

Body mass index (BMI) is a simple indicator of weight gain that is often used to differentiate obesity and overweight in adults. It is defined as a person's weight in kilograms divided by a square of his height in meters (kg/m^2).

In adults, the WHO defines obesity and overweight as follows

- obesity is a BMI ≥30.
- overweight is a BMI ≥25.

BMI provides a very useful measure of obesity as it is the same for both sexes and all ages of adults. However, it should not be considered a fixed guideline because it may not be compatible with the same level of obesity in different people. In children, age needs to be considered when defining obesity.

PATHOPHYSIOLOGY

Hypertrophic versus hypercellular obesity

The adipocyte, which is the cellular basis for obesity, may be increased in size or number in obese people. Hypertrophic obesity, characterized by enlarged fat cells, is common in

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android obesity. Hypercellular obesity is more pronounced than obesity; it is most commonly found in overweight people in childhood or adolescence, but it is also frequently found in obese studies.[1]

Hypertrophic obesity usually begins in adulthood, is associated with an increased risk of cardiovascular disease, and is a quick response to weight loss measures. In contrast, patients with hypercellular obesity find it difficult to lose weight through non-surgical interventions.[1]

Adipocytes

The adipocyte is increasingly found to be a complex and functional metabolic cell. Currently, the adipocyte is seen as an active endocrine gland that produces several peptides and metabolites that may be suitable for weight control; these read deeply. [1]

Most adipocytokines produced by adipocytes are pro-inflammatory or play a role in blood clotting. Others are involved in insulin sensitivity and appetite control. However, the function of these many identified cytokines is still unknown or unclear.

Proinflammatory adipocyte products include:[81]

- Tumor necrosis factor-alpha
- Interleukin 6
- Monocyte chemoattractant protein–1 (MCP-1)

Metabolism and function

Key enzymes involved in adipocyte metabolism and function include the following:

- Endothelial-derived lipoprotein lipase - Lipid storage
- Hormone-sensitive lipase - Lipid elaboration and release from adipocyte depots
- Acyl-coenzyme A (acyl-CoA) synthetases - Fatty acid synthesis

In addition, a cascade of enzymes is involved in beta-oxidation and fatty acid metabolism.[1]

Development

Another area of active research is the investigation of indicators of preadipocytes to adipocytes. Recognizing that this process occurs in white and brown adipose tissue, even in adults, has increased its potential importance in improving obesity and returning to obesity after weight loss.[1]

Among the identified components in this process are the following transcription factors:

- Peroxisome proliferator-activated receptor–gamma (PPAR-gamma)
- Retinoid-X receptor ligands
- Perilipin
- Adipocyte differentiation-related protein (ADRP)
- CCAAT/enhancer-binding proteins (C/EBP) alpha, beta, and delta[1]

Hormonal influences on appetite

In addition to neurotransmitters and neurogenic signals, hormones affect appetite and food intake in many ways. In addition to neurotransmitters and neurogenic signals, many hormones affect hunger and food intake. Endocannabinoids, by their effects on endocannabinoid receptors, increase appetite, improve nutrient absorption, and promote lipogenesis. The hormone Melanocortin alters appetite by its effects on various melanocortin receptors. Many intestinal hormones play a key role in saturating the body, including glucagon-like peptide-1 (GLP-1), neuropeptide YY (PYY), and cholecystokinin. Leptin and pancreatic amylin are also potent satiety hormones. On the other hand, ghrelin, released from the stomach fundus, is a major hunger hormone. [1]

Odor detection threshold

Smell plays an important role in food behavior. Differences in odor limits (*i.e.,* very low concentrations of the human sense of smell) were found in a study that measured thresholds in 8 soft-headed, fasting people before and during the 2 hours of a hyperinsulinemic-euglycemic clamp. Increased insulin levels have led to a decrease in the ability to smell, which may have reduced the appetite. Therefore, the action of insulin in the bulb olfactory may be involved in the saturation process and may be of clinical interest as potential pathogenesis of obesity.[82]

Leptin

Leptin is a 16-kD protein that is mainly produced in the white adipose tissue beneath the skin and, to a lesser extent, in the placenta, skeletal muscle, and abdominal fundus in mice. Leptin has several functions in carbohydrate, bone, and reproductive metabolism that have been revealed, but its role in regulating body weight is the main reason for its prominence. The major role of leptin in regulating body weight is a sign of satiety in the hypothalamus and thus a reduction in diet and fat storage while correcting energy costs and carbohydrate metabolism, preventing weight gain. Women have higher leptin levels than men and are strongly associated with BMI.[83]

Patients with anorexia nervosa syndrome have a decrease in night time elevations in plasma melatonin and leptin levels as well as high circadian levels of plasma cortisol. These people have morning anorexia, evening hyperphagia, and insomnia. In another study, patients with anorexia nervosa syndrome averaged 3.6 waking hours per night; 52% of this awakening was associated with diet, with an average dietary intake of 1134 kcal.[1]

Genetics

Mutations that lead to damage to the leptin receptor in the hypothalamus are possible. These changes lead to initial obesity and hyperphagia despite normal or elevated leptin levels, hypogonadotropic hypogonadism, and defective thyrotropin production.[1]

Murray *et al*. first reported a series of leptin gene mutations that improved leptin's internal bioactivity but were associated with weight loss rather than obesity. This successive variation within the gene leptin is also associated with delayed puberty.[84]

Obesity outcomes

Adela Hruby *et al.* conclude the outcomes of obesity on the basis of risk factors, comorbidities, mortality rate, and economic burden associated with obesity in various points like diabetes, heart and vascular diseases, cancer, trauma, infection, mental health, and economic burden.[6]

Risk factors (non-exhaustive):

1 Individual
- energy intake over energy needs
- Calorie-dense, nutrient-poor food choices (*e.g.,* sugar-sweetened beverages)
- Low physical activity
- Sedentariness
- Little or excess sleep
- Genetics
- Pre- and perinatal exposures
- Certain diseases (e.g., Cushing's disease)
- Psychological conditions (e.g., depression, stress)
- Specific drugs (e.g., steroids)

2 Socioeconomic
- Low education
- Poverty

3 Environmental
- Lack of access to physical activity resources/low walkability neighborhood
- Food deserts (*i.e.,* geographical areas with little to no ready access to healthy food, such as fresh produce/grocery)
- Viruses
- Microbiota
- "Obesogens" (e.g., endocrine-disrupting chemicals)
- Obese social ties

Comorbidities and Sequelae (non-exhaustive)
- Type 2 diabetes
- Hypertension
- Dyslipidemia
- Heart and vascular diseases
- Osteoarthritis
- Infertility
- Certain cancers (e.g., esophageal, colon, postmenopausal breast)

Risk factors (non-exhaustive)
- Respiratory conditions/diseases (e.g., sleep apnea, asthma)
- Liver diseases (e.g., non-alcoholic fatty liver disease, non-alcoholic steatohepatitis)
- Gallstones
- Trauma treatment/survival
- Infection
- Psychological conditions (e.g., depression, psychosocial function)
- Physical disability
- Years of life lost/early mortality
- Absenteeism/loss of productivity
- Higher medical costs

SEMAGLUTIDE

Semaglutide has a 94% homology with human GLP-1.[8] Converting a GLP-1 RA into a pill form was cumbersome since digestion and absorption of an active compound are more complex, where it has to withstand the stomach acidity and penetrate intestinal structures with low permeability while maintaining a consistency that can eventually be circulated into the body.[9] Oral Semaglutide is a semaglutide compound with an absorption enhancer, a sodium N- (8 - [2-hydroxybenzoyl] amino) caprylate (SNAC).[7] SNAC provides enough GLP-1 durability to be properly absorbed in the stomach and ultimately enables drug circulation into the blood.[17] SNAC provides a local increase in pH that helps protect semaglutide from proteolytic degradation in the stomach[10] and facilitates the absorption of semaglutide in a concentrated manner into the gastric epithelium.[7] There is 300 mg of SNAC in each oral semaglutide tablet.[11]

Absorption and pharmacokinetics of semaglutide

Oral semaglutide is absorbed into the stomach, and the presence of food may block this process. A dietary impact study conducted on healthy volunteers (N = 78) reported that people who received oral semaglutide once daily in a fasting state (n = 26) had moderate exposure, and this was not the case in the diet where the exposure was. can be average (11 out of 25 people) or visual (14 out of 25 people). Therefore, it is recommended that the administration of oral semaglutide should be in a fasting state. The study also examined the effects of fluid volume (when swallowing a tablet) on the pharmacokinetics of semaglutide.[7]

The effects of oral semaglutide on fasting and post-prandial glucose and lipid metabolism were investigated in a double-blind crossover trial of 15 people with T2D. Oral semaglutide significantly improved fasting and post-prandial glucose metabolism and lipid metabolism as well as delayed abortion during the first post-prandial hour, corresponding to s.c. semaglutide in obese subjects.[12]

Mechanism of action of Semaglutide

Glucagon-like peptide-1 (GLP-1) is a digestive hormone released in the gut in response to food intake that acts as a satiety signal, stimulates insulin release, inhibits glucagon production, and regulates gastric emptying.[13]

Specifically, GLP-1 binds to GLP-1 Rs, which stimulates the activation of adenyl cyclase. Consequently, this sequence causes cyclic adenosine monophosphate (cAMP) levels to rise. Increased cAMP levels activate protein kinase A (PKA), and cAMP regulates guanine nucleotide exchange factor 2 (Epac2), thus producing a signal for increased insulin secretion.[14] This mechanism is important for treating T2D, which is characterized by insulin deficiency that results in chronic and progressive hyperglycemia.[15]

In addition, GLP-1 has other potentially beneficial effects from the perspective of cardiovascular risk, including natriuresis, diuresis, blood pressure reduction, and improvements in inflammation.[16]

As anti-obesity medications, GLP-1 RAs are the latest class of drugs to be approved for the treatment of obesity.[9] The GLP-1 RAs harness the beneficial physiologic effects of GLP-1 by enhancing GLP-1 receptor signalling well above physiologic levels; hence, these agents lead to glucose-lowering with a low risk of hypoglycemia and produce weight loss. Several agents in this class have been approved to date to treat type 2 diabetes mellitus: exenatide, lixisenatide, liraglutide, dulaglutide, albiglutide, exenatide extended-release, and semaglutide. Furthermore, liraglutide is also approved for the medical treatment of obesity, and semaglutide has been currently approved in some countries and under-investigation in some for that indication.[9]

Benefits of 10% weight loss or more in patients with overweight or obesity

A review article by Abd A. Tehrani *et al.*[17] explained the health outcomes of 10% weight loss or more in patients with overweight or obesity. A significant weight loss may be necessary to achieve the improvement or release of certain weight-related problems. Therefore, this study reviewed the effect of weight loss (≥10%). Many studies report significant weight loss and appropriate outcomes have used bariatric surgery or lifestyle modification.[17]

The results stated that the benefits of weight loss were seen in patients with a variety of obesity-related problems or obesity, including the development of co-morbid conditions such as type 2 diabetes and hypertension, and many more. Improvements in glucose metabolism and cardiovascular risk factors were observed in patients who gained significant weight loss through lifestyle interventions or pharmacotherapy (phentermine/topiramate 15/92 mg once daily or subcutaneous semaglutide 2.4 mg once a week). Other benefits associated with significant weight loss include reduced risk of cancer and the development of knee osteoarthritis, sleep apnea, endpoints related to childbirth, and health-related quality of life. Although costly, bariatric surgery is currently the most expensive intervention, although many weight management programs are considered costly.[17]

Overall, weight loss has a profound effect on weight-related problems and obesity. Massive weight loss should be the mainstay of primary care where moderate weight loss has had insufficient effects on obesity-related problems and in overweight patients.[17]

DATA FROM CLINICAL TRIALS

SUSTAIN Trials

SUSTAIN 1

This study was conducted worldwide. This study aimed to investigate the efficacy and safety of semaglutide once a week compared with a placebo in drug-control subjects with type 2 diabetes.[18]

SUSTAIN 2

The study was conducted in Africa, Asia, Europe and South America. The trial was intended to evaluate the efficacy and safety of semaglutide once a week compared with sitagliptin once a day as a supplement to metformin and/or TZD (a thiazolidinedione) in patients with type 2 diabetes.[19]

SUSTAIN 3

The study was conducted in Europe and North and South America. The trial is aimed at investigating the efficacy and safety of semaglutide once a week against exenatide ER (extended-release once a week as an addition to 1-2 oral anti-diabetic drugs in subjects with type 2 diabetes.[20]

SUSTAIN 4

The study was conducted in Africa, North and South America, Asia, and Europe. The study aimed to compare the effect of the effect once a week of two doses of semaglutide versus insulin glargine once a day on glycemic control after 30 weeks of treatment in non-insulin-dependent people with type 2 diabetes.[21]

SUSTAIN 5

The study was conducted in Asia, Europe and the USA. The trials were aimed at investigating the efficacy and safety of semaglutide once a week compared with placebo as add-on basal insulin only or basal insulin combined with metformin in patients with type 2 diabetes.[22]

SUSTAIN 6

This study was conducted worldwide. The trial aimed to assess cardiac and other long-term effects of semaglutide in subjects with type 2 diabetes. The trial was conducted, i.e., the duration of the trial (up to 148 weeks) would depend on the increase in major cardiovascular events (MACE) in this study and the remaining study program. MACE events will be monitored throughout the study, which will be terminated systematically in the event of the suspension mentioned above requirements.[23]

SUSTAIN 7

The study was conducted in Asia, Europe and the United States of America. The trial aimed to investigate the efficacy and safety of semaglutide compared to dulaglutide as a supplement to metformin in subjects with type 2 diabetes.[24]

SUSTAIN 8

This study conducted in Africa, Asia, Europe, and North and South America in a prospective study was to compare the effect of dosing once a week dosing on subcutaneous semaglutide (1.0 mg) compared with the oral dose of canagliflozin once daily (300 mg) in glycemic control in subjects with type 2 diabetes in post-metformin treatment.[25]

SUSTAIN 9

The study was conducted in Asia, Europe, and North America. The experiments were aimed at comparing the effect of semaglutide s.c. 1.0 mg once a week compared with placebo

Table 1: Results of SUSTAIN Trials

SUSTAIN- 1	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	
HbA1c %	-1.47	-1.56	-0.00	
Weight(kg)	-3.68	-4.67	-0.89	
SUSTAIN -2	Semaglutide 0.5 mg + Sitagliptin Placebo	Semaglutide 1.0 mg + Sitagliptin Placebo	Sitagliptin + Semaglutide Placebo	
HbA1c %	-1.32 (0.05)	-1.61	-0.55	
Weight(kg)	-4.28 (0.25)	-6.13 (0.25)	-1.93	
SUSTAIN 3	Semaglutide 0.5 mg	exenatide 2.0 mg		
HbA1c %	-1.54	-0.92		
Weight(kg)	-5.63	-1.85		
SUSTAIN 4	Semaglutide 0.5 mg	Semaglutide 1 mg	Insulin glargine	
HbA1c %	-1.21	-1.64	-0.83	
Weight(kg)	-3.47	-5.17	-1.15	
SUSTAIN 5	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo	
HbA1c %	-1.45	-1.85	-0.09	
Weight(kg)	-3.67	-6.42	-1.36	
SUSTAIN 6	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Placebo 0.5 mg	Placebo 1 mg
HbA1c %	-1.75	-2.11	-1.02	-0.88
Weight(kg)	-3.57	-4.88	-0.62	
Unit of Measure: percentage of subjects				
Cardiovascular death	1.6	1.9		
Non-fatal MI	2.5	3.7		
Non-fatal Stroke	1.5	2.5		
Revascularisation	2.6	4.2		
UAP requiring hospitalization	1.1	1.3		
Hospitalization for heart failure	2.7	2.4		
SUSTAIN 7	Semaglutide 0.5 mg	Semaglutide 1.0 mg	Dulaglutide 0.75 mg	Dulaglutide 1.5 mg
HbA1c %	-1.51	-1.78	-1.11	-1.37
weight(kg)	-4.56	-6.53	-2.30	-2.98
SUSTAIN 8	Semaglutide + Canagliflozin Placebo	Canagliflozin + Semaglutide Placebo		
HbA1c %	-1.5	-1.0		
Weight(kg)	-5.7	-4.3		
SUSTAIN 9	SEMAGLUTIDE	PLACEBO		
HbA1c %	-1. 6,	-0.2		
Weight(kg)	-4.7	-1.0		

as a supplement of SGLT-2 inhibitor monotherapy or in combination with metformin or sulfonylurea in glycemic control after 30 weeks of treatment in patients with the disease type 2 diabetes. Subjects remain on their pre-trial medication[26]

All sustain trial results are summarised in Table 1.

PIONEER

PIONEER 1

This study was conducted worldwide. This trial aims to investigate the efficacy and safety of oral semaglutide against placebo in subjects with type 2 diabetes treated with diet and exercise only.[27]

PIONEER 2

This study was conducted worldwide. This trial is aimed at investigating the dosage and safety of oral semaglutide against empagliflozin in type 2 diabetes studies.[28]

PIONEER 3

This study was conducted worldwide. The experiments aimed to investigate the efficacy and long-term safety of oral semaglutide compared with sitagliptin in subjects with type 2 diabetes.[29]

Table 2: Results of PIONEER Trials

PIONEER 1	Oral Semaglutide 3 mg	Oral Semaglutide 7 mg	Oral Semaglutide 14 mg	Placebo
HbA1c %	-0.9	-1.4	-1.6	-0.3
Bodyweight(kg)	-1.8	-2.8	-4.3	-1.6
PIONEER 2	Oral Semaglutide 14 mg	Empagliflozin 25 mg		
HbA1c %	-1.5	-0.9		
Bodyweight(kg)	-4.3	-3.9		
PIONEER 3	Oral Semaglutide 3 mg	Oral Semaglutide 7 mg	Oral Semaglutide 14 mg	Sitagliptin 100 mg
HbA1c %	-0.6	-1.2	-1.4	-0.8
Bodyweight(kg)	-1.2	-2.2	-3.2	-0.6
PIONEER 4	Oral Semaglutide 14 mg	Liraglutide 1.8 mg	Placebo	
HbA1c %	-1.4	-1.2	-0.1	
Bodyweight(kg)	-4.7	-3.3	-0.7	
PIONEER 5	Oral Semaglutide 14 mg	Placebo		
HbA1c %	-1.2	-0.1		
Bodyweight(kg)	-3.9	-0.9		
PIONEER 6	Oral Semaglutide 14 mg	Placebo		
HbA1c %	-1.0	-0.3		
Bodyweight(kg)	-4.2	-0.8		
Cardiovascular death	0.9%	1.9%		
Non-fatal myocardial infarction	2.3%	1.9%		
Non-fatal stroke	0.8%	1.0%		
Unstable angina requiring hospitalization	0.7%	0.4%		
Heart failure requiring hospitalization	1.3%	1.5%		
PIONEER 7	Oral Semaglutide Flex	Sitagliptin 100 mg- Main Phase		
HbA1c %	-1.3	-0.8		
Bodyweight(kg)	-2.7	-0.7		
PIONEER 8	Oral Semaglutide 3 mg	Oral Semaglutide 7 mg	Oral Semaglutide 14 mg	Placebo
HbA1c %	-0.5	-1.0	-1.3	-0.1
Bodyweight(kg)	-1.4	-2.6	-3.7	-0.5
PIONEER 9	Oral Semaglutide 3 mg	Oral Semaglutide 7 mg	Oral Semaglutide 14 mg	Liraglutide 0.9 mg
HbA1c %	-1.0	-1.4	-1.5	-1.3
Bodyweight(kg)	0.0	-0.8	-2.9	0.5
PIONEER 10	Oral Semaglutide 3 mg	Oral Semaglutide 7 mg	Oral Semaglutide 14 mg	Dulaglutide 0.75 mg
HbA1c %	-0.8	-1.4	-1.8	-1.4
Bodyweight(kg)	0.0	-0.9	-1.7	1.0

PIONEER 4

This study was conducted worldwide. This trial aims to investigate the efficacy and safety of oral semaglutide compared to liraglutide and placebo in studies with type 2 diabetes mellitus.[30]

PIONEER 5

This study was conducted worldwide. This trial aims to investigate the efficacy and safety of oral semaglutide against placebo in subjects with type 2 diabetes and moderate renal impairment.[31]

Table 3: STEP Trials:

Trial name	*No. of participants*	*duration*	*Semaglutide dose*	*Status*	*Weight loss*
STEP 1 trial(Obese or overweight people with related comorbidities, but not diabetes)	1961	68 weeks	2.4 mg	Complete	14.9%
STEP 2 trial (Overweight or obese people with type 2 diabetes)	1210	68 weeks	1 mg 2.4 mg	Complete	6.99% 9.64%
STEP 3(Overweight or obese people with related comorbidities, but not diabetes)	611	68 weeks	2.4 mg	Complete	16 %
STEP 4(Overweight or obese people with related comorbidities, but not diabetes)	902	68 weeks	2.4 mg for the first 20 weeks, after which they were randomly allotted to receive either semaglutide or placebo for the remaining 48 weeks.	complete	participants who continued to take semaglutide after randomization lost a total 17.4% weight loss over the whole trial, whereas those who switched to placebo regained an average 6.9%, giving a total weight loss of 5.0%.
STEP 5(Obese or overweight people with related comorbidities, but not diabetes)	304	2 years	This trial is testing the durability of weight loss with semaglutide 2.4 mg versus placebo across a full 2 years of treatment.	Completed	Results not published
STEP 6(Obese or overweight East Asian people with related comorbidities.)			2.4mg/week 1.7 mg/week	complete	13.2% 9.6%
STEP 7(Overweight or obese people with or without type 2 diabetes)	375	44 weeks	2.4 mg	recruiting	No results yet
STEP 8(Overweight or obese people with type 2 diabetes)			Semaglutide (2.4 mg) Liraglutide (3 mg)	complete	15.8% 6.4%

PIONEER 6

This study was conducted worldwide. The trial is aimed at investigating the cardiac safety of oral semaglutide in subjects with type 2 diabetes.[32]

PIONEER 7

This study was conducted worldwide. This trial aims to investigate the efficacy and safety of oral semaglutide using flexible dosage adjustments based on clinical trials compared with sitagliptin in mellitus type diabetes mellitus.[33]

PIONEER 8

This study was conducted worldwide. The trial aimed to investigate the efficacy and safety of oral semaglutide compared with placebo in subjects with Insulin-dependent diabetes mellitus. Throughout the study, all subjects should continue with pre-study insulin treatment (basal, basal-bolus, or a pre-mixed regimen that includes a soluble insulin combination). People who were treated with metformin in addition to insulin treatment should continue with metformin treatment throughout the study.[34]

PIONEER 9

This study was conducted in Asia. This trial aimed to investigate the relationship of dose-response once per day of three doses of levels (3, 7, and 14 mg) of oral semaglutide compared with placebo as monotherapy for glycemic control in Japanese subjects with type 2 diabetes.[35]

PIONEER 10

This study was conducted in Asia. This trial aims to investigate the safety and efficacy of oral semaglutide compared to dulaglutide in combination with one oral anti-diabetic drug in Japanese subjects with type 2 diabetes. [36]

All sustain trial results are summarised in Table 2.

DATA ON NON-DIABETICS

STEP trials, simplified in Table 3, are testing semaglutide at the higher dose of 2.4 mg/week, specifically for promoting weight loss, regardless of type 2 diabetes.[37, 84-90]

Table 4: Difference in GLPs

GLP-1 analog	*Date of FDA approval*	*Dose*	*Route of administration*	*A1c % decrease*	*Kg Weight loss*
Oral Semaglutide	September 20, 2019	14 mg	Oral	1.4	4.7 to 5.0 kg
Semaglutide	December 5, 2017	1.0 mg	Subcutaneous	1.9	6.4 kg
Liraglutide	January 25, 2010	1.8 mg	Subcutaneous	0.9 to 1.1	3.1to 3.2 kg
Dulaglutide	September 18, 2014	1.5 mg	Subcutaneous	1.4	3.0 kg
Exenatide	April 28, 2005	2 mg	Subcutaneous	1.38	1.51 kg

Semaglutide vs Other GLP-1 Ras

The difference in GLPs has been simplified in Table 4 under major headings of A1c % decrease and weight change(kg).

SEMAGLUTIDE VS LIRAGLUTIDE

Sugar *et al*. published a network meta-analysis that is intended to confirm the long-term effects of semaglutide QW against liraglutide OD in HbA1c % and weight change in patients with T2DM. Dose-dependent effect was observed in all interested doses, i.e., semaglutide (0.5 mg, 1 mg) and liraglutide (1.2 mg, 1.8 mg). While liraglutide 3 mg is included in a single RCT as part of this NMA, this is likely to lead to more reliable intervals and no significance.[38]

In the NMA published by Witkowski *et al*.,[15] Semaglutide 1 mg QW was significantly more effective compared with other GLP-1 in weight loss at 24 ± 4 weeks. Also, our analysis showed consistent semaglutide 1 mg QW consistency over liraglutide OD even in long-term use. In a phase II study by Nauck *et al*.,[9] Comparing 12-week weight loss versus liraglutide reported significant weight loss with semaglutide versus liraglutide. Both doses of semaglutide once a week (0.8 mg and 1.6 mg) were significant in weight loss compared to liraglutide 1.8 mg OD. However, the amounts of semaglutide used in the trial were tested (non-FDA approved). Additionally, the dose increase protocol varied between semaglutide arms. The reported high levels of semaglutide 0.8 mg QW compared to liraglutide 1.8 mg were found to be consistent with semaglutide 1 mg QW and semaglutide 0.5 mg QW produced in SUCRA NMA score points. In the recently published SUSTAIN 10, phase 3b trial, liraglutide 1.2 mg was compared with subcutaneous glucose 1 mg over 30 weeks. Semaglutide 1 mg showed a significant increase over liraglutide 1.2 mg with a treatment difference of 0.69% in HbA1c % reduction. The experiments were short-lived, so the predictable long-term effect of semaglutide was not achieved as stated in the study-limiting phase. However, the treatment variance reported in SUSTAIN 10 supported these NMA effects. Webb *et al*.[40] NMA. Including long-term RCTs that reported significant elevations in injectable semaglutide than other GLP-1 RA-induced liraglutide.[38]

SEMAGLUTIDE ANORECTIC EFFECTS ON CRAVINGS AND INTAKE

The effects of GLP-1 on food intake have been of considerable attention in clinical and basic studies.[41]

GLP-10 s peripheral effects on food intake point towards a role for vagal afferents by the vagus nerve. The vagal afferents neurons (VANs) of the NG express GLP-1R [42] and innervate the gastrointestinal tract, liver, and portal vein.[43] Endogenous GLP-1 acts as a paracrine to promote GLP-1R on the dendritic terminals of the celiac and gastric branches of VANs that innervate the gut, reducing food intake via vagal-NTS glutamatergic signalling and also mediate insulin release via vago-vagal reflex. [44] Knocking down GLP-1Rs in VANs by injecting a lentiviral vector in the NG increases meal size, accelerates gastric emptying, increases postmeal glycemia, and blunts insulin release.[45]

Also, subdiaphragmatic vagotomy reduces the anorexic effect of peripherally GLP-1 administration.[46] Indeed, GLP-1R on VANs is modulated by feeding since GLP-1Rs expressed on vagal afferent neurons are trafficked to the membrane in response to a meal in 18 h fast and then re-feed rats, giving a possible promising explanation of the observation exogenously administered GLP-1 only inhibits food intake after feeding.[47] All were together, suggesting that GLP-1 receptors in VANs contributed to the incretin-linked effects after a meal.[45]

However, evidence shows that other additional mechanisms may be involved in GLP-1 peripheral effects contributing to food intake reduction. In this regard, the activation of areas outside the blood-brain barrier could have relevant effects on eating, since peripherally injected 125I-labeled GLP-1 binds to the subfornical organ and the AP, which both have close neuroanatomical connections with hypothalamic areas involved in water and appetite homeostasis.[48]

Peripherally, intestinal GLP-1 acts as a shorter-term prandial satiation signal.[49-51] It is secreted in response to food ingestion[53] reduces meal size in human's[52] and increases intermeal intervals, accounting for its suppressive effect on food intake.[49]

STRESS AND THE MOTIVATION TO FEED AND GLP ASSOCIATION

The primary source of endogenous GLP-1 within the brain is a population of preproglucagon neurons (PPG) in the caudal portion of the nucleus of the solitary tract (NTS).[54,55]

GLP-1 regulates brain areas that modulate food reward with particular physiological relevance in controlling feeding behavior.[56] Moreover, GLP-1 plays a major role in overall physiological processes in response to stress,[57,58] and this peptide is critical in maintaining energy homeostasis controlling satiety and hedonic aspects of food intake

concerning stress. [59-61] GLP-1R agonists (GLP-1RAs), such as exenatide, liraglutide, albiglutide, dulaglutide, and recently semaglutide, approved for the treatment of type2 DM and obesity, have become a promising pharmacological option for cutting food intake and body weight[62,63] and new as yet unrecognized therapeutic indications could be developed.

The PBN contains several subpopulations of neurons that regulate taste,[64] integrate neural signals associated with satiety from neuronal populations on the PVN, and receive inhibitory projections from AgRP neurons.[65]

PBN receives excitatory glutamate signaling from NTS neurons' subpopulations that integrate visceral and gustatory inputs.[66] GLP-1 producing neurons from the NTS project to the lateral PBN[67] and local activation with Ex-4 inhibits food intake of chow and palatable food, the motivation to work for palatable food, and decreases body weight gain,[67] thereby implicating this brain region in the hedonic aspect of feeding.[68] Moreover, Ex-4 increases neuronal firing, and the expression of calcitonin gene-related peptide (CGRP) in this nucleus leads to anorexia.

Different studies in diet-induced obesity mice and obese humans suggest central resistance to different metabolic hormones that control food intake, such as leptin or GLP-1.[69] Gut-brain communication is altered by high-fat consumption [70] and impairs the anorectic response to Ex-4,[71] altering the anorectic response to peripheral administration of GLP-1R agonists, delaying the onset but also prolonging the action on the depression of food intake.[72] Furthermore, in monogenic obesity (1% of total cases of obesity), the PCSK1 gene encoding the PC1/3 enzyme losses its function or is mutated.[73]

OTHER ANTI-OBESITY MEDICATIONS TO LOOK AT IN THE FUTURE

Setmelanotide

Setmelanotide is one of the many MC4R agonists that have been considered potential anti-obesity drugs. Setmelanotide was developed in the form of a personal drug approach, directing the drug to people with disabilities along the melanocortin pathway. In the study, Setmelanotide showed excellent results in two patients with pro-opiomelanocortin deficiency (POMC), reversing hyperphagia and producing significant weight loss in both patients.4 When given to patients with leptin receptor (LEPR) deficiency, bremelanotide produced an important clinical trial. Weight loss and hyperphagia.[5] The drug was also studied in seven patients with Bardet Biedl syndrome, which showed reduced appetite and resulted in weight loss at 1 year of 16.3% (90% confidence interval [CI], -19.9 % To –12.8%; n = 7). Bardet Biedl continues to be tested as a possible indicator of setmelanotide.

Setmelanotide was approved by the US Food and Drug Administration[11] for "chronic weight management (weight loss and weight loss for at least 1 year) in patients 6 years of age and older in obesity due to three abnormal genetic conditions: POMC deficiency, PCSK1 deficiency, and the lack of LEPR.[74]

Tirzepatide

Tirzepatide, a single dual-action molecule given once a week by injection, directs both the GLP-1 receptor and the glucose-insulin peptide (GIP) receptor. A phase 2 trial produced a weight loss rate of up to 12% in 26 weeks at a dose of 15 mg/day and had significant effects on glycemia. Tirzepatide was tested for obesity in the Study of Tirzepatide (LY3298176) for Participants With Obesity or Obesity (SURMOUNT-1), a phase 2 double-blind, placebo-controlled phase with 2,400 participants with obesity and comorbidity, but not diabetes. The drug is also tested for cognitive impairment. type 2 diabetes in a series of studies, SURPASS. The results of a single phase 3 study were published publicly but not yet published in a peer-reviewed format. In that study, the highest dose of tirzepatide(15 mg) produced 13.1% weight loss over 40 weeks in people with type 2 diabetes 2.35 A 5 mg dose of tirzepatide was associated with 8.5% weight loss in the study. The safety and effectiveness of tirzepatide in obese people will be closely monitored. The combined identification of GLP-1 and GIP is interesting, and it will be important to understand how the mechanisms of tirzepatide produce weight loss — appetite, lipolysis and energy expenditure effects should all be investigated.[74]

Bimagrumab

Bimagrumab is a human monoclonal antibody that binds to the activin type II receptor to block natural lines that poorly regulate bone growth.[36,37] Bimagrumab has been tested in a double-blind, placebo-controlled, 48-week, phase 2 randomized clinical trial33 for adults with type 2 diabetes and BMI 28-40 kg/m^2. Bimagrumab is administered at 10 mg/kg up to 1,200 mg in 5% dextrose solution and compared with placebo every 4 weeks for 48 weeks; both groups received dietary and exercise counseling. One of the strengths of the research was the body composition used by both DEXA and magnetic resonance imaging. By week 48, bimagrumab vs placebo changes noted were as follows: fat weight, –20.5% (–7.5 kg; 80% CI, –8.3 to -6.6 kg) vs. -0.5% (-0.18 kg; 80% CI, –0.99 to 0.63 kg) ($p < 0.001$); weight loss, 3.6% (1.70 kg; 80% CI, 1.1 to 2.3 kg) vs. -0.8% (–0.4 kg; 80% CI, –1.0 to 0.1 kg) ($p < 0.001$).[38] Instead, both weight loss and fat loss by a normal weight of 25: 75,29 bimagrumab was associated with weight loss fat and weight gain.[38] Safety will need to be monitored further; there were cases of elevated pancreas and liver enzymes by bimagrumab compared with placebo in this small study.[74]

OTHER USES OF GLP-1 RAs: (WHAT TO EXPECT IN THE FUTURE)

Second-line oral anti-diabetic drug

NAFLD

Gardener H. *et al*., in an article, reviewed GLP-1 therapies may be valuable for treating non-alcoholic fatty liver disease (NAFLD) and obesity. Several clinical trials are underway in testing oral semaglutide alone or in combination with other medications developed to treat NAFLD.[75]

NAFLD is a common liver disease and particularly exists in higher frequency in patients with type 2 diabetes mellitus.[76] It eventually leads to non-alcoholic steato hepatitis (NASH) and liver cirrhosis. It is important to treat NAFLD and NASH before it progresses into a more dangerous stage of liver fibrosis. NAFLD and NASH are potentially reversible with lifestyle intervention and potentially by a few drugs. Still, hepatic cirrhosis is irreversible and frequently leads to hepatic-cell failure, hepatocellular carcinoma, and death.[77] GLP-1 RAs have been shown to slow the progression of fatty liver disease in a study examining patients with T2D and NASH.[78]

After 72 weeks, a similar percentage of patients in the 0.4 mg treatment and placebo groups improved 1 fibrosis stage (43% vs. 33%) in a trial conducted by Philip N. Newsome *et al.* A total of 37% of the 0.4 mg semaglutide recipients and 15% of the placebo cohort had both non-alcoholic steatohepatitis resolution and improvising the 1 fibrosis stage.[91]

Cardiovascular benefits

The researchers are doing the study to see if semaglutide may reduce the risk of having cardiovascular events in patients with overweight or obese and with prior cardiovascular disease. SELECT (www.clinicaltrials.gov, NCT03574597) is a randomized, double-blind, placebo-controlled trial comparing semaglutide and placebo as a supplement to the standard of care to prevent major adverse cardiac events (MACE) in patients. with established CVD and overweight or obesity.[13]

The main purpose of SELECT is to indicate semaglutide levels of 2.4 mg s.c. Versus placebo where both are offered as a supplement to the standard of care at cardiovascular risk a reduction the reduction of MACE events, which is defined as a time shift randomization in the first appearance of a composite conclusion involving cardiovascular death, non-lethal MI, or non-lethal stroke. The second reassuring conclusions are the time from randomization to cardiovascular death, and the time from randomization to the death of the underlying cause.

Additional secondary objectives are to compare the effect of semaglutide in a dose of 2.4 mg s.c. once weekly versus placebo on a broad range of secondary cardiometabolic outcomes that are being measured, including cardiovascular risk factors, glucose metabolism, body weight, and renal function. [13]

Pcos treatmenT

In obese girls with the polycystic ovarian syndrome, testosterone and obesity combine to create unique pathology to increase metabolic disease involving fatty liver and insulin resistance, which alterations in GLP-1 activity may mediate. The researchers are doing a clinical trial to compare the semaglutide *vs*. lifestyle intervention in treating PCOS-TEAL (ClinicalTrials.gov Identifier: NCT03919929**)**. The investigators will treat girls with obesity and polycystic ovarian syndrome for 4 months with glucagon-like peptide-1 receptor agonist compared to dietary intervention to primarily lower hepatic fat and secondarily improve whole body and adipose insulin sensitivity. Mechanisms of hepatic metabolism, including rates of de novo lipogenesis and relative mitochondrial flux will also be assessed.[79]

Limitations

Acute Kidney Injury Associated with Semaglutide

David J. Leehey *et al*.,[80] a case study of kidney injury in patients taking glucagon-like peptide 1 (GLP-1) receptor agonists has been reported. Two patients were presented with chronic kidney disease due to diabetic kidney disease, which was accompanied by a rapid decline in kidney function and an increase in proteinuria after being given the GLP-1 receptor agonist semaglutide. In one patient, kidney biopsy showed improved circulation and nodular glomerulosclerosis associated with interstitial lymphoplasmacytic and eosinophilic infiltrate and evidence of acute tubular injury. It is recommended that caution be exercised with these agents in patients with moderate or severe chronic kidney disease due to limited kidney maintenance in the event of a serious kidney event. Because many kidney adverse events occur in patients with severe gastrointestinal symptoms, such patients should be tested in a laboratory and discontinued medication in the event of severe renal impairment.

The association of AKI with GLP-1 receptor agonists and especially semaglutide is not the cause. However, it is concerned that AKI events associated with GLP-1 agonists may have serious side effects, including in some cases, the need for hemodialysis. Long-term outcomes of patients receiving AKI associated with GLP-agonists- 1 receptor is also not the same. We recommend that caution be exercised with these agents in patients with moderate to severe CKD due to limited kidney retention in the event of a serious kidney event. Because most AKI cases occur in patients with severe abdominal symptoms, such patients should be tested in a laboratory and discontinued medication in the event of severe renal impairment.[80]

- Its long-term safety is not established, particularly its effect on worsening retinopathy.
- It takes 8 weeks of dose escalation to reach the maximum dose (14 mg/d), leading to a delay in reaching maximum efficacy

- Has to be taken on an empty stomach with water, and not to take any drink, food, or other oral medications for at least 30 minutes afterward.

CONCLUSION

Semaglutide has shown its efficacy in various trials so far to be used for obesity and overweight with or without T2DM and other comorbidities. Trials also show the results of comparison of semaglutide with other GLP-1 agonists, and a major reduction in HbA1c (%) and weight (kg) 2.4 mg dose has been approved by the FDA now. Although the risk of AKI might limit the use of semaglutide in kidney disease patients, it is advised to be used with caution and regular monitoring.

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