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Article

Glucagon-Like Peptide 1 Receptor Agonists, the Past, and Now–Focus on Its Anti-Obesity Effect

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[3] Department of Medical Imaging and Radiological Science, Central Taiwan University of Science and Technology, Taichung, Taiwan. Running title: obesity, anti-obesity, glucagon-like peptide 1 receptor agonists
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1. Introduction

Obesity contributes directly to many cardiovascular risk factors, including dyslipidemia, insulin resistance, type 2 diabetes mellitus (T2DM), hypertension, and obstructive sleep disorders. The US Food and Drug Administration (FDA) has approved six drugs to treat overweight and obesity up to date (Table. 1) [1], including orlistat (Xenical), phentermine-topiramate (Qsymia), naltrexone-bupropion (Contrave), liraglutide (Saxenda), setmelanotide (Imcivree), and semaglutide (Wegovy). These drugs result in different degrees of weight loss and improvement in cardiometabolic risk factors. However, their long-term safety, cardiovascular morbidity, and mortality remain a major concern [2]. The glucagon-like peptide 1 receptor agonists (GLP-1 RAs) [3] are new therapeutic options for managing these metabolic disorders. GLP-1 is a hormone released by the gut after stimulation by food intake. It induces insulin release, inhibits glucagon secretion, delays gastric emptying, and increases satiety sensation (Fig. 1). GLP-1RA was initially developed to improve glycemic control in T2DM. It also has several potential benefits in cardiovascular risk reduction, including natriuresis, blood pressure reduction, improved vascular endothelium function, decreased atherosclerosis progression [4], and inflammation [5]. It reduced the risk of cardiovascular disease in several large cardiovascular outcomes trials (CVOTs) [6] in patients with T2DM. Following significant weight reductions in T2DM [7], GLP-1RA was studied in overweight (body-mass index (BMI) 25) and obese (BMI 30) patients with and without diabetes.

2. GLP-1 mechanism of action

GLP-1 is secreted by gut enteroendocrine L-cells in the distal ileum to the colon and specific neurons within the nucleus of the solitary tract in the brainstem (Figure. 1). Its secretion is stimulated by various nutrients, neural and endocrine factors [8]. GLP-1 regulates food-related blood sugar by stimulating insulin release and inhibiting glucagon secretion in the pancreas. GLP-1 also prolongs gastric emptying time, increases satiety, decreases appetite after food consumption, regulates nutrient absorption, and limits weight gain. Based on different pharmacokinetics, GLP-1 RAs can be divided into short-acting and long-acting agents. Short-acting GLP-1 RAs have reduced effectiveness on overnight and early morning plasma glucose but maintain their long-term effect on gastric emptying during treatment. In contrast, long-acting GLP-1 RAs have more persistent effects on overnight and fasting plasma glucose and HbA1c.

Table 1. Food and Drug Administration- approved anti-obesity medications

Medication	Year approved	Approved For age	Mechanism	Rout of administration	Percentage of weight reduction
Orlistat (Xenical)	1999	Adults or children over 12 years old	Lipase inhibitor	Oral, three times per day	5-10%
Phentermine-topiramate (Qsymia)	2012	Adults	Decrease neurotransmitter-mediated appetite - increase satiety	Oral, once daily	5-10%
Naltrexone-bupropion (Contrave)	2014	Adults	Opioid antagonist / dual norepinephrine and dopamine reuptake inhibitor	Oral, once or twice daily	5-10%
Liraglutide (Saxenda)	2014	Adults or children over 12 years old	GLP-1 receptor agonist	Subcutaneous injection, once daily	5-10%
Setmelanotide (IMCIVREE)	2020	Patients over 6 years old with three specific rare gene diseases	Melanocortin 4 (MC4) receptor agonist	Subcutaneous injection, once daily	10%
Semaglutide (Wegovy)	2021	Adults	GLP-1 receptor agonist	Subcutaneous injection, once weekly	15%

3. Short and prolonged effects of GLP1-RA in an obesity trial

In the LEADER trial [9], 9340 T2DM patients with high cardiovascular risk received liraglutide (1.8 mg/day, subcutaneously) or placebo treatment. The primary outcome was a composite of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke. Liraglutide reduced glycated hemoglobin (HbA1c), blood pressure, and body weight during the LEADER trial. The major cardiovascular adverse events were lower with liraglutide than with placebo at the end of the study. In obesity without T2DM subjects [10], liraglutide (doses from 1.2 to 3.0 mg/day, subcutaneously, n = 90–95) or placebo (n = 98) administered for 20 weeks. Participants on liraglutide lost significantly more weight bodyweight than on placebo. The mean weight loss with liraglutide 3.0 mg was 7.2 kg compared with 2.8 kg with placebo. In December 2014, the FDA approved liraglutide 3 mg for adults with obesity (BMI $\geq$ 30) or excess weight (BMI $\geq$ 27) with weight-related medical problems. In the SUSTAIN-6 trial [11], patients with T2DM and established cardiovascular or chronic kidney disease received once weekly semaglutide (0.5 mg or 1.0 mg) or placebo for 104 weeks. The rate of cardiovascular death, nonfatal myocardial infarction, or nonfatal stroke was significantly lower among patients receiving semaglutide than placebo. Furthermore, the mean body weight in the semaglutide (0.5 mg) group was 2.9 kg lower, and the semaglutide (1.0 mg) group was 4.3 kg lower than the placebo group ($P < 0.001$ for both comparisons). Health-related quality of life (HRQoL), including depression, worry, self-care, and functional ability, was also improved in the semaglutide treatment group. Semaglutide injection version was approved by FDA for T2DM treatment in December 2017. Later on, several higher dose (2.4 mg) semaglutide clinical trials for bodyweight control were conducted.

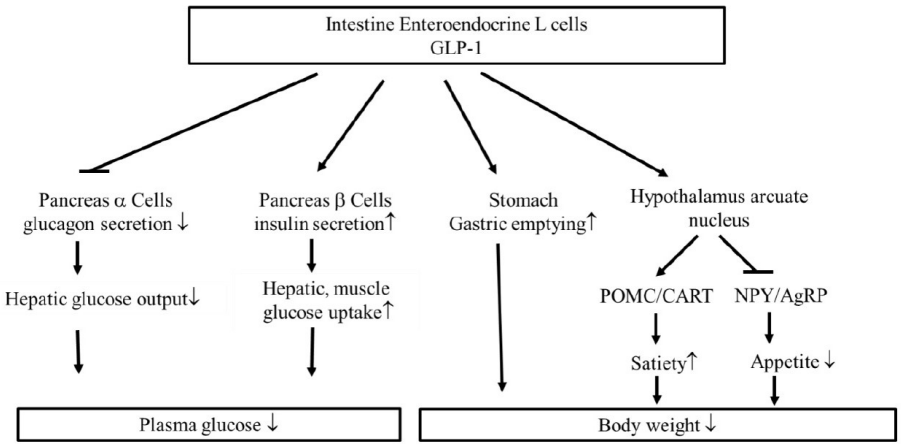

Figure 1. (A) Initial chest x-ray of our patient, which showed multiple patches in bilateral peripheral lung fields. (B) Subsequent chest x-ray at ICU, which showed rapid progression of the pulmonary lesions despite discontinuation of amiodarone and treatment with moxifloxacin. (C) HRCT before corticosteroid treatment, which showed alveolar and interstitial opacities with diffuse distribution in bilateral lung fields. The attenuation of the opacities wasn't significantly increased. (D) Subsequent HRCT after corticosteroid treatment for 18 days, which showed almost complete resolution of the lesions.

4. The Semaglutide Treatment Effect in People (STEP) clinical trials with overweight and obesity program

The STEP trials evaluated semaglutide 2.4 mg subcutaneously once weekly on weight loss, safety, and tolerability in adults with overweight or obesity (Table. 2, 3). Eight phase 3 trials included different groups of weight management participants. The primary endpoint was the change in body weight from baseline to the end of treatment. In the STEP 1 trial [12], 1961 individuals without diabetes participated with a BMI over 30 or BMI 27 with 1 weight-related condition were enrolled. They were assigned in a 2:1 ratio to receive treatment with semaglutide (2.4 mg, weekly) or placebo for 68 weeks. The primary endpoint was the percentage change in body weight. In the semaglutide group, bodyweight changed from baseline to week 68 was 14.9% (15.3 kg) compared with 2.4% (2.6 kg) in the placebo group ($P < 0.001$). There was greater improvement in cardiometabolic risk factors, including blood pressure, HbA1c levels, and physical function score. The most common adverse events were gastrointestinal upset, including nausea, vomiting, and diarrhea. However, most symptoms were transient and improved with time. In the STEP 2 trial [13], 1210 patients with type 2 diabetes participated with obesity or overweight. They were assigned to the semaglutide 2.4 mg group, 1.0 mg group, or placebo. At the end of 68 weeks, the change in bodyweight from baseline was 9.6%, 7.0%, and 3.4%, respectively. HbA1c improved in all three groups, semaglutide 2.4 mg (1.6%), 1.0 mg (1.5%), and placebo (0.4%). Greater improvements in physical functioning scores for HRQoL were seen with semaglutide 2·4 mg than placebo. Gastrointestinal adverse events were reported in semaglutide 2·4 mg (63.5%), 1.0 mg (57·5%), and 1.0 mg (34·3%). The STEP 3 trial [14] compared the effeteness between semaglutide, 2.4 mg, with intensive behavioral therapy (IBT) versus IBT only. In the medical treatment with the IBT group, the results in bodyweight reduction were 16% compared with 5.7% in the IBT only group. The STEP 4 trial[15] evaluated the effect of continuing versus withdrawing after semaglutide treatment for 20 weeks. The treatment group received continuous semaglutide 2.4 mg subcutaneously until the end of 68 weeks, and the placebo group stopped semaglutide after 20 weeks of treatment. In the treatment group, the mean body weight from 0 to 68 weeks was -17.4% compare with 5% in the placebo group. Waist circumference (9.7 cm) and physical function score also improved. Several ongoing STEP trials are evaluating semaglutide effects on different time intervals and different populations. The STEP 5 trial (NN9536-4378) evaluates the long-term safety and efficacy

Table 2. Summary of STEP trials primary and secondary end points at end of studies

	STEP 1		**STEP 2**		**STEP 3**		**STEP 4**	
	Semaglutide, 2.4 mg	Placebo	Semaglutide, 2.4 mg	Placebo	Semaglutide, 2.4 mg	Placebo	Semaglutide, 2.4 mg	Placebo
BW changed								
BW reduction over 5%	*86.4%	31.0%	*68.8%	28.5%	*89.8%	50.0%	*90.5%	50.0%
BW reduction over 10%	*69.1%	12.0%	*45.6%	8.2%	*79.3%	27.4%	*80.8%	20.9%
BW reduction over 15%	*50.5%	4.9%	*25.8%	0.3%	*59.6%	12.8%	*65.5%	9.8%
BW reduction over 20%	*32%	1.7%	*13.1%	1.6%	*38.6%	4.3%	*41.2%	5.1%
Physical parameters								
Waist circumference (cm)	*-13.54	-4.13	*-9.4	-4.5	*-16.3	-6.2	*-7.3	3.00
HbA1C (%)	*-0.45	-0.15	*-1.6%	-0.40%	*-0.56	-0.28	*-0.2	0.10
Systolic blood pressure (mmHg)	*-6.16	-1.06	*-3.9	-0.5	*-8.01	-0.6	*0.1	4.9
SF-36 physical function score	*2.21	0.41	*2.5	1	*3	2	*0.8	-0.9
IWQOL-Lite-CT score	*14.67	5.25	*10.1	5.3	nil	nil	nil	nil
Lipid levels, (ratio of week 68 to baseline)								
T-Cholesterol	0.97	1.00	0.99	0.99	*-3.8	2.1	*5	11
HDL-C	1.05	1.01	1.07	1.04	6.5	5	18	18
LDL-C	0.97	1.01	1	1	*-4.7	2.6	*1	6
VLDL-C	0.78	0.93	0.79	0.9	*-22.5	-6.6	*-6	15
free fatty acid	0.83	0.93	0.84	0.99	*-11.9	4	*-18	-14
Triglycerides	0.78	0.93	0.78	0.91	*-22.5	-6.5	*-6	15
CRP, (ratio of week 68 to baseline)	0.47	0.85	0.51	0.83	*-59.6	-22.9	nil	nil

Inclusion criteria of STEP trial including STEP 1: BMI over 30 or BMI over 27 with 1 weight-related condition; STEP 2: diabetes participated with obesity or overweight; STEP 3 non diabetes with intensive behavioral therapy or not; STEP 4 continuing vs withdrawing after semaglutide treatment for 20 weeks. (*$p<0.05$)
STEP: Semaglutide Treatment Effect in People clinical trial; BW: body weight; BMI: body-mass index.

of semaglutide 2.4 mg weekly for up to 104 weeks. The STEP 6 (NN9536-4382) trial evaluates weight management in overweight or obese Japanese subjects with semaglutide 2.4 mg or 1.7 mg weekly. The STEP 7 China Multi-Regional Clinical Trial (NN9536-4379) investigates weight management in Chinese subjects with semaglutide 2.4 mg weekly. The STEP 8 trial (NN9536-4376) compares the efficacy and safety of semaglutide 2.4 mg weekly versus liraglutide 3.0 mg OD versus placebo in subjects with obesity. The SELECT (Semaglutide Effects on Heart Disease and Stroke in Patients with Overweight or Obesity) cardiovascular outcomes trial [16] investigates subjects with overweight or obesity to prevent major adverse cardiovascular events in patients with established cardiovascular disease. About 17,500 volunteers are enrolled from different sites across six continents worldwide. Eligibility criteria, including age 45 years, BMI of 27 kg/m2, established cardiovascular disease, and HbA1c < 6.5%. The primary outcome and composite endpoint included cardiovascular death, nonfatal

Table 3. Summary of STEP trials reported adverse events and safety of interest

	STEP 1		**STEP 2**		**STEP 3**		**STEP 4**	
	Semaglutide, 2.4 mg	Placebo	Semaglutide, 2.4 mg	Placebo	Semaglutide, 2.4 mg	Placebo	Semaglutide, 2.4 mg	Placebo
Adverse events reported								
Diarrhea	31.50%	15.90%	23.10%	11.90%	36.10%	22.10%	14.40%	7.10%
Nausea	44.20%	17.40%	33.70%	9.20%	58.20%	22.10%	14.00%	4.90%
Constipation	23.40%	9.50%	17.40%	5.50%	36.90%	24.50%	11.60%	6.30%
Nasopharyngitis	21.50%	20.30%	16.90%	14.70%	22.10%	24.00%	10.80%	14.60%
Vomiting	24.80%	6.60%	21.80%	2.70%	27.30%	10.80%	10.30%	3.00%
Safety areas of interest								
Gastrointestinal disorders	74.20%	47.90%	63.50%	34.30%	82.80%	63.20%	41.90%	26.10%
Psychiatric disorders	9.50%	12.70%	6.00%	3.70%	14.70%	11.80%	8.60%	13.10%
Cardiovascular disorders	8.20%	11.50%	1.50%	1.20%	9.80%	10.80%	4.90%	11.20%
Allergic reactions	7.40%	8.20%	6.50%	4.50%	8.60%	9.30%	4.90%	4.10%
Gallbladder-related disorders	2.60%	1.20%	0.20%	0.70%	4.90%	1.50%	2.80%	3.70%

STEP: Semaglutide Treatment Effect in People clinical trial

myocardial infarction, or nonfatal stroke. The study began to enroll patients in October 2018 and is estimated to complete in September 2023.

5. Clinical impact of GLP-1 RA anti-obesity trial

In a non-diabetes adult with overweight or obesity, weight loss of at least 10% to 15% is recommended [17], but the target is challenging to achieve with diet control alone. In the STEP 1 trial, with the same lifestyle intervention, participants receiving semaglutide 2.4 mg lost 14.9% of their body weight compared with 2.4% for placebo. In the STEP 2 trial, in T2DM, increasing the semaglutide dose from 1.0 mg to 2.4 mg had little effect on increasing plasma glucose control (HbA1c 0.1% more reduced) but had a large impact on body weight, cardiometabolic risk factor reduction, and physical function improvement. These results may be predominantly due to BMI reduction rather than blood sugar control. STEP 3 trial results suggested that when used as an adjunct to IBT and a low-calorie diet, an additional semaglutide 2.4 mg once daily had significantly greater mean weight loss than the placebo group (16.0% for semaglutide with IBT versus 5.7% for IBT only; $P < 0.001$). It improved the serum lipid profile, including reducing total cholesterol, low-density lipoprotein cholesterol, triglycerides, and C-reactive protein ($P < 0.001$, $P < 0.01$). The combination of STEP 1 and STEP 3 trial results suggests that lifestyle intervention or even IBT may not contribute to significant body weight loss compared with semaglutide treatment. However, the serum lipid profile improved only with semaglutide in the IBT group, but not in the lifestyle intervention group. In the STEP 4 trial, patients receiving discontinuous semaglutide after 20 weeks of treatment still had a 5% reduction in body weight at the end of 68 weeks. The results suggested that long-term semaglutide treatment was necessary to maintain ideal body weight.

6. Conclusions

Obesity is a systemic disease that leads to higher morbidity and mortality associated with cardiovascular disease. Three major components in treating overweight are lifestyle habits, drug therapy, and bariatric surgery [18]. Early prevention with healthy dietary habits and regular physical activity are essential to fight against obesity. However, weight loss through diet control and exercise in obese subjects (BMI over 30) can be achieved in 10% to 20% of patients. Many people maintain the changes in lifestyle habits for a long time but gain weight after one to two years when they stop exercising. Bariatric surgery is effective and lasts the longest time. Nevertheless, it remains the last weight loss option because it is an invasive and expensive procedure.

Weight loss with anti-obesity drugs is currently a popular and rapidly developing trend. However, its associated adverse effects, including increased cardiovascular risk, development of cancer, depression, or other mental health issues, are major concerns. For patients with weight control problems in the outpatient department, lifestyle habit modifications are the first recommendation. If patients repeatedly fail to lose weight by controlling their diet and exercising, effective and safe anti-obesity medication might be considered. An anti-obesity drug that improved cardiovascular outcomes would be a more persuasive option. It would instill confidence in medical doctors to prescribe it. At present, gastric bypass surgery is the last choice for severe obesity patients whose dieting strategies and medical treatments fail.

Conflicts of Interest:
The authors declare no conflict of interest.

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