

Liraglutide for the treatment of obesity

Elmien Bronkhorst¹, Natalie Schellack²

¹Senior Lecturer, Department of Pharmacy, Faculty of Health Sciences, Sefako Makgatho Health Sciences University (SMU)

²Associate Professor, Department of Pharmacy, Faculty of Health Sciences, Sefako Makgatho Health Sciences University (SMU)

Corresponding author, email: elmien.bronkhorst@smu.ac.za

Abstract

Obesity and being overweight have become significant global health concerns, and may actually be seen as chronic disease conditions or even as a worldwide epidemic. In addition to the necessary life-style modifications required to effect weight-loss, which constitutes an essential healthcare intervention in this patient population, the use of adjunctive pharmacotherapeutic agents is often required. This article provides an overview of the first injectable treatment option, namely liraglutide, in the management of obesity, or of patients that are overweight in the presence of significant co-morbid conditions.

Keywords: liraglutide, overweight, obesity, weight-loss, incretin, GLP-1, type 2 diabetes mellitus

Introduction

Obesity and being overweight have become significant global health concerns, and may actually be seen as chronic disease conditions or even as a worldwide epidemic.^{1,2,3} According to the World Health Organization (WHO) the prevalence of obesity more than doubled between 1980 and 2014. In 2014, around 13% of the world's population was overweight and 39% of adults were obese. Obesity in children under the age of 5 years in underdeveloped countries is estimated to be higher than 30%. Obesity and overweight can be classified by using the body mass index (BMI), which can be defined as a person's weight in kilograms divided by the square of his height in meters (kg/m²). By using this index, being overweight can be defined as a BMI greater than or equal to (\geq) 25 kg/m² and obesity as a BMI \geq 30 kg/m², with morbid obesity being classified as a BMI \geq 40 kg/m².^{2,4,5} The fundamental cause of the global rise in the prevalence of overweight and obesity can be attributed to the increased intake of energy-dense foods that are high in saturated fat, and a decrease in physical activity because of sedentary lifestyles caused by increasing urbanization, changed modes of transportation and extended working hours.⁴ Co-morbidities associated with obesity include cardiovascular morbidity and mortality, type 2 diabetes mellitus, various cancers and dyslipidaemia. Obesity can reduce one's overall health-related quality of life.¹ Weight-loss is an important life-style modification in all of these chronic diseases, but losing weight through lifestyle intervention alone is usually difficult to maintain.⁶

Obesity

The WHO defines obesity and overweight as excessive or abnormal fat accumulation that may impair a person's health,

which usually exceeds 20% or more of an individual's ideal body weight. As mentioned before, overweight and obesity can be classified by using a simple index of weight-for-height calculations, referred to as the BMI. Refer to Table 1.

Table 1: Classifying or grading of the level of obesity by utilising the BMI⁴

Level of obesity	Corresponding BMI*
Overweight	\geq 25 kg/m ²
Obese	\geq 30 kg/m ²
Morbidly obese	\geq 40 kg/m ²

*BMI: body mass index

More recently, the tripling in the prevalence of type 2 diabetes worldwide has been attributed to the increase in the rate of obesity.⁶ The prevalence of type 2 diabetes is an increasing public health problem globally, and targeted behaviours like physical exercise and healthy eating are important in both the prevention and treatment of diabetes mellitus.⁷ The first-line treatment of obesity is still lifestyle modification, but the limitation is poor long-term compliance and control. Pharmaceutical intervention should be seen as an additional therapeutic aid to such lifestyle changes.⁸

Rapid increases in the prevalence of morbid obesity have been reported worldwide, and an ever-increasing move away from the average BMI is being observed.⁹ Clinically, severe obesity appears to be an integral part of the United States (US) population's weight distribution. This is true of the US as *the* high-income country with the highest mean body weight amongst other high-income countries (1-in-3 adults with a BMI of more than 30 kg/m²), but it is also true of most other countries worldwide.⁹

In a large survey conducted by the National Center for Health Statistics, the prevalence of diabetes mellitus in overweight individuals was above 80%, while obese patients had a 49% prevalence of diabetes. In contrast to this, the prevalence of diabetes in the group of patients with a BMI < 25 kg/m² was the lowest at 8%. The findings from this study suggest that more effort should be taken to combat obesity, as obesity is a modifiable risk factor for the development of diabetes.⁵ During the Look AHEAD trial, participants randomised to lifestyle intervention lost an average of 8.6% of their initial body weight, compared to 0.7% in the control group. This illustrates the importance of lifestyle modifications such as those used during the Look AHEAD trial. These included on-site treatment sessions with the goal to reduce initial body weight by at least 7%. The on-site treatment sessions were scheduled for a four-years period, with the frequency of visits reducing as time progressed. The goal of these interventions was to reduce body weight and maintain the weight-loss through dietary intervention or a reduction in calorie intake, and an increase in the intake of fruit and vegetables, whilst also increasing the level of physical activity.⁵

Furthermore, severe obesity can pose more complex health issues than just being a risk factor in co-morbid diseases. The need for additional resources, like larger imaging equipment, operating tables or wheelchairs, may place an additional burden on physicians' offices and hospitals.⁹

Liraglutide

Liraglutide is an analogue of the incretin hormone, glucagon-like peptide-1 (GLP-1), with a dual benefit on glycaemic control *and* body weight.¹ Liraglutide has been approved for the treatment of diabetes mellitus at dosages of 1.2 and 1.8 mg daily. At these

dosages, significant weight loss has been observed in diabetic patients.¹ Once-daily dosages of 3 mg have been shown to have potential benefits for weight management.⁶

Following ingestion of food, incretin hormones (gastric inhibitory polypeptide (GIP) and GLP-1) are secreted from the gastrointestinal tract. Insulin secretion, in response to elevated glucose levels, has been shown to increase when intravenous GLP-1 is administered. Exogenous GLP-1 receptor agonists mimic endogenous GLP-1 and inhibit the breakdown of endogenous incretin hormones. GLP-1 receptor agonists stimulate glucose-dependent insulin secretion and suppress inappropriate glucagon secretion. These agents may also instil a feeling of satiety by delaying gastric emptying.^{10,11} The mechanism of action of liraglutide is illustrated in Figure 1.

As an injectable agent, liraglutide is administered subcutaneously in the abdomen, thigh or upper arm and it can be dosed without regard to the timing of meals.³

Liraglutide for weight loss

Liraglutide was approved by the US Food and Drug Administration (FDA) for the treatment of obesity in 2014, under a risk evaluation and mitigation strategy, which consists of a communication plan to inform healthcare providers about serious risks.¹² The specific indication is for chronic weight management in patients with at least one weight-related co-morbid condition (e.g. dyslipidaemia, hypertension or diabetes mellitus type 2) and an initial body mass index of ≥ 27 kg/m² (overweight), or an initial body mass index of ≥ 30 kg/m² (obese).^{2,6,12}

Weight-loss with liraglutide is dosage-dependent up to 3.0 mg per day. Weight-loss through the use of liraglutide can be attributed to reduced appetite and energy intake, rather

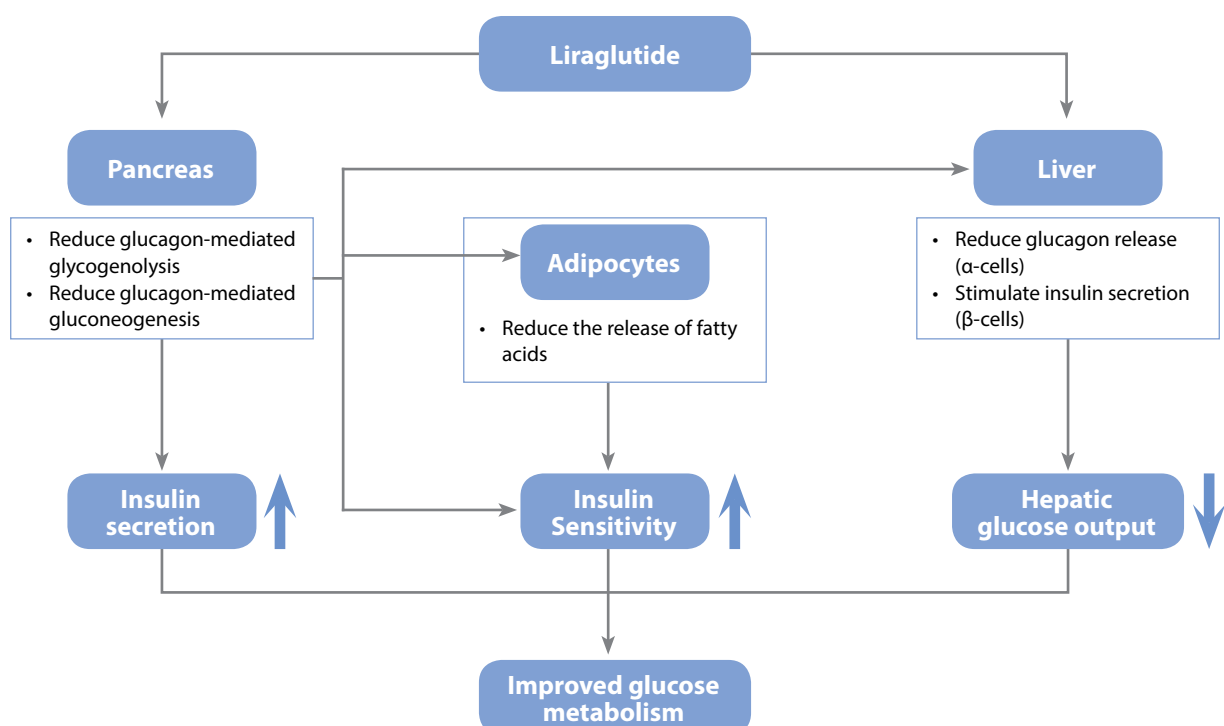


Figure 1: The mechanism of action of liraglutide (adapted from Neumiller, 2009).¹⁰

than by increased energy expenditure.⁶ Liraglutide should be injected subcutaneously on a once-daily basis, and must be used in conjunction with a reduced-calorie diet and increased physical activity. It may result in meaningful weight-loss, but also decrease the risk of developing type 2 diabetes mellitus.^{2,6} The three specific, primary co-endpoints of the Small Changes and Lasting Effects (SCALE) Trial assessed at week 56 are portrayed in Table II, and were the weight change from baseline, the proportion of patients who lost at least 5% of their baseline body weight, and patients who lost more than 10% of their baseline body weight. Statistically significant improvements were seen with patients on the liraglutide group compared to placebo.

Table II: Co-primary endpoints in the SCALE Trial

Outcomes	Liraglutide group	Placebo group	P value
Change in body weight	-8,4 kg	-2.8 kg	< 0.001
Loss of ≥ 5% of initial body weight	63.2%	27.1%	< 0.001
Loss of > 10% of initial body weight	33.1%	10.6%	< 0.001

Data extracted from Pi-Sunyer et al, 2015²

The use of long-term pharmacotherapy to maintain weight-loss is recommended for the treatment of obesity.¹¹ Four alternative oral obesity drugs, namely orlistat, lorcaserin, phentermine-topiramate and bupropion/naltrexone are approved in the US for the treatment of obesity.¹² Liraglutide is the first sub-cutaneous drug approved for weight-loss and proved to be more efficacious for initiating and maintaining weight-loss than orlistat and placebo, and has also shown a greater maintenance of weight-loss over an extended period of time.¹¹

The side-effect profile includes mild gastro-intestinal disturbances, and less than 1% of subjects may have more serious side-effects like acute gallbladder disease, acute pancreatitis and malignant neoplasms (thyroid C-cell tumours). Liraglutide has no significant clinical drug interactions.¹¹

Significance of weight-loss

Weight-loss of as little as 5-10% has been shown to reduce complications related to obesity and significantly improves the quality of life.⁶ Liraglutide treatment was associated with higher scores for overall physical and mental health, and a higher total score indicating a better quality of life was seen on the Impact of Weight on Quality of Life-Lite (IWQOL-Lite) questionnaire.²

Obesity is strongly associated with obstructive sleep apnoea, and significant weight-loss has been shown to reduce the severity of the disease. In a randomized, double-blinded, parallel group trial, the effects of liraglutide 3.0 mg has been shown to significantly reduce the apnoea-hypopnea index of patients suffering from sleep apnoea, whilst simultaneously increasing saturation, sleep quantity and efficiency, and ultimately the quality of life.¹³

Health benefits are evident with a reduction in body weight of as little as 3-5%. This includes decreased blood pressure, a decrease in the likelihood of developing type 2 diabetes, with a stable haemoglobin A1c. Further weight loss can also improve the level of low-density lipoprotein cholesterol and reduce the likelihood of the need for pharmacotherapy to control hypertension.¹¹

Conclusion

Obesity has become a global health concern for which weight-loss is an intervention of ever-increasing significance. In terms of pharmacotherapeutic support in an effort to reduce body weight, the more traditional approach usually involves one of the approved oral treatment options. However, liraglutide has become an alternative, injectable option in this regard. At a dosage of 3.0 mg once-daily, liraglutide is associated with clinically meaningful weight-loss when used in combination with proper diet and exercise in overweight or obese patients. Weight-loss with liraglutide is sustainable and patients maintain their body weight up to two years after the treatment course.

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