**Discovery and Development of Semaglutide as Anti-Obesity Medication to Reduce Cardiovascular Risk in Diabetic Patients**

Sengar Yashwardhan Pratap Singh\*, Milan Prabhakar, Mohd Suleman, Mohd Anas, Yogesh Joshi

Department of Pharmacy Practice, School of Pharmaceutical Sciences, Shri Guru Ram Rai University, Dehradun-248001, Uttarakhand, India

\***Corresponding Author:** yash.singh10598@gmail.com

**ABSTRACT**

Obesity and type 2 diabetes (T2D) are major global health concerns, with increasing prevalence worldwide. Both conditions pose a substantial risk for cardiovascular disease (CVD) and cardiometabolic complications. Traditional glycaemic control in T2D has been challenging, leading to the development of glucagon-like peptide-1 receptor agonists (GLP-1RAs) like semaglutide. Semaglutide, with its longer half-life, offers once-weekly administration and has shown efficacy in reducing weight and CVD risk. Semaglutide improves incretin function by activating GLP-1 receptors, leading to increased insulin secretion, reduced glucagon release, and suppressed hepatic gluconeogenesis. It also promotes weight loss through decreased energy intake and delayed gastric motility. Obesity and T2D have adverse effects on the immune and thromboembolic systems, increasing the risk of infections and CVD. Weight loss can significantly improve metabolic function and reduce diabetes comorbidities. Semaglutide, with its favorable pharmacokinetics and efficacy, provides a valuable treatment option in managing obesity and reducing cardiovascular risk in diabetic patients. However, it is essential to consider potential adverse effects and individual patient factors when prescribing semaglutide for optimal outcomes.

**Keywords:** Semaglutide, Obesity, Cardiovascular Disease, Type 2 Diabetes

**I. INTRODUCTION**

Obesity is a major global health care issue, with more than 600 million adults living with obesity worldwide. Obesity is a disease defined by the accumulation of excess adipose tissue, which is harmful to an individual’s health. It is a highly prevalent disease with a serious, chronic, relapsing course. The prevalence of obesity has risen globally for the past several decades, a trend predicted to continue. Worldwide obesity prevalence is 13%, but many countries have a much higher prevalence; for example, prevalence in adults increased from 31% to 42% between 1999-2000 and 2017-2018 in the USA, with an increase from 10% to 40% across most European countries over a 10-year period to 2017 [1-7].

People with obesity have an increased risk of developing cardiovascular (CV) disease (CVD) and cardiometabolic complications, such as type 2 diabetes (T2D)(8). Cardiovascular disease (CVD) is a leading cause of morbidity and mortality among individuals with diabetes.(9). Obesity is also associated with poor outcomes following infections such as influenza and SARS-CoV-2 [8-11].

When managing obesity to reduce cardiovascular risk in diabetic patients, a comprehensive treatment approach is necessary to address two conditions simultaneously. This approach should focus on lifestyle modifications and Pharmacological treatments to achieve optimal outcomes. Guidelines recommend lifestyle modification as the primary treatment for overweight or obesity, but the achieved weight loss is usually modest and often regained later [12-18].

Older pharmacological options for chronic weight management, such as orlistat, phentermine-topiramate and naltrexone-bupropion. Liraglutide 3.0 mg once daily administered subcutaneously was the first GLP-1 receptor agonist (GLP-1RA) to be approved for weight management. Pharmacological treatments for obesity provide a valuable adjunct to lifestyle interventions, but until recently the available agents only offered moderate weight loss over that achieved with lifestyle intervention. Semaglutide is a new anti-obesity medication that has been shown to be effective in reducing weight and CVD risk. Semaglutide is a potent long-acting glucagon-like peptide-1 (GLP-1) analogue shown to reduce energy intake, reduce hunger and increase feelings of satiety and fullness. This effect has been shown to arise via GLP-1 receptor activation in the central nervous system, with further indirect modulation of neuronal activity involved in appetite regulation and food intake and preference [7].

**II. DISCOVERY AND DEVELOPMENT OF SEMAGLUTIDE**

In managing type 2 diabetes mellitus, glycemic control has traditionally been the primary goal, however multifactorial approaches such as optimizing hyperglycemia, obesity, hypertension, dyslipidaemia, and cardiovascular factors are equally significant. Despite of various treatment options, a control on glycaemic level is still very challenging in clinical practice without having side effects like hypoglycaemic episodes. The development of glucagon-like peptide-1 (GLP-1) receptor agonists and recombinant human proteins brings hope for effective diabetes management [19-23].

Major incretin hormone GLP-1 acts through a variety of mechanisms, such as reduced hepatic gluconeogenesis, increased insulin secretion (glucose-dependent), and inhibition of glucagon release. It also results in delayed gastric emptying, reduced appetite and energy intake. It has special significance for the treatment of obese type 2 diabetes patients due to the reduction of HbA1c levels along with body weight without any risk of hypoglycemia. However, Dipeptidyl Peptidase-4 (DPP-4) and Neutral Endopeptidase mediated degradation makes it a candidate with short half-life (1-2 min), which is a major obstacle in its therapeutic utility. As a result, other GLP-1 receptor agonists, such as semaglutide, dulaglutide, and liraglutide, were designed to work similarly to GLP-1 but being less susceptible to proteolytic degradation. GLP-1 receptor agonists such as exendin based therapies (exenatide, lixisenatide) and GLP-1 analogues (semaglutide, liraglutide and dulaglutide) has been used clinically [21,24-30].

Semaglutide, a GLP-1 receptor agonist, is now available in subcutaneous and oral forms, marking the first approved oral GLP-1 receptor agonist. Originally approved as a second-line treatment for improved glycemic control in type 2 diabetes, it is currently being investigated for its potential as an anti-obesity medication. The STEP Phase 3a clinical development program assessed the safety and effectiveness of semaglutide as a once-weekly subcutaneous treatment for weight management in adults with obesity or overweight and at least one weight-related comorbidity [31-32].

**III. UNDERSTANDING SEMAGLUTIDE**

Based on the extensive body of research that contributed to the development of liraglutide, semaglutide has been developed. Semaglutide has an even longer half-life than liraglutide, which allows for once-weekly dosing instead of once daily. Although significant improvements have been noted over once or twice daily subcutaneous dosing, the injecting route could be a barrier for some potential users. When combined with semaglutide, an absorption enhancer known as sodium N-[8-(2-hydroxybenzoyl)amino]caprylate, or SNAC, was shown to produce therapeutic levels of the latter. SNAC provides transient effects on transcellular pathways, safeguarding semaglutide from proteolytic degradation in the stomach and promoting its absorption across the gastric mucosa. Comparatively, oral and subcutaneous semaglutide demonstrated similar glycemic and weight responses when exposed to equivalent doses [33-35].

1. **Pharmacokinetics of Semaglutide:** Table 1 represents the comparative analysis of pharmacokinetic parameters between subcutaneous (s.c.) and oral semaglutide [31].

**Table 1: Pharmacokinetics of Semaglutide**

|  |  |  |
| --- | --- | --- |
| **Characteristics** | **Semaglutide (s.c. injection)** | **Semaglutide (oral)** |
| **Absorption** | 89% | 0.4-1% |
| **Absolute bioavailability** | 65 ng/ml (0.5 mg weekly once) | 6.7 nmol/L (7 mg once daily) |
| **Steady state plasma conc.** | 123 ng/ml (1 mg weekly once) | 14.6 nmol/L (14 mg once daily) |
| **Time to achieve steady state conc.** | 4-5 weeks | 4-5 weeks |
| **Time to achieve maximum conc.** | 1–3 days | 01 hour |
| **Distribution** |
| Volume of distribution | 12.5 liters | 8 liters |
| Protein binding |  > 99% |  > 99% |
| **Metabolic pathway** | Proteolytic degradation followed by fatty acid oxidation | Proteolytic degradation followed by fatty acid oxidation |
| **Elimination profile** |
| Elimination t1/2 | 01 week | 01 week |
| Rate of clearance | 0.05 litres/ hour | 0.04 litres/ hour |

1. **Mechanism of Semaglutide:** Semaglutide enhances incretin function by activating GLP-1 receptors, leading to several mechanisms like glucose-dependent insulin secretion, inhibition of glucagon release, and reduced hepatic gluconeogenesis. This results in decreased fasting and postprandial glucose levels. It also improves β-cell functioning and increases insulin production, as indicated by a favorable proinsulin to insulin ratio. Furthermore, improved insulin sensitivity is observed, likely due to overall body weight reduction. Semaglutide also promotes weight loss through decreased energy intake and delayed gastric motility [36-40].

1. **Indications for Semaglutide:** As per the recommendation of American Diabetes Association 2020, the indications for Semaglutide are listed in Table 2 [31].

**Table 2: Indications for Semaglutide (As per American Diabetes Association 2020)**

|  |  |
| --- | --- |
| **Parameters** | **Indication** |
| **Efficacy** | High |
| **Cost** | High |
| **Oral/Injectable** | Both available |
| **Weight loss** | Yes |
| **Risk of Hypoglycaemia** | No, Semaglutide monotherapy |
| Yes, Combination with insulin or other hypoglycaemic drugs; needs dose reduction |
| **Cardiovascular risk** | Reduces cardiovascular risk |
| **Need for dose adjustment in geriatrics, renal and hepatic impairment** | Not necessary |
| **Preferred conditions** | Requirement of greater glycaemic control |
| Need for injectable therapy to reduce HbA1c |
| Need to switch from injectable to oral therapy |
| If possible, preferred over insulin |
| In cardiovascular diseases of atherosclerotic origin and renal impairment |
| Intolerance to SGLT-2 inhibitors |
| Weight reduction is essential |
| **Precautions** | Avoid in- Medullary carcinoma of thyroid, Pancreatitis, Multiple Endocrine Neoplasia Syndrome type 2,Progressive retinopathy,Congestive Heart Failure (As per EMA) |

1. **Adverse Effects of Semaglutide:** Adverse effects associate with Semaglutide are hypoglycemia, gastrointestinal effects (nausea, vomiting and diarrhea), pancreatitis and pancreatic cancer, cardiovascular disease, thyroid cancer, gallbladder­ cholelithiasis, acute kidney injury, diabetic retinopathy and allergic reactions [41].
2. **Obesity, Diabetes, and Cardiovascular Risk:** People with diabetes and obesity generally have an increased risk of infections, including influenza, and of secondary bacterial infections, and the risk increases with increasing levels of glycated hemoglobin (HbA1C). Even short-term elevated blood glucose levels decrease the immune response to viral infections and increase the risk of secondary bacterial infections in the lungs. A dysregulated immune system in diabetes and obesity possibly helps to explain the "cytokine storm" and the abnormal response of lymphocytes, neutrophils and macrophages seen in the sickest patients with COVID-19. Obese insulin-resistant individuals have disturbances in the thromboembolic system characterized by endothelial dysfunction, hyperfibrinogenemia, increased platelet aggregation, and increased amounts of plasminogen activator inhibitor 1, which has a prothrombotic effect. Obesity often correlates with glucose intolerance, insulin resistance, dyslipidemia, and hypertension, collectively termed metabolic syndrome. There are similarities between the abnormalities seen in metabolic syndrome and polycystic ovary syndrome (PCOS), leading to the hypothesis that both conditions may share a common pathogenesis involving hyperinsulinemia and glucose intolerance. The excessive accumulation of body fat leads to various metabolic abnormalities and diseases, such as insulin resistance, atherogenic dyslipidemia, nonalcoholic fatty liver disease (NAFLD), β-cell dysfunction, prediabetes, and type 2 diabetes. As body mass index (BMI), a measure of adiposity, rises, the risk of developing type 2 diabetes also increases progressively [42-49].

Individuals who are obese and have a predominant accumulation of upper body fat, including abdominal subcutaneous and intra-abdominal fat, intrahepatic triglycerides, intramyocellular lipids, and pancreatic fat, face a higher risk of developing type 2 diabetes compared to those with a lower body fat distribution (gluteofemoral). Interestingly, higher gluteofemoral body fat mass is associated with beneficial effects, such as reduced plasma triglyceride levels and increased HDL cholesterol concentrations, lower fasting blood glucose and insulin levels, improved oral glucose tolerance and insulin sensitivity. This association applies to lean, overweight, and obese individuals, indicating that having more gluteofemoral fat may confer protection against type 2 diabetes regardless of body weight. Type 2 diabetes arises from insulin resistance affecting multiple organs and a decrease in β-cell insulin secretion. The global rise in obesity prevalence is a significant factor contributing to the increased incidence of type 2 diabetes, as obesity impacts both insulin function and β-cell performance [50,51].

Obesity leads to higher levels of free fatty acids (FFAs) being released into the bloodstream and delivered to various body tissues. The belief that elevated plasma FFA concentrations are a significant cause of liver and muscle insulin resistance in obese individuals has been widely held. However, this notion has been challenged due to conflicting findings from various studies and doubts regarding the applicability of data from experimental interventions to real-world situations. In individuals with obesity under resting conditions, the release rate of free fatty acids (FFAs) into the bloodstream is lower compared to lean individuals concerning body fat mass. However, due to the substantial volume of body fat present, the rate of FFAs released relative to body fat-free mass is higher in those with obesity compared to lean individuals. Both obesity and type 2 diabetes negatively impact intrahepatic lipid metabolism, leading to nonalcoholic fatty liver disease (NAFLD). Approximately two-thirds of adults with obesity or type 2 diabetes are affected by NAFLD. Hepatic steatosis is mainly a result of elevated triglyceride production, rather than reduced fatty acid oxidation or decreased triglyceride export via very-low-density-lipoprotein (VLDL) secretion. Insulin resistance and chronic hyperinsulinemia increase hepatic de novo lipogenesis (fatty acid synthesis from glucose) and the delivery of lipogenic substrates to the liver (i.e. glucose, fatty acids released from hydrolysis of subcutaneous and intra-peritoneal adipose tissue triglycerides, fatty acids released from hepatic hydrolysis of plasma triglycerides, and fatty acids that spill over into the systemic circulation during postprandial lipolysis of triglycerides in chylomicrons). Weight loss can have profound therapeutic effects on metabolic function, type 2 diabetes, and diabetes comorbidities [52-62].

Diseases such as T2DM that induce high levels of vascular injury are accompanied by an elevated number of circulating endothelial cells (CECs). T2DM-related risk factors such as dyslipidemia, hyperglycemia, and hyperinsulinemia as well as other conditions (e.g., inadequate physical activity, smoking, and high blood pressure) facilitate the formation of atherosclerotic plaques/lesions. Dyslipidemia, due to the elevated flux of FFA from insulin-resistant tissues and spillover from entry into adipocytes, is considered as an important risk factor for developing CVD among diabetic patients. This is because dyslipidemia promotes inflammation, endothelial dysfunction, and platelet hyperactivation. Macroangiopathies, by inducing atherosclerosis in the coronary, carotid, and peripheral arteries, increase the risk of myocardial infarction (MI), stroke and peripheral artery disease (PAD). Macrovascular complications due to EC dysfunction are considered as an important cause of mortality and morbidity among diabetic patients [63-67].

**IV. CONCLUSION**

Obesity is a significant global health concern, affecting millions of adults worldwide and increasing the risk of various chronic diseases, including cardiovascular disease (CVD) and type 2 diabetes (T2D). Managing obesity in diabetic patients is crucial for reducing cardiovascular risk, and a comprehensive approach involving lifestyle modifications and pharmacological treatments is necessary. Semaglutide, a GLP-1 receptor agonist, has emerged as a promising anti-obesity medication with potential benefits for reducing cardiovascular risk in diabetic patients. Its mechanism of action includes enhanced insulin secretion, inhibition of glucagon release, suppressed hepatic gluconeogenesis, and reduced appetite and energy intake. Semaglutide has shown efficacy in weight management, making it a valuable treatment option for individuals with obesity and overweight. The pharmacokinetics of semaglutide, whether administered subcutaneously or orally, provide flexibility and convenience for patients. While there are adverse effects associated with semaglutide, its potential benefits in reducing cardiovascular risk outweigh the risks, especially when used in carefully selected patient populations.

Obesity and diabetes are closely interlinked, and their combined presence increases the risk of infections and cardiovascular complications. Addressing these conditions through weight management and improved glycemic control can positively impact overall health and reduce the risk of complications. Weight loss has a profound impact on metabolic function and comorbidities associated with diabetes, including dyslipidemia and insulin resistance. Furthermore, weight loss can alleviate the burden on the cardiovascular system, reducing the risk of atherosclerosis and related macrovascular complications.

In summary, semaglutide shows promise as an effective anti-obesity medication with potential benefits for reducing cardiovascular risk in diabetic patients. Combined with lifestyle modifications, semaglutide can be a valuable tool in managing obesity and diabetes and improving overall health outcomes. However, it is essential to consider individual patient characteristics and medical history when prescribing this medication. Further research and clinical trials are warranted to explore the long-term safety and efficacy of semaglutide in reducing cardiovascular risk in diabetic patients. Ultimately, a multidisciplinary approach involving healthcare professionals and patients' active participation is crucial in the successful management of obesity and diabetes to mitigate cardiovascular risk and improve patient outcomes

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