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

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**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 stands as a significant global healthcare challenge, impacting over 600 million adults worldwide. It is characterized by the accumulation of excess adipose tissue, posing significant health risks. This condition, marked by a chronic, relapsing course, has seen a substantial increase in its prevalence over the past few decades, and this trend is expected to persist. While the global prevalence of obesity is at 13%, numerous nations experience even higher rates. For instance, the prevalence of obesity in adults surged from 31% to 42% between 1999-2000 and 2017-2018 in the United States. Similarly, over a decade leading up to 2017, European countries witnessed an escalation from 10% to 40% in obesity rates. [1-7].

Obese people are more likely to suffer from cardiovascular disease (CVD) and its consequences, including type 2 diabetes (T2D)(8). One of the main causes of morbidity and death in people with diabetes is cardiovascular disease (CVD).(9). Obesity is also linked to poor outcomes after illnesses like the flu 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].

Earlier medications for long-term weight control, include orlistat, phentermine-topiramate, and naltrexone-bupropion. The first GLP-1 receptor agonist (GLP-1RA) to get weight-management approval was liraglutide 3.0 mg once day injected subcutaneously. Pharmacological therapies for obesity are an important complement to lifestyle changes, but up until recently, the agents on the market only provided modest weight reduction gains above those made by lifestyle changes. The effectiveness of the novel anti-obesity drug semaglutide in lowering weight and the risk of CVD has been demonstrated. Semaglutide is a powerful long-acting glucagon-like peptide-1 (GLP-1) analogue that has been demonstrated to decrease calorie intake, decrease appetite, and promote feelings of satiety and fullness. This impact has been demonstrated to result from central nervous system GLP-1 receptor activation, with further indirect modulation of neuronal activity involved in appetite control, food intake, and food choice. [7].

**II. DISCOVERY AND DEVELOPMENT OF SEMAGLUTIDE**

Glycemic control has always been the main objective in the management of type 2 diabetes mellitus, however multifactorial treatments including optimising hyperglycemia, obesity, hypertension, dyslipidaemia, and cardiovascular variables are equally important. Despite a variety of therapeutic options, maintaining a stable blood sugar level in a clinical setting without experiencing adverse consequences like hypoglycemic episodes is still extremely challenging. Hope for successful diabetes control is provided by the development of glucagon-like peptide-1 (GLP-1) receptor agonists and recombinant human proteins. [19-23].

The major incretin hormone GLP-1 exerts its effects through a range of mechanisms, including the reduction of hepatic gluconeogenesis, increased insulin secretion based on glucose levels, and inhibition of glucagon release. Furthermore, it induces delayed gastric emptying, leading to decreased appetite and energy intake. Its particular significance lies in treating individuals with obese type 2 diabetes, as it not only lowers HbA1c levels but also aids in weight loss, all without the risk of hypoglycemia. However, its therapeutic efficacy is hindered by its short half-life (1-2 minutes) due to degradation mediated by Dipeptidyl Peptidase-4 (DPP-4) and Neutral Endopeptidase.To overcome this challenge, alternative GLP-1 receptor agonists like semaglutide, dulaglutide, and liraglutide have been developed. These analogues are designed to mimic GLP-1's actions but are less prone to proteolytic degradation. Notably, therapies based on exendin (e.g., exenatide, lixisenatide) and GLP-1 analogues (e.g., semaglutide, liraglutide, dulaglutide) have been successfully employed in clinical practice. [21,24-30].

The first approved oral GLP-1 receptor agonist, semaglutide, a GLP-1 receptor agonist, is currently marketed in subcutaneous and oral dosage forms. It was first approved as a second-line therapy for type 2 diabetes to help with glycemic control, but it is additionally being investigated for use as an anti-obesity drug. In people with obesity or overweight and at least one weight-related comorbidity, semaglutide was tested as a once-weekly subcutaneous therapy for weight control in the STEP Phase 3a clinical research programme. [31-32].

**III. UNDERSTANDING SEMAGLUTIDE**

The development of semaglutide was based on the extensive amount of research that occurred during the development of liraglutide. Semaglutide has a half-life that is much longer than that of liraglutide, enabling once-weekly dosage as opposed to once daily. The injectable approach may be a barrier for some potential users, despite the fact that there have been noticeable gains over once or twice daily subcutaneous doses. Sodium N-[8-(2-hydroxybenzoyl)amino]caprylate, also known as SNAC, is an absorption enhancer that has been demonstrated to provide therapeutic amounts of semaglutide when paired with the later. Semaglutide is protected from proteolytic breakdown in the stomach and is promoted to be absorbed through the gastric mucosa thanks to SNAC's brief effects on transcellular pathways. 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 stimulates GLP-1 receptors to improve incretin function, leading to several mechanisms like glucose-dependent insulin secretion, decreased hepatic gluconeogenesis and suppression of glucagon release. As a result, fasting and postprandial glucose levels are reduced. It also improves β-cell functioning and increases insulin production, as indicated by a beneficial 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, The dosage must be lowered when used in combination with insulin or other hypoglycemic medications. |
| **Cardiovascular risk** | lowers the risk of heart disease |
| **Need for dose adjustment in geriatrics, renal and hepatic impairment** | Not necessary |
| **Preferred conditions** | Greater glycaemic control is necessary. |
| To lower HbA1c, injectable treatment is required. |
| Switching from injectable to oral treatment is necessary |
| Whenever possible, prefer to insulin |
| renal impairment and atherosclerotic-related cardiovascular disorders |
| Inability to tolerate SGLT-2 inhibitors |
| It's essential to lose weight. |
| **Precautions** | Avoid in- Multiple Endocrine Neoplasia Syndrome type 2, Pancreatitis, Thyroid Medullary Carcinoma, Progressive Retinopathy, and Congestive Heart Failure (According to 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). The immunological response to viral infections is lowered and the risk of subsequent bacterial infections in the lungs is increased even in the short term when blood glucose levels are raised. The "cytokine storm" and abnormal lymphocyte, neutrophil, and macrophage responses reported in the sickest COVID-19 patients may be explained by an immune system that is dysregulated in patients with diabetes and obesity. 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 frequently has a correlation with metabolic syndrome, also known as glucose intolerance, insulin resistance, dyslipidemia, and hypertension. 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. When body fat builds up excessively, it can cause several metabolic disorders and illnesses, including insulin resistance, atherogenic dyslipidemia, nonalcoholic fatty liver disease (NAFLD), -cell dysfunction, prediabetes, and type 2 diabetes. Type 2 diabetes risk gradually rises along with body mass index (BMI), a measure of obesity. [42-49].

Obese people who have a higher concentration of upper body fat, such as abdominal subcutaneous and intra-abdominal fat, intrahepatic triglycerides, intramyocellular lipids, and pancreatic fat are more likely to develop type 2 diabetes than people who have a lower concentration of body fat (gluteofemoral). It's interesting to note that higher gluteofemoral body fat mass is linked to positive outcomes including enhanced oral glucose tolerance and insulin sensitivity, lower fasting blood sugar and insulin levels, higher HDL cholesterol concentrations, lower plasma triglyceride levels, and increased HDL cholesterol concentrations. According to this relationship, which holds true for lean, overweight, and obese people alike, having greater gluteofemoral fat may offer protection against type 2 diabetes regardless of weight. Insulin resistance that affects several organs and a reduction in insulin production from beta cells are the causes of type 2 diabetes. Because obesity affects both insulin function and beta cell performance, it is a primary factor in the growth in type 2 diabetes incidence worldwide. [50,51].

Obesity results in elevated levels of free fatty acids (FFAs) that are released into the bloodstream and distributed throughout the body. The conventional belief that increased plasma FFA concentrations play a major role in inducing insulin resistance in the liver and muscles of obese individuals has been widely accepted. Nevertheless, this viewpoint has faced challenges due to conflicting findings across studies and uncertainties about how results from controlled experimental interventions translate to real-world scenarios. In resting conditions among obese individuals, the rate at which free fatty acids (FFAs) are released into the bloodstream is comparatively lower than in lean individuals, considering their body fat mass. However, due to the substantial overall body fat content, the relative rate of FFAs released in relation to body fat-free mass is higher in those with obesity compared to their lean counterparts. Both obesity and type 2 diabetes negatively impact the metabolism of lipids within the liver, contributing to the development of nonalcoholic fatty liver disease (NAFLD). This condition affects approximately two-thirds of adults with obesity or type 2 diabetes. The accumulation of fat in the liver primarily results from increased triglyceride production rather than a reduction in fatty acid oxidation or impaired triglyceride export through very-low-density-lipoprotein (VLDL) secretion. Insulin resistance and chronic hyperinsulinemia lead to heightened hepatic de novo lipogenesis, which is the process of synthesizing fatty acids from glucose. This is accompanied by an augmented delivery of lipogenic substrates to the liver, including glucose and fatty acids derived from the breakdown of triglycerides in adipose tissues (both subcutaneous and intra-peritoneal), as well as from the hydrolysis of plasma triglycerides. Additionally, fatty acids released during postprandial lipolysis of triglycerides in chylomicrons contribute to this phenomenon. Significantly, weight loss can yield substantial therapeutic benefits by positively affecting metabolic function, type 2 diabetes management, and associated comorbidities. [52-62].

Circulating endothelial cells (CECs) are seen in greater quantities in conditions like T2DM that cause severe vascular damage. The development of atherosclerotic plaques and lesions is facilitated by T2DM-related risk factors such dyslipidemia, hyperglycemia, and hyperinsulinemia as well as other diseases (such as inadequate physical activity, smoking, and high blood pressure). Dyslipidemia is regarded as a major risk factor for developing CVD in diabetes patients because of the increased flow of FFA from insulin-resistant tissues and spillover from entrance into adipocytes. The reason for this is that dyslipidemia encourages inflammatory response, endothelial dysfunction, and platelet hyperactivation. The risk of myocardial infarction (MI), stroke, and peripheral artery disease (PAD) is increased by macroangiopathies because they cause atherosclerosis in the coronary, carotid, and peripheral arteries. One of the main causes of death and morbidity in diabetes patients is thought to be macrovascular problems carried due to EC dysfunction. [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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