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Newly-emerging side effects of semaglutide and liraglutide usage associated with weight loss treatment

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A. Study design/planning
B. Data collection/entry
C. Data analysis/statistics
D. Data interpretation
E. Preparation of manuscript
F. Literature analysis/search
G. Funds collection

Abstract

GLP-1 agonists, such as semaglutide and liraglutide, are some of the most promising drugs in therapy for treating obesity in patients with type 2 diabetes as well as patients without diabetes. With many positive effects, not only in treating obesity but also in positively affecting blood glucose levels, blood pressure and cardiac muscle, they are among the most commonly used drugs in the general practitioner's office. However, with the increasing popularity of drugs such as semaglutide and liraglutide, questions about the safety of using these medications are also on the rise. It is widely known that drugs such as semaglutide act on receptors GLP-1 and delay gastric emptying, which in the longer time period can lead to gastroparesis. Additionally, patients may experience rapid loss of facial fat due to quick weight loss, leading to a condition known as "Ozempic face". Acute pancreatitis may occur in patients using semaglutide or liraglutide due to the presence of GLP-1 receptors on the pancreatic islets, which can cause hyperplasia and inflammation during the use of these drugs.

Keywords: semaglutide, gastroparesis, liraglutide, pancreatitis, obesity

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Introduction

Obesity is a persistent medical condition with significant health implications, including insulin resistance, high blood pressure and abnormal lipid levels, which are linked to serious chronic diseases such as type 2 diabetes, heart failure and non-alcoholic fatty liver disease and colorectal cancer, ultimately shortening lifespan [1,2]. The global occurrence of overweight and obesity, characterized by a body mass index (BMI) falling within the range of 25.0-29.9 kg/m^2 and ≥30.0 kg/m^2 respectively, has nearly tripled since the 1970s. Presently, close to 40% of adults are classified as overweight, with 13% meeting the criteria for obesity, and these figures have been steadily rising [3,4]. Pharmacotherapy plays a crucial role in assisting individuals with obesity in achieving and sustaining their desired weight loss goals. By effectively managing weight, pharmacological interventions can help mitigate the risk of complications associated with obesity [5,6].

Aim of the work

Obesity is one of the most pressing problems in modern world. The consequences of obesity affect nearly every organ in the human body. GLP-1 agonists such as semaglutide and liraglutide have gained recognition not only in the treatment of type 2 diabetes but have also been approved for the treatment of obesity. This article aims to take a closer look at a range of side effects that may occur in patients using GLP-1 agonists for the treatment of obesity in patients with or without diabetes. Widely documented side effects such as gastroparesis, newly emerging terms in medicine regarding GLP-1 agonists such as "Ozempic face", and rare but extremely dangerous side effect such as acute pancreatitis are discussed. Another topic that is discussed in this article is the risk awaiting patients using GLP-1 agonists for obesity, which is weight regain after discontinuation of the therapy.

Methods

This article is a literature review based on publications on PubMed using key words: semaglutide; liraglutide; obesity; gastroparesis; pancreatitis. The search was limited to articles published between the years 2015-2024, with the greatest focus on the last 4 years.

Literature review results

Glucagon-like peptide-1 (GLP1) is a peptide hormone released from L cells located in the small and large intestines, as well as from neurons in the nucleus of tractus solitarius (NTS) of the caudal brain stem. Due to its potent incretin effects, long-acting GLP-1 agonists are currently used as pharmacological treatments for type 2 diabetes mellitus. These analogues have also demonstrated efficacy in reducing food intake and body weight in both human clinical trials and experimental animal models [7]. Furthermore, they effectively enhance glycemic control by promoting insulin release and suppressing glucagon secretion without hypoglycemia [3]. Glucagon-like peptide-1 receptor agonists (GLP-1RAs), such as liraglutide and semaglutide, were originally designed for the management of type 2 diabetes. However, they have been discovered to be efficacious not only in lowering blood glucose levels but also in promoting weight loss [5]. With a concerning rise in the prevalence of type 2 diabetes (T2D) and its associated complications, there is an urgent demand for effective treatment approaches for its debilitating condition. However,

beyond exploring the potential benefits of new glucose-lowering medications, healthcare providers are increasingly prioritizing the evaluation of the long-term safety implications of these medications [8].

Semaglutide, the latest addition to the class of glucagon-like peptide-1 receptor agonists (GLP-1RAs), stands out as the substance available in both subcutaneous and oral formulations. Despite the notable benefits of GLP-1RAs in enhancing glycemic control and facilitating weight loss, ongoing concern has surfaced regarding their safety profile over time [8]. Semaglutide, a synthetic version of GLP-1, has been demonstrated to decrease energy consumption, suppress appetite, and enhance the feeling of fullness and satisfaction. These effects are attributed to the activation of GLP-1 receptors in the brain, which subsequently modulate neuronal activity associated with appetite control and dietary habits, leading to reduced food intake and altered food preferences [9]. In adults struggling with excess weight or obesity, weekly administration of subcutaneous semaglutide at a 2.4 mg dose alongside lifestyle changes led to substantial weight loss and improved cardiometabolism [10]. Ozempic and Wegovy are two medications that contain semaglutide, with Wegovy being the newest drug registered specifically for the treatment of obesity [3]. In December 2014, the GLP-1 analogue liraglutide, marketed under the trade name Saxenda, received approval from the Food and Drug Administration (FDA) for the treatment of obesity and weight loss in obese individuals [7]. A once-daily subcutaneous formulation of liraglutide 3.0 mg was developed specifically for the treatment of obesity [5].

Even though liraglutide and semaglutide were significantly linked to weight loss in adults with or without diabetes, closer look needs to be taken into the side effects of GLP-1 agonists such as gastroparesis, acute pancreatitis, "Ozempic face" and weight regain after discontinuation of the treatment. Some of these side effects are commonly encountered and widely described, such as gastroparesis. Some, such as "Ozempic face" are quite recent discoveries, and there is little research information about them. Some, such as acute pancreatitis, are uncertain, and research is ongoing regarding the significance of GLP-1 agonists with respect to these side effects [11,12].

Gastroparesis is characterized by a slowed process of gastric emptying without any physical blockage of the stomach outlet. We can distinguish two-most common types of gastroparesis: idiopathic gastroparesis and diabetic gastroparesis [12]. Key symptoms maintain feelings of fullness or satiety shortly after eating, along with nausea, vomiting, and bloating. It's worth noting that abdominal discomfort is gaining recognition as a prevalent symptom of this condition [13,14]. Although semaglutide is typically well received, it can occasionally lead to a variety of gastrointestinal adverse effects. The precise mechanism by which semaglutide may induce gastroparesis (delayed stomach emptying) is not fully understood. However, it is known that GLP-1 receptors play a role in regulating stomach emptying and motility. Stimulation of these receptors by semaglutide may contribute to gastroparesis by slowing the emptying of the stomach. In many cases, discontinuing semaglutide results in alleviation of symptoms such as nausea, abdominal discomfort, and vomiting. Through its action on the glucagon-like peptide-1 (GLP-1) receptor, semaglutide enhances incretin activity, leading to improved blood glucose levels via several mechanisms. These mechanisms include increased insulin secretion in response to glucose, reduced production of glucose by the liver (hepatic gluconeogenesis), slowed emptying of the stomach (delayed gastric emptying), and decreased release of glucagon, which raises blood sugar levels. Additionally, semaglutide aids in weight loss by delaying gastric emptying and reducing energy intake [12].

Many public figures, including actors, celebrities, and social media influencers have been open about their weight-loss journey with medications such as Ozempic. What is disturbing is that these individuals

often avoid discussing the complications, which can result in multifactorial harm, one of which, next to gastroparesis, is a facial feature given the newly-coined term "Ozempic face" [15]. The creation of the term "Ozempic face" is owed to the renowned American dermatologist Dr Paul Jarrod Frank to denote the unique gaunt facial appearance seen in these patients [16]. The swift reduction of weight and fat induced by semaglutide (Ozempic) may result in what is commonly referred to as "Ozempic face", whose proximate cause is the decrease in facial volume and fat, leading to the emergence of wrinkles and sagging skin, making it look dull. Consequently, the plastic surgery field encounters difficulties in addressing the facial alterations linked to rapid weight loss, which has prompted them to come up with newer methods of filling in fat tissue deficits on the face [17].

Patients undergoing weight loss while using Ozempic may encounter rapid reduction of fat throughout their bodies, mainly including their facial region. Facial volume, which is essential for a youthful look, mainly consists of fat. As fat diminishes rapidly in Ozempic users, wrinkles become more noticeable, and the skin begins to sag in various facial areas such as the temples, cheeks, tear troughs, jawline, and in the emergence of more pronounced marionette lines. In addition to fat loss, Ozempic can also prompt alterations in lip, cheek, and chin size, disrupting facial harmony. Patients on Ozempic may appear gaunt not only due to volume reduction but also due to changes in facial skin, including decreased collagen and elastin. These effects are particularly striking in older individuals with already diminished levels of elastin and collagen in their skin. Moreover, the loss of fatty acids can compromise the skin barrier, leading to dryness and a lackluster appearance. The rapid depletion of vitamins and nutrients during weight loss can worsen these issues, underscoring the importance of closely monitoring one's diet to ensure adequate nutritional intake. Clinical trials examining the use of semaglutide such as Ozempic and similar products for weight loss rarely mention facial fat loss as an adverse effect, which may lead to a failure to notice the issue on the part of the specialists who prescribe medications such as semaglutide for diabetes or obesity, which then causes new problems for their patients [16,17].

Pancreatitis is a medical condition that is one of the leading reasons for people to be admitted to the hospital. It is characterized by inflammation of the pancreas, the chief characteristic symptoms of which are severe abdominal pain that often radiates to the back, nausea and vomiting, fever, rapid pulse, jaundice, and digestive symptoms such as diarrhea or oily stools. Pancreatitis can be caused by many factors, with alcohol consumption and gallstones foremost among them [18,19]. In the years following the introduction of GLP-1 receptor agonists (GLP-1RAs), there were associations reported between these medications and the development of acute pancreatitis as well as concerns raised regarding their potential association with pancreatic cancer. Therapy with GLP-1 agonists contributes to the development of acute pancreatitis by stimulating receptors in Islets of Langerhans that respond to GLP-1 receptors. This stimulation leads to cell hypertrophy, hyperplasia and inflammation, ultimately resulting in acute pancreatitis [20]. In recent years, numerous studies have been conducted with different outcomes [21]. It follows that the patient with obesity or diabetes that are under the treatment with GLP-1 agonists usually have coexisting risk factors that can lead to pancreatitis such as obesity, cholecystitis and other co-medications [8]. Bogdan Augustin Chis, MD, and Daniela Fodor, MD, from Department of Internal Medicine of the University of Medicine in Romania have presented an interesting report of a case linking the use of GLP-1 agonists with pancreatitis. The patient was a 67-year-old women who was admitted to the emergency room because of severe gastric pain radiating to the hypochondrium. The patient also was presenting symptoms such as nausea, vomiting and suffered a worsening of the symptoms over the next 5 days. The patient had

started treatment with GLP-1 agonists 3 months prior to treat type 2 diabetes – no additional medications or alcohol were consumed. Lab reports showed high lipase levels, hyperamylasemia and as well as high glycaemia and elevated CRP. Computer tomography was conducted, giving no changes in gallbladder nor in the biliary duct area. The case of this patient was interpreted as acute pancreatitis. The GLP-1 agonist (lixisenatide) was interrupted and intensive hydration of the patient was initiated, followed by a fast of 48 h. After 24 hours the lipase and amylase levels started to drop as the glucose level started to normalize [22]. Many reports have linked GLP-1 receptor agonists (GLP-1 RAs) to the occurrence of acute pancreatitis (AP), chronic pancreatitis (CP), and pancreatic adenocarcinoma. A cohort study was conducted with a total of 182,428 patients. The study indicated that current users of incretin medications were found to have a 1.5 times higher risk of experiencing one or another form of pancreatitis compared to users of non-insulin anti-diabetic (NIAD) medications. Specifically, among new users of incretin medications, the risk of one or another form of pancreatitis and of acute pancreatitis was elevated by 2.1 and 2.0 times, respectively, compared to NIAD users [23].

On the other hand, there were studies that presented different outcomes. Randomized and non-randomized clinical trials were conducted on patients using GLP-1 agonists or DPP-4 inhibitors in adults with type 2 diabetes compared to patients in a placebo group in an attempt to assess the risk of acute pancreatitis. The results showed that the was no risk correlation between GLP-1 agonists and pancreatitis compared to the placebo. Estimates based on the type of incretin indicated comparable findings (1.05 (0.37 to 2.94) for GLP-1 agonists versus control; 1.06 (0.46 to 2.45) for DPP-4 inhibitors versus control) [24].

As previously stated, the occurrence of acute pancreatitis in patients is rare and not fully proven. It is worth considering such possibility in patients using GLP-1 agonists, especially with coexisting conditions such as excess alcohol consumption, gall stones and hypertriglyceridemia [22,23].

In patients struggling with obesity, pharmacological treatment serves as an addition alongside lifestyle changes for prolonged weight loss effects, aiming for the preservation of weight loss goals. After GLP-1 agonists were listed as a treatment for obesity, questions emerged as to the length of time patients can take these medications and if the weight loss would continue after cessation of medication, or if discontinuing the GLP-1 agonists would induce weight regain [25,26]. A study was conducted, the results of which stated that twelve months following the cessation of weekly subcutaneous semaglutide 2.4 mg and lifestyle changes, participants regained approximately two-thirds of their initial weight loss, experiencing comparable alterations in cardiometabolic parameters. These results underscore the persistent nature of obesity and advocate for continued therapy to sustain advancements in weight management and overall health [27,28]. In another randomized clinical trial in which the participants were adults suffering for obesity or were overweight and who continued treatment with 2.4 mg/per week semaglutide continued to lose weight compared to patients taking a placebo, who gained weight. This indicates that therapy with GLP-1 agonists should be extended by patients even for some time after reaching the target weight. However, great attention should be paid to educating the patient about lifestyle changes, diet, and implementing physical activity to maintain weight and prevent weight regain possibly even exceeding the initial start weight [29,30].

Conclusions

GLP-1 agonists have many side effects, but gastrointestinal effects such as nausea, vomiting and abdominal pain, which may result from gastroparesis, are prominent. Acting through GLP receptors, which are also found in the pancreas, they can lead to hyperplasia and inflammation, resulting in acute pancreatitis. Rapid weight loss achieved with drugs such as semaglutide or liraglutide may lead to fat loss in critical areas of the face, resulting in the neologism "Ozempic face". Despite many positive effects of semaglutide and liraglutide, their increasing popularity worldwide for weight-loss purposes raises concerns. Physicians prescribing these kind of drugs for type 2 diabetes or obesity therapy should inform patients about the range of possible negative side effects as well as the benefits of the drugs.

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