SEMAGLUTIDE: A REVOLUTIONARY DIABETES DRUG, OR A FAD CELEBRITY ENDORSEMENT?

POORVA KASTURE
School of Molecular and Cellular Biology, University of Illinois Urbana-Champaign

ABSTRACT
This comprehensive review explores the social and health effects of semaglutide, a GLP-1 receptor agonist, and evaluates its efficacy as a treatment for Type 2 diabetes. This paper delves into its mechanism of action, detailing its similarities to the glucagon-like peptide-1 (GLP-1) hormone to regulate insulin secretion, slow gastric emptying, and reduce appetite. Additionally, it examines the drug's impact on various physiological systems, including its cardiovascular benefits and potential side effects such as gastrointestinal distress, pancreatitis, and potential long-term risks. Furthermore, this review compares semaglutide to other widely used diabetes medications, such as insulin and metformin, assessing its advantages and limitations in glycemic control and other factors, such as weight loss and frequency of cardiovascular events by analyzing clinical data. Beyond its medical applications, this review investigates semaglutide's rising status as a social drug, particularly in the context of weight loss. The influence of celebrity endorsements and media representation has contributed to a surge in demand for semaglutide as an off-label weight loss solution, affecting public perception and access to the medication. This review aims to explore the societal effects of these endorsements, particularly their impact on body image, healthcare accessibility through the lens of social media and semaglutide's availability for diabetes patients. Additionally, this review evaluates the implications of semaglutide's popularity on healthcare equity, particularly for low-income and uninsured populations. With high costs and limited insurance coverage, semaglutide's accessibility remains a critical issue, potentially exacerbating health disparities and limiting treatment options for those who need it most. The paper will also consider future developments, including emerging alternatives and innovations in diabetes treatment, assessing how they might address these challenges. By synthesising medical research, social commentary, and healthcare policy discussions, this review provides a comprehensive analysis of semaglutide's role in modern medicine and society. It aims to offer insight into the broader implications of its rise as both a diabetes treatment and a social phenomenon, ultimately assessing its potential benefits and ethical concerns in public health.

INTRODUCTION

With the ever changing nature of the healthcare industry, breakthroughs in any field are sure to catch the public and scientific communities' attention. One such breakthrough has been semaglutide, an injectable medication developed to treat type 2 diabetes. While effective at lowering blood sugar levels and promoting weight loss, its fame is thanks to a combination of celebrity influence and social media. Having made its way onto several platforms, its popularity has soared over the past few months. Semaglutide is also known more widely as its brand name, Ozempic (a drug that's FDA approved to treat type 2 diabetes) and Wegovy (a drug that's FDA approved for weight loss); both of which will be used to reference the drug. The treatments have the same active ingredients, except Wegovy has a higher maximum dose of 2.4 mg compared to 2.0 mg of Ozempic (Wegovy®, n.d.). The objective of this project is to unfold the social and health benefits, drawbacks, and grey areas with regards to the recent surge in demand for both medications.

This review aims to separate the fame from science and shed light on the true impact that the drug has had on individuals with type 2 diabetes and the healthcare system. In addition, this review will deeply scrutinize its value as a genuine innovation to improve quality of life in patients with diabetes in comparison to its widespread rumours and misconceptions as a 'miracle' drug amongst the general public.

THE MECHANISMS OF SEMAGLUTIDE

Semaglutide is prescribed as an injector pen of a specific dosage, which patients inject into their lower abdomen, and belongs to a family of drugs known as glucagon-like-peptide (GLP-1) receptor agonists. These drugs mimic a hormone that stimulates the pancreas to release insulin, while suppressing the release of another hormone called glucagon, which in turn helps reduce hunger (Els, 2024). Its structure consists of 31 amino acids, linearly joined through peptide bonds, having a 94% similarity to human GLP-1 (Kalra & Sahay, 2020). It does, however, contain amino acid substitutions at amino acid position 8. Substituting the amino acid alanine to a-methyl amine prevents dipeptidyl peptidase-4 (DPP-4) degeneration, which enhances the uptake of glucose by cells. It also includes a substitution at position 34, replacing lysine with arginine. This helps it bind to albumin; a prominent protein found in blood plasma.

Semaglutide works in 3 main ways: by increasing insulin production, inhibiting the release of glucagon, and slowing gastric emptying—which increases the feeling of satiety (Mahapatra, Karuppasamy, & Sahoo, 2022). In addition, its main mechanisms involve the inhibition of glucagon release and suppression of hepatic gluconeogenesis, a process that forms glucose from various other non-carbohydrate, organic compounds. Overall, this augments insulin production, increasing glucose uptake into cells, and thus lowering blood sugar levels in type 2 diabetics.

Additionally, the interaction of GLP-1 and its receptor, GLP-1R, happens through a mechanism that ultimately increases insulin production. First, GLP-1 binds to GLP-1R, which then stimulates the release of the enzyme adenylyl cyclase, stimulating the production of a messenger (adenosine monophosphate, or cAMP) from ATP. This triggers the release of protein kinase A (PKA), which can close the K+ ion channel, causing the voltage-dependent Ca2+ channel to open (Klec, Ziomek, Pichler, Malli, & Graier, 2019). Further pathways additionally increase the Ca2+ concentration inside the cell. This ion plays a significant role in the Krebs cycle on dehydrogenases, enzymes that stimulate ATP production, which in turn has a positive correlation with the glucose intake of cells (Traaseth, Elfering, Solien, Haynes, & Giulivi, 2004).

Another way that semaglutide works is by inhibiting glucagon. Within type 2 diabetes, elevated glucagon levels result in hyperglycaemia. The drug works with insulin homeostatically to regulate blood glucose levels and is counterregulatory to insulin and catabolic in nature, meaning it breaks down molecules. Glucagon is released by alpha cells in the pancreas, but in type 2 diabetes, these cells are dysfunctional, causing hyperglycaemia in fasted states and after food intake (Rix et al., 2019). The mechanism behind this works similarly to the release of insulin from beta cells, which are cells in the pancreas that make insulin. First, glucose is uptaken by the glucose

transporter 1 in the cell membrane, which goes through glycolysis to ultimately produce ATP. However, since this is reflective of blood glucose levels, lower ATP production closes K+ ion channels, which are ATP-dependent. As a result, this causes depolarisation of the cell, thus opening the Ca2+ channels, which are the main trigger for the release of glucagon into the extracellular space (Zhao et al., 2021).

These mechanisms can thus influence organs. In the liver, fat content, glucose production, and plasma enzymes decrease. As a result, this keeps blood sugar levels down. In the pancreas, insulin secretion increases, therefore increasing the efficiency at which cells take up glucose, therefore decreasing blood glucose levels (Pang, Feng, Ling, & Jin, 2022). Due to slower gastric emptying, the feeling of satiety increases, which can help in the weight loss to decrease complications from type 2 diabetes patients. As a result, less ghrelin (the 'hunger' hormone) is released from the stomach, instead promoting the release of leptin (the 'fullness' hormone) and subsequently decreased appetite.

EVALUATING SEMAGLUTIDE AS A TREATMENT FOR DIABETES

EFFECT ON HbA1C LEVELS

HbA1c levels refer to glycated haemoglobin levels and are the primary measurement to assess blood sugar levels. A reduction in HbA1c levels indicates a better control of blood sugar and is thus important to measure efficacy of semaglutide as a treatment for diabetes.

According to a meta-analysis by Y. Al Hindi and A. Avery, a 14.0 mg dose of oral semaglutide significantly reduced HbA1c levels, the mean difference being a reduction of 1.30%. In another study from the PIONEER phase 3 program, a large-scale study that assessed the efficacy and safety of oral semaglutide, patients with higher baseline HbA1c levels had a higher decrease in mean HbA1c levels (Aroda et al., 2022). The mean percentage difference was 1.7%- 2.6% for those with levels above 9.0%. In some cases, some ethnicities such as Asians had a larger percentage decrease with a 14 mg dose of oral semaglutide, from around -1.5% to 1.8% for the baseline of more than 7% (Buse et al., 2020). In another phase of the PIONEER program, it was found that with flexible dosage, the mean difference in glycated haemoglobin levels was 0.1%, and 52% of patients achieved an HbA1c level below 7% with oral semaglutide. These statistics provide significant evidence for improvement in blood sugar levels, which is important for patients suffering from diabetes as it reduces the risk of diabetes related complications like diabetic retinopathy (vision loss), kidney disease and cardiovascular diseases.

However, do subcutaneous forms of semaglutide have a higher efficacy? In one study, patients who were considered 'pre-diabetic', and had a HbA1c level of 8.0% to 8.1%, with a subcutaneous dose of 14 mg of semaglutide were found to have a reduction of 1.6% at 30 weeks of medication (Meier, 2021). This was superior to the placebo. For people with diabetes, who had a mean initial HbA1c level of 62 mmol/mol, the mean decrease in HbA1c was -12.6 mmol/mol (the naïve group). Those who were 'experienced' with semaglutide had a mean reduction by 5.6 mmol/mol, with each group reaching levels below 54 mmol/mol within 2 years (Vilsbøll, Lindahl, Nielsen, & Tikkanen, 2023).

Another study done by Novo Nordisk, the company that produced Ozempic, found that there was a 77% decrease in Fasting plasma glucose (FPG) levels (44 from 191), along with 62% of people reaching HbA1c levels under less than 7% within 56 weeks (Novo Nordisk, 2020). However, since the study was funded and carried out with the associated institution, it is important to note that it may have been subject to funding bias.

In conclusion, these studies, when compiled together, show an overall efficacy in reducing Hb1Ac levels. Additionally, most statistical t-tests show mean reductions at the 5% significance level to be less than or equal to the critical value, showing a significant improvement in HbA1c and FPG levels from baseline.

WEIGHT LOSS EFFECTS

In a landmark double-blind study, participants on semaglutide dose of 2.4 mg showed a mean weight loss of 14.9% in 68 weeks from their baseline, compared to the control group of 2.9%, which contained 655 individuals over the

age of 18 without diabetes (Wilding et al., 2021).

An additional study showed that the mean weight loss of 5.9% after 3 months, whereas after 6 months 10.9% in patients without diabetes (Ghusn et al., 2022). However, patients with type 2 diabetes lost less weight than those without type 2 diabetes, with a mean of 3.9% of patients with diabetes, and 6% for patients without diabetes.

Further evidence is shown through a randomised clinical trial that took place as part of the STEP 3 trials. This trial was a 68-week phase 3a trial that aimed to examine weight loss effects of semaglutide in overweight or obese patients (Wadden et al., 2021). Overall, it showed a decrease in body weight of 16% for the semaglutide group, and 5.7% for the placebo group, with higher proportions of participants on semaglutide showing at least a 15% decrease in body weight. However, gastrointestinal complaints were more frequent within the semaglutide test group. 82% of participants submitted complaints, whereas this number was 19.6% lower in the placebo group. It is also important to note that participants had been placed on lower energy diets, along with intense behavioural therapy of around 30 sessions over the 68-week period for the trial.

However, it is important to note that most of the studies analysed above have used BMI as their main indicator of weight change. Even though it is an extremely common and useful quantitative value to use, it still may not be a fully valid indicator of improved health outcomes due to its inaccuracies in measuring actual fat loss, as it only takes mass into account. Therefore, valid conclusions about reduced relative risk of diabetes may not be able to be drawn. However, the HbA1c levels, along with accurate indicators such as waist-to-hip ratio throughout the mentioned studies may show that semaglutide is a valid drug to be used in supervised weight loss.

CARDIAC IMPLICATIONS

One study showed a rate of non-fatal stroke in 1.6% of patients who received semaglutide, compared to 2.7% of patients who received a placebo (Marso et al., 2016). Additionally, the rates of non-fatal heart attacks in the semaglutide versus placebo group were 2.9% and 3.9% respectively. However, 83% of the patients were said to have already established cardiovascular disease, chronic kidney disease or both. Therefore, it is important to note that the number of cardiac events that occurred in this trial may have been higher than that of a trial that selected patients who only had type 2 diabetes and no other cardiac conditions. Additionally, this study was funded by Novo Nordisk, the company that produces a commercial injection of semaglutide, meaning that the study may have been subject to funding bias.

In the SUSTAIN trials, the probability of a cardiac outcome was calculated using the Ghosh-Lin estimator, which is a statistical method used to analyze recurrent events. In this case, the expected number of hospitalisations due to heart failure over a time (Rogers, Yaroshinsky, Pocock, Stokar, & Pogoda, 2016). It was found that the risk of a cardiac event was significantly lower within the semaglutide group than within the placebo, with a hazard ratio of 0.74. This means that there is a 26% lower chance of the semaglutide group experiencing a cardiac event. The graph from the study is attached on the left. It shows the relationship between time and the probability of another event, with a clear correlation of lower probability of a cardiac event with a placebo compared to semaglutide (Kolkailah, Lingvay, Dobrecky-Mery, et al., 2023).

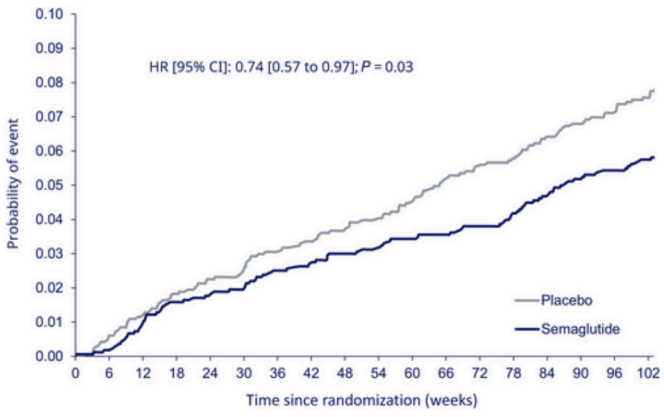

Figure 1: A Kaplan-Meier curve showing the cumulative probability of a cardiovascular event over 104 weeks in patients receiving semaglutide versus placebo (Marso et al., 2016).

Additionally, semaglutide's mechanisms involve improving lipid profiles, as well as reducing

blood pressure. For instance, semaglutide increases levels of high-density lipoprotein (HDL) while decreasing levels of low-density lipoprotein (LDL). This suggests that semaglutide may be protective against cardiac events and atherosclerosis.

Overall, throughout all the implications of semaglutide, it can be seen as an effective treatment for type 2 diabetes, with several clinical trials showing promise in not only lowering blood sugar levels but also decreasing risks of cardiac events and obesity. These factors may help patients improve quality of life and potentially achieve remission.

EFFICACY OF SEMAGLUTIDE COMPARED TO OTHER MEDICATIONS

In the following section, several common diabetes medications will be addressed, many of which belong to a different class of drugs as compared to semaglutide. By assessing medications in different classes, it will allow for different mechanisms to be compared and assess their advantages and disadvantages for patients with diabetes. Their mechanisms, efficacy, and benefits and limitations compared to semaglutide will be discussed.

METFORMIN

Metformin is usually the first line of treatment for type 2 diabetes, and belongs to a class of drugs called biguanides, which work by reducing liver glucose production and decreasing intestinal uptake of glucose without affecting the amount of insulin released from the pancreas (DrugBank, n.d.). Its mechanism is different to that of semaglutide, as it does not increase insulin secretion to control blood sugar levels. Additionally, metformin has shown evidence to be one of the only medications suitable for children from the ages of 10-16 for the treatment of type 2 diabetes and prevent pre-diabetes in children from progressing into type 2 diabetes. This is because of its safety and lower risk for diabetic ketoacidosis, which is known to cause several deaths in emerging and developing countries (Poovazhagi, 2014; Soliman, De Sanctis, Alaaraj, & Hamed, 2020). Metformin has also been shown to improve insulin sensitivity and induce ovulation in people with polycystic ovarian syndrome (PCOS): one study showed an ovulation rate of 100% with metformin as compared to 37% with a placebo (Practice Committee of the American Society for Reproductive Medicine, 2017). With rates of obesity and other risk factors for type 2 diabetes increasing with time, this may make metformin a valuable drug for treatment of insulin sensitivity in women and children. However, semaglutide was only recently approved by the US food and drug administration for use in treatment of obesity in teenagers but has not been approved for paediatric type 2 diabetes, instead being used only in adults (Novo Nordisk USA, 2022). However, weight management with semaglutide may decrease risk of teens developing type 2 diabetes later as adults.

As mentioned before, metformin has also shown incidences of lactic acidosis. Although the prevalence of lactic acidosis with metformin is low, there is still some concern with its complications. This may be due to its mechanism blocking an enzyme called pyruvate carboxylase, which acts during the first step of gluconeogenesis, a metabolic process by which glucose is produced in the liver (Blough, Moreland, & Mora, 2015). This may lead to a build-up of lactic acid in the bloodstream because of inhibited mitochondrial respiration in the liver. However, the instances of this have been rare, and can be prevented through careful prescription (DeFronzo, Fleming, Chen, & Bicsak, 2016). For instance, if a patient has liver or kidney problems, they may be prescribed a different medication instead.

Overall, because of its safety for children, metformin may be a superior drug that is applicable to a wider population than just adults with diabetes. However, due to lactic acidosis and liver/kidney problems, this drug may not be as suitable for certain conditions.

LIRAGLUTIDE

Liraglutide belongs to the same class of drugs as semaglutide, acting as a GLP-1 receptor agonist and having similar effects on the body to control glucose levels like semaglutide.

To examine its efficacy against semaglutide, one study showed a decrease in weight of 15.8% for the semaglutide group compared to a decrease of 6.4% in the liraglutide group. However, the study was done on adults without type 2 diabetes (Rubino et al., 2022). Looking at

its efficacy for reducing blood sugar levels, one study found a greater net decrease of Hba1c levels with doses of semaglutide up to 0.3 mg/day; however, greater gastrointestinal complaints were observed with semaglutide than liraglutide (Lingvay et al., 2018).

Additionally, another study showed that semaglutide had a decrease in HbA1c levels of 1.64% at a dosage of 1 mg, compared to 1.47% of Liraglutide at a dosage of 1.2 mg. In addition to being more effective at lowering HbA1c levels, semaglutide was also associated with greater weight loss than liraglutide, resulting in an average weight loss of 6.8-9.4 kg over 26 weeks, while people who took liraglutide lost an average of 3.8- 5.8 kg (Trujillo, Nuffer, & Smith, 2021).

Another study found that semaglutide was 0.5% more effective at reducing HbA1c levels than liraglutide, both giving a reduction of 1.8% and 1.3%, respectively. Additionally, semaglutide also showed a 3.5% more mean reduction in body weight from baseline than liraglutide (Nauck, Quast, Wefers, & Meier, 2021). However, it should be noted that valid results may not be drawn from just a few studies; therefore, it would be important to analyse a variety of sources to determine efficacy of both drugs. Examining the side effects of both drugs, both seem to have similar side effects, such as gastrointestinal complaints, chills, joint pain, and loss of appetite (Mayo Clinic, 2023).

Overall, even though they share mechanisms, semaglutide may prove slightly more beneficial for patients who are looking to lose weight and prevent future gastrointestinal complaints more associated with Liraglutide use (Malkin, Russel-Szymczyk, Liidemann, Volke, & Hunt, 2019).

INSULIN

Insulin is a hormone, usually homeostatically released by the body after eating to bring down blood sugar levels and absorb glucose into cells. However, in the case of type 2 diabetes, cells stop or become less responsive to insulin. In other cases, the pancreas may produce non-functional insulin. Eventually, insulin therapy may need to be started to prevent microvascular complications, like damage to nerves, leading to loss of feeling in the feet (Mayo Clinic Staff, 2023).

However, insulin and semaglutide both have different mechanisms of action. The main difference is that insulin therapy introduces synthetic insulin, while semaglutide stimulates the body's own production of insulin.

Insulin works by binding to the alpha subunit of the insulin receptor, which is a glycoprotein on the cell surface. This binding causes a conformational change, which activates the beta subunits. These activated subunits use ATP to add phosphate groups to themselves. This triggers a signalling pathway that regulates metabolism, including the storage of glucose as glycogen (UpToDate editors, 2023). To examine efficacy of insulin as compared to semaglutide, a study was done which showed insulin to be less effective at reducing HbA1c levels compared to semaglutide, showing a decrease of 1.64% for 1 mg, and 1.38% for 0.5 mg of semaglutide, but a decrease of 0.83% for insulin at both of these tested doses. In addition, insulin resulted in higher instances of hypoglycaemia than semaglutide (Aroda et al., 2017). Another study showed semaglutide was associated with greater weight loss compared to basal-bolus insulin, resulting in a range of 6.8-9.4 kg weight loss, in addition to a 0.36% decrease in HbA1c levels in patients who had a combined therapy of both insulin and semaglutide (Lingvay et al., 2023).

In other instances, semaglutide was added to regimens of patients already receiving insulin therapy, and only the effects of semaglutide were measured (Rodbard et al., 2018; Wright & Aroda, 2020). Therefore, these studies could not be used to evaluate efficacy of semaglutide against insulin therapy.

In previous trials where researchers conducted a meta-analysis of current knowledge about GLP-1 receptor agonists, semaglutide showed greater weight loss than insulin therapy, which led to a 1.15 kg weight gain with insulin, whereas a 5.17 kg weight loss was noted for the same dosage of insulin (Nauck, Quast, Wefers, & Meier, 2021). Insulin therapy may cause weight gain due to excess glucose entering cells than needed, resulting in glucose being stored as fat.

Another factor to consider is cost and availability. Insulin is widely available in

healthcare and has been in use for treatment of type 2 diabetes for several years. However, semaglutide is a very recent drug implemented into the regimens of patients. It is not as widely available as insulin around the world, being abundant in mainly western countries. As for cost, both insulin and semaglutide can be extremely expensive. However, it is much more likely that insulin therapy, not semaglutide, is covered by insurance, making it a much more cost-effective solution for patients to implement. In one study, semaglutide was found to have an average direct cost of £800 higher (around $1080) than insulin, part of which was offset due to lower diabetes related complications (Evans et al., 2023).

In conclusion, semaglutide may be a more effective treatment for type 2 diabetes compared to insulin. However, it may not suit patients who live in eastern countries or lower income patients due to semaglutide's high costs.

SITAGLIPTIN

Sitagliptin belongs to a class of medications known as DPP-4 inhibitors. It works by slowing down inactivation of incretins, a group of hormones that work to decrease blood glucose levels. This mechanism increases insulin secretion and decreases glucagon secretion, which is dependent on glucose homeostasis. As a result, the drug causes decreased HbA1c levels (DrugBank, n.d.).

Sitagliptin was found to be less effective at weight loss than semaglutide, showing a 6.4% decrease compared to a 15.8% in semaglutide at the same dosage. However, this study was conducted on patients without diabetes (Rubino et al., 2022). In another study, semaglutide was also found to have a greater reduction in HbA1c levels, with a treatment difference of 0.17% (Alsugair et al., 2021).

Sitagliptin and other DPP4 inhibitors are associated with a few cases of bullous pemphigoid (BP): a skin disease associated with blisters and eczema-like lesions. However, the frequency of DPP4 associated with BP was found to be around 0.00859%, making it extremely rare (Alsugair et al., 2021). On the other hand, semaglutide is associated with milder side effects, such as nausea, vomiting and other gastrointestinal complaints.

As for cost, a Swedish study found that semaglutide was found to be far more expensive than sitagliptin, costing around $22,300 per quality adjusted life year (QALY) compared to $11,200 per QALY for sitagliptin (Eliasson et al., 2022). QALY is the academic standard for measuring how well all distinct kinds of medical treatments may improve quality of lives (ICER, 2024). These prices also do not take insurance into account. It was concluded, however, that semaglutide was more cost efficient, as it was a better value for the money. This was concluded by a base-case analysis, and the robustness was evaluated with deterministic and probabilistic sensitivity analysis (Eliasson et al., 2022). Again, it is also important to note that these costs may not be representative of the global costs of sitagliptin. For instance, Swedish prices of sitagliptin or semaglutide may be cheaper than the rest of the world per year. This is significant, as Sweden is known as one of the most expensive countries in Europe.

EMPAGLIFLOZIN

Empagliflozin belongs to a class of medication known as SGLT-2 inhibitors. It works by reducing the re-uptake of glucose by the kidney tubules and increasing urinary excretion of glucose through the urine. Additionally, it also reduces sodium load due to its diuretic properties (meaning that it helps increase production of urine) (Sizar, Podder, & Talati, 2023).

Semaglutide provided a larger reduction in HbA1c levels, with levels being reduced by 1.3% for semaglutide, but 0.9% for empagliflozin for the same oral dosage of 14 mg, with the study being conducted over 52 weeks as a randomized clinical trial. Semaglutide also proved superior in terms of weight loss, with patients losing 0.9 kg more with semaglutide (Rodbard et al., 2019). Additionally, another meta-analysis showed that semaglutide was superior in reducing both weight and HbA1c levels, with patients losing an average of 1.65 kg more on semaglutide and reducing A1c levels by 0.61% more (Lingvay et al., 2020). It should however be noted that in both of these studies, patients were also on metformin monotherapy, which may have reduced change in weight and

HbA1c levels. Furthermore, empagliflozin has been associated with an extended lifetime, with the estimated life expectancy at patients aged 45 years was 32.1 with empagliflozin, but only 27.6 years with placebo. With confidence intervals considered, it was estimated that life expectancy would be increased by 1-5 years with empagliflozin for patients with established heart disease (Bhatt et al., 2018). As for semaglutide, a mean life span increase of 1.7 years without any cardiovascular disease was estimated, meaning that increase in lifespans may overlap for both medications – therefore, both drugs are correlated with an extended lifetime in patients.

To consider cost: semaglutide was shown to cost an average of $1100 per month compared to empagliflozin, which was shown to cost around $635 per month, making it a more affordable option than semaglutide (Vuong, 2023; Drugs.com, n.d.).

It is also important to note that instances of urinary tract infections and yeast infections have been linked to empagliflozin, with average incidences of 4.2% for 10 mg doses of the medication. Any urinary tract or yeast infections were observed 4% more often in women than men (Unnikrishnan, Kalra, Purandare, & Vasnawala, 2018).

In conclusion, semaglutide was shown to be more effective at reducing blood sugar levels and weight than empagliflozin. However, due to the association with urinary tract or yeast infections, the medication may not be suitable for patients with a history of any genital infections. Again, when prescribing medications, physicians may also need to take the financial capability of a patient into account. Therefore, semaglutide may be unsuitable for lower income patients, especially without insurance coverage.

SOCIAL EFFECTS OF SEMAGLUTIDE: AN OUTLINE

Semaglutide is more popularly known by its brand names, Ozempic and Wegovy, both developed by the Swedish Novo Nordisk. However, given its benefits in terms of weight loss, Ozempic has especially been the centre of several discussions on social media platforms, with several celebrities also sharing their experiences online—some denying their claims of using the drug for weight loss purposes, and others voicing their opinions on the benefits and dangers of the drug.

Both Wegovy and Ozempic have been approved by the US FDA, but for different purposes: Ozempic as a treatment to lower glycated haemoglobin levels, and Wegovy as a weight loss drug—essentially a higher dosage of semaglutide. This section of the article will explore the social effects that semaglutide has had on the medical, celebrity and civilian industries.

CELEBRITY ENDORSEMENT AND PUBLIC PERCEPTION

Ozempic has made a significant impact on social media platforms, with patient testimonials, advertisements, and even debates among doctors about the drug's benefits and risks. However, what stands out the most are the celebrity rumors that circulate online. For example, Elon Musk confirmed using Ozempic in a 2022 reply on X (formerly Twitter) while Kim Kardashian has faced ongoing speculation about using the drug to fit into a dress for the annual Met Gala—a high-profile fundraising event celebrating fashion. The SKIMS founder has repeatedly denied these claims (Head, n.d.). However, several medical professionals have taken to social media sites to help stop the spread of misinformation about the 'miracle' drug, many addressing that the drug could be harmful if put into the wrong hands. For instance, Dr. Mikhail Varshavski, a family medicine physician, says that many people are using Ozempic for off-brand weight loss purposes and not in the titration method (slowly increasing the dose over time) as recommended, which could worsen side effects and often has the opposite intended effect. Additionally, he touched on the drug not being the 'miracle' drug the public expected, with its unsupervised misuse increasing side effects, and often having extremely taxing effects on one's mental health (Varshavski, 2023). In addition, Abbey Sharp, a registered dietitian, has also advised that "these weight loss drugs are not magic, and they still require a calorie deficit to work," in addition to claiming that "medicine is all about risk and benefit," suggesting that individuals should carefully consider the risk-benefit analysis to start taking

Ozempic (Abbey's Kitchen, n.d.). Even though these professionals, and many others, have helped combat misinformation and misuse, celebrity endorsement has painted a picture of the drug being somewhat of a quick fix. Sharp mentions that "this is not to help you fit into your wedding dress. This is nutrition medical therapy for a chronic disease intended to be utilized for life."

On the other hand, others are sharing their success stories all over media platforms. One woman highlights the positive impact that Ozempic had on her, quoting that "hikes that were punishing a few years ago felt easy this summer," and that she "weighed less than she did in high school." However, nothing about side effects was mentioned in this story (Marcus, 2023). Another review also mentioned mild, commonly reported side effects that cleared up within 2 weeks, quoting "the drug feels too good to be true" (Zell, 2021). These reviews are just a few examples of the hundreds of thousands of reviews circling social media sites all over the world. It is important to note that many of these reviews have been extremely contrasting, with some experiencing debilitating nausea and inability to eat at all, and others having the "best feeling of their lives." This reveals that the reviews left on online sites may be skewed, or that semaglutide truly has varying effects from person to person. Semaglutide has clearly reached far and wide, contributing to a tapestry of experiences and reviews that continue to influence public perception.

IMPACT ON DIABETICS AND THE UNINSURED

With a surging demand for the drug, Novo Nordisk saw an increase of 26% in their annual sales from 2021, making over $25 billion in net sales in 2022 (Novo Nordisk, 2022). However, the increase in sales was so large that diabetics began to suffer a shortage of the medication they desperately needed to survive. This may have increased their risk of heart diseases and diabetic ketoacidosis. Another problem this caused was differential pricing at the international level, with the United States having much higher prices of Ozempic per pen than Denmark ($934 in the US, versus $770 in Denmark) (Novo Nordisk, 2022; Apoteket.dk, n.d.). With the United States having one of the highest global rates of obesity and diabetes, this differential pricing has made affording the drug extremely difficult for the uninsured. The effect of the shortage on diabetics was clearly seen all over the world, with the Australian government advising doctors to "continue to consider alternatives to semaglutide until supply is expected to stabilise after 31 December 2023" (Therapeutic Goods Administration [TGA], 2023). The US FDA has also placed both Ozempic and Wegovy on its shortage database, only adding to the complexity of the issue, and leaving diabetics and the uninsured in uncertainty about their health outcomes (FDA Drug Shortages, n.d.).

Additionally, this shortage has left many questioning whether this is a symptom of inequality, laying bare already existing disparities in the healthcare system. For instance, Black and Hispanic patients in the USA were found to historically have poorer health outcomes than white patients (24.9% of the Black population was found to be in poor or fair health, as compared to 6.3% of the white population) (Mahajan et al., 2021). A larger proportion of the Black population that used semaglutide faced the most barriers in affording its injections, with the proportion of Black adults not covered under insurance being around 16.4% compared to 8.7% for white eligible adults (Lu, Liu, & Krumholz, 2022). This highlights the shocking discrepancy between socio-economic factors and how they intertwine with access to certain medications.

POTENTIAL FUTURE DEVELOPMENTS AND ALTERNATIVES

Due to the semaglutide shortage, the general population has started to seek alternatives that have similar effects and are more widely available to help speed up their weight loss journey. In this section, we will cover newer medications and future alternatives for the treatment of type 2 diabetes.

In recent months, a new drug seems to have taken over the diabetes market: Mounjaro. It contains the active ingredient tirzepatide, a glucose-dependent GIP/GLP-1 receptor co-agonist. This means it acts as an incretin hormone, triggering the same pathway as semaglutide. Tirzepatide has been shown to improve insulin sensitivity and delay gastric emptying, both of which contribute to weight loss, much like semaglutide (DrugBank, n.d.). Tirzepatide is different from semaglutide because it acts as a dual receptor agonist—making it more effective than semaglutide in many cases, as it targets the gastric inhibitory polypeptide (or

GIP), which improves insulin secretion, enhances fat metabolism, and helps regulate appetite as well as GLP-1. For instance, tirzepatide proved superior to semaglutide, decreasing HbA1c levels by 1.86 percentage points than semaglutide at the 5 mg dose (Juan et al., 2021). Additionally, it was shown to decrease weight by about 17% of the mean body weight, compared to 12.4% with semaglutide. It was also shown to be a cheaper alternative, with the estimated cost being around $860 lower than semaglutide per 1% of weight lost (Azuri et al., 2023). This reduction in cost and higher efficacy may be what has caused "Ozempic to take a back seat," according to Dr. Seshadri, an internal medicine physician practicing in Abu Dhabi.

In addition, there are several future treatments to diabetes that have yet to be fully put into use. For instance, modifying gut flora to prevent diabetic complications such as diabetic nephropathy. It has been shown that diabetic patients often have gut dysbiosis: an imbalance in the bacteria that reside in the gut of humans. This problem can potentially lead to more insulin resistance, chronic inflammation, and obesity: problems that all contribute to the development of type 2 diabetes. Additionally, the composition of these bacteria has been shown to be different in patients of type 2 diabetes, implying that they may have a role to play in the pathophysiology of type 2 diabetes (Zheng, Bao, Dongsheng, & Chunsheng, 2022). One study showed that a microbiota transplant from healthy lean donors significantly reduced their insulin resistance, and that this was dependent on higher diversity of gut flora than baseline (Kootte et al., 2017). Overall, this evidence shows promise in treating patients' insulin sensitivity, and ultimately, type 2 diabetes.

Another promising treatment is stem cell transplants of beta cells. These stem cells can come from a variety of sources, including pluripotent, multipotent, and mesenchymal stem cells. The first two types of cells can be sourced from leftover embryos from in-vitro fertilisation (IVF) or be programmed from adult cells. This is particularly useful, as it can create cells specific to the patient and reduce chances of rejection (Takahashi & Yamanaka, 2006). One animal study showed reversal of diabetes in mice within 40 days with the use of embryonic stem cells, proving more effective than previously used multipotent stem cells sourced from the innermost layer of the gut (Rezania et al., 2014). This could be because of the insulin-producing beta cells being regenerated in mice, allowing for improved blood sugar control.

Furthermore, a contact lens that can sense blood glucose level has been in development. This revolutionary method is not the first wearable technology, though, as automated insulin pumps are widely used for monitoring. However, with it being so portable, minimally invasive, and a viable option, it could have massive impacts and potential in the world of diabetes treatment (Kim et al., 2022). It works through sensing glucose levels in tears through fluorescent glucose sensors (Mohamed et al., 2022). For instance, changes in glucose levels would turn the lens from pink to blue. This evolutionary device may provide a more discreet and continuous monitoring solution for patients to consider in their diabetes treatment.

CONCLUSION

In conclusion, semaglutide has proven itself to be a multifaceted drug with significant implications in both clinical and social contexts. Its mechanism as a GLP-1 receptor agonist allows it to effectively reduce HbA1c levels, promote weight loss, and improve cardiovascular outcomes in patients with type 2 diabetes. When compared to other medications across different classes—including metformin, insulin, liraglutide, sitagliptin, and empagliflozin—semaglutide generally seems to offer superior glycemic control and weight-related benefits, although its cost and limited paediatric application present important limitations.

Socially, the drug's rise in popularity, fueled by celebrity endorsements and media exposure, has sparked widespread off-label use, shifting public belief and complicating access for diabetic patients due to increased demand and global shortages. These issues have also magnified pre-existing disparities in healthcare access, especially among low-income and uninsured populations. Finally, while newer alternatives like tirzepatide and future innovations such as microbiome therapy and stem cell research show promise, semaglutide remains a powerful, though controversial, tool

in modern diabetes care. Ultimately, a balanced view—grounded in evidence, ethical considerations, and equitable access—is needed to navigate semaglutide's double role as a medical treatment and social phenomenon.

REFERENCES

1. Abbey's Kitchen. (n.d.). The Truth About Ozempic: A Dietitian's Perspective.

2. Administration, T. G. (2025, April 9). About the Ozempic (semaglutide) shortage. Therapeutic Goods Administration (TGA).

3. Alsugair HA, Alshugair IF, Alharbi TJ, Bin Rsheed AM, Tourkmani AM, Al-Madani W. Weekly Semaglutide vs. Liraglutide Efficacy Profile: A Network Meta-Analysis. Healthcare (Basel). 2021 Aug 30;9(9):1125.

4. Apoteket.dk.Ozempic®.

5. Aroda VR, Bain SC, Cariou B, Piletič M, Rose L, Axelsen M, Rowe E, DeVries JH. Efficacy and safety of once-weekly semaglutide versus once-daily insulin glargine as add-on to metformin (with or without sulfonylureas) in insulin-naive patients with type 2 diabetes (SUSTAIN 4): a randomised, open-label, parallel-group, multicentre, multinational, phase 3a trial. Lancet Diabetes Endocrinol. 2017 May.

6. Aroda VR, Bauer R, Christiansen E, Haluzík M, Kallenbach K, Montanya E, Rosenstock J, Meier JJ. Efficacy and safety of oral semaglutide by subgroups of patient characteristics in the PIONEER phase 3 programme. Diabetes Obes Metab. 2022 Jul.

7. Azuri J, Hammerman A, Aboalhasan E, Sluckis B, Arbel R. Tirzepatide versus semaglutide for weight loss in patients with type 2 diabetes mellitus: A value for money analysis. Diabetes Obes Metab. 2023 Apr.

8. Bhatt, D. L., Steg, P. G., Emdin, C. A., James, S. K., Živkovic, G., Chin, K. H., ... & Desai, A. K. (2018). Long-term benefit of empagliflozin on life expectancy in patients with type 2 diabetes mellitus and established cardiovascular disease.

9. Blough B, Moreland A, Mora A Jr. Metformin-induced lactic acidosis with emphasis on the anion gap. Proc (Bayl Univ Med Cent). 2015 Jan 28.

10. Buse JB, Bode BW, Mertens A, et al. Long-term efficacy and safety of oral semaglutide and the effect of switching from sitagliptin to oral semaglutide in patients with type 2 diabetes: a 52- week, randomized, open-label extension of the PIONEER 7 trial.

11. DeFronzo R, Fleming GA, Chen K, Bicsak TA. Metformin-associated lactic acidosis: Current perspectives on causes and risk. Metabolism. 2016 Feb.

12. Drugbank, Tirzepatide.

13. DrugBank. (n.d.). Metformin.

14. DrugBank. Sitagliptin.

15. Drugs.com. Jardiance price guide.

16. E Mohamed, M Rosalia, A Fahad, S Ahmed E., A Israr, B Haider "Wearable Smart Contact Lenses for Continual Glucose Monitoring: A Review" Frontiers in Medicine Volume 9 2022.

17. Eliasson B, Ericsson Å, Fridhammar A, Nilsson A, Persson S, Chubb B. Long-Term Cost Effectiveness of Oral Semaglutide Versus Empagliflozin and Sitagliptin for the Treatment of Type 2 Diabetes in the Swedish Setting. Pharmacoecon Open. 2022 May.

18. Eugene E. Wright Jr & Vanita R. Aroda (2020) Clinical review of the efficacy and safety of oral semaglutide in patients with type 2 diabetes considered for injectable GLP-1 receptor agonist therapy or currently on insulin therapy, Postgraduate Medicine.

19. Evans M, Chubb B, Malkin SJP, Berry S, Lawson J, Hunt B. Once-weekly semaglutide versus insulin aspart for the treatment of type 2 diabetes in the UK: A long-term cost-effectiveness analysis based on SUSTAIN 11. Diabetes Obes Metab. 2023 Feb;25(2):491-500.

20. FDA approves once-weekly Wegovy injection for the treatment of obesity in teens aged 12 years and older. Novo Nordisk USA. December 23, 2022.

21. FDA drug shortages (no date) FDA Drug Shortages.

22. Ghusn W, De la Rosa A, Sacoto D, Cifuentes L, Campos A, Feris F, Hurtado MD, Acosta A. Weight Loss Outcomes Associated With Semaglutide Treatment for Patients With Overweight or Obesity. JAMA Netw Open. 2022 Sep 1.

23. Head. A, 'A diabetes drug is going viral for its supposed weight loss benefits—but there's a seriously dark problem here'.

24. Helena W Rodbard et al, Semaglutide Added to Basal Insulin in Type 2 Diabetes (SUSTAIN 5): A Randomized, Controlled Trial, The Journal of Clinical Endocrinology & Metabolism, Volume 103, Issue 6, June 2018, Pages 2291–2301.

25. Helena W. Rodbard, Julio Rosenstock, Luis H. Canani, Chaicharn Deerochanawong, Janusz Gumprecht, Søren Østergaard Lindberg, Ildiko Lingvay, Anette Luther Søndergaard, Marianne Bach Treppendahl, Eduard Montanya, PIONEER 2 Investigators; Oral Semaglutide Versus Empagliflozin in Patients With Type 2 Diabetes Uncontrolled on Metformin: The PIONEER 2 Trial. Diabetes Care 1 December 2019.

26. https://twitter.com/elonmusk/status/1576367983051489281.

27. https://www.marieclaire.co.uk/life/health-fitness/ozempic-for-weight-loss.

28. Ildiko Lingvay and others, Efficacy of Once-Weekly Semaglutide vs Empagliflozin Added to Metformin in Type 2 Diabetes: Patient-Level Meta-analysis, The Journal of Clinical Endocrinology & Metabolism, Volume 105, Issue 12, December 2020, Pages e4593–e4604.

29. Ildiko Lingvay, Cyrus V. Desouza, Katarina S. Lalic, Ludger Rose, Thomas Hansen, Jeppe Zacho, Thomas R. Pieber; A 26-Week Randomized Controlled Trial of Semaglutide Once Daily Versus Liraglutide and Placebo in Patients With Type 2 Diabetes Suboptimally Controlled on Diet and Exercise With or Without Metformin. Diabetes Care 1 September 2018.

30. Juan P. and Davies, Melanie J. and Rosenstock, Julio and Perez Manghi, Federico C. Fernandez Lando Laura and Bergman, Brandon K. and Liu, Bing and Cui, Xuewei and Brown, Katelyn.

31. Juan Pang, Jia Nuo Feng, Wenhua Ling, Tianru Jin, The anti-inflammatory feature of glucagon-like peptide-1 and its based diabetes drugs—Therapeutic potential exploration in lung injury, Acta Pharmaceutica Sinica B, Volume 12, Issue 11, 2022.

32. K Poorva, Interview with Dr Sunil Sheshadri – internal medicine physician, date of interview: 27/08/2023

33. Kalra, Sanjay & Sahay, Rakesh. (2020). A Review on Semaglutide: An Oral Glucagon-Like Peptide 1 Receptor Agonist in Management of Type 2 Diabetes Mellitus. Diabetes Therapy.

34. Khang T. Vuong (2023, March 8). Semaglutide drugs Rybelsus, Ozempic, Wegovy cost with & without insurance?.

35. Kim SK, Lee GH, Jeon C, Han HH, Kim SJ, Mok JW, Joo CK, Shin S, Sim JY, Myung D, Bao Z, Hahn SK. Bimetallic Nanocatalysts Immobilized in Nanoporous Hydrogels for Long-Term Robust Continuous Glucose Monitoring of Smart Contact Lens. AdvMater. 2022 May.

36. Klec C, Ziomek G, Pichler M, Malli R, Graier WF. Calcium Signaling in ß-cell Physiology and Pathology: A Revisit. Int J Mol Sci. 2019 Dec.

37. Kolkailah, AA, Lingvay, I, Dobrecky-Mery, I, et al. Effects of once-weekly subcutaneous semaglutide on coronary artery disease outcomes in patients with type 2 diabetes with or at high risk for cardiovascular disease: Insights from the SUSTAIN-6 trial. Diabetes Obes Metab. 2023.

38. Kootte RS, Levin E, Salojärvi J, Smits LP, Hartstra AV, Udayappan SD, Hermes G, Bouter KE, Koopen AM, Holst JJ, Knop FK, Blaak EE, Zhao J, Smidt H, Harms AC, Hankemeijer T, Bergman JJGHM, Romijn HA, Schaap FG, Olde Damink SWM, Ackermans MT, Dallinga-Thie GM, Zoetendal E, de Vos WM, Serlie MJ, Stroes ESG, Groen AK, Nieuwdorp M. Improvement of Insulin Sensitivity after Lean Donor Feces in Metabolic Syndrome Is Driven by Baseline Intestinal Microbiota Composition. Cell Metab.

39. Lingvay I, Catarig AM, Lawson J, Chubb B, Gorst-Rasmussen A, Evans LM. An Indirect Comparison of Basal Insulin Plus Once-Weekly Semaglutide and Fully Optimised Basal-Bolus Insulin in Type 2 Diabetes. Diabetes Ther. 2023 Jan.

40. Lu, Y., Liu, Y., & Krumholz, H. M. (2022). Racial and Ethnic Disparities in Financial Barriers Among Overweight and Obese Adults Eligible for Semaglutide in the United States. Journal of the American Heart Association.

41. Mahajan S, Caraballo C, Lu Y, Valero-Elizondo J, Massey D, Annapureddy AR, Roy B, Riley C, Murugiah K, Onuma O, Nunez-Smith M, Forman HP, Nasir K, Herrin J, Krumholz HM. Trends in Differences in Health Status and Health Care Access and Affordability by Race and Ethnicity in the United States, 1999-2018. JAMA. 2021 Aug 17.

42. Mahapatra MK, Karuppasamy M, Sahoo BM. Semaglutide, a glucagon like peptide-1 receptor agonist with cardiovascular benefits for management of type 2 diabetes. Rev Endocr Metab Disord. 2022 Jun.

43. Marcus, R. (2023, June 6). Ozempic and Weight Loss. The Washington Post.

44. Marso SP, Bain SC, Consoli A, Eliaschewitz FG, Jódar E, Leiter LA, Lingvay I, Rosenstock J, Seufert J, Warren ML, Woo V, Hansen O, Holst AG, Pettersson J, Vilsbøll T; SUSTAIN-6 Investigators. Semaglutide and Cardiovascular Outcomes in Patients with Type 2 Diabetes. N Engl J Med. 2016 Nov 10.

45. Mayo Clinic Staff. (2023, February 1). Diabetes Treatment: In Depth.

46. Mayo Clinic. (2023, February 1). Liraglutide (Subcutaneous Route) Side Effects.

47. Meier JJ. Efficacy of Semaglutide in a Subcutaneous and an Oral Formulation. Front Endocrinol (Lausanne). 2021 Jun 25.

48. N Traaseth, S Elfering, J Solien, V Haynes, C Giulivi, Role of calcium signaling in the activation of mitochondrial nitric oxide synthase and citric acid cycle, Biochimica et Biophysica Acta (BBA) - Bioenergetics, Volume 1658, Issues 1–2,2004, Pages 64-71, ISSN 0005-2728.

49. Nauck MA, Quast DR, Wefers J, Meier JJ. GLP-1 receptor agonists in the treatment of type 2 diabetes - state-of-the-art. Mol Metab. 2021 Apr.

50. Novo Nordisk, December 2022 [annual report 2022].

51. Novo Nordisk, "Ozempic Australian product information November 2020".

52. Novo Nordisk. Ozempic® (semaglutide) injection 0.5 mg, 1 mg, 2 mg List Price & Insurance Coverage Explained | NovoCare®.

53. Pharmacoeconomic Review Report: Semaglutide (Ozempic): (Novo Nordisk Canada Inc.): Indication: For the treatment of adults patients with type 2 diabetes mellitus to improve glycemic control, in combination with metformin (second-line treatment), and in combination with metformin and sulfonylurea (third-line treatment) [Internet]. Ottawa (ON): Canadian Agency for Drugs and Technologies in Health; 2019 Jun.

54. Practice Committee of the American Society for Reproductive Medicine. Practice Committee of the American Society for Reproductive Medicine. Role of metformin for ovulation induction in infertile patients with polycystic ovary syndrome (PCOS): a guideline. Fertil Steril. 2017 Sep.

55. Prasad F, De R, Korann V, et al. Semaglutide for the treatment of antipsychotic-associated weight gain in patients not responding to metformin – a case series. Therapeutic Advances in Psychopharmacology. 2023.

56. Rezania A, Bruin JE, Arora P, Rubin A, Batushansky I, Asadi A, O'Dwyer S, Quiskamp N, Mojibian M, Albrecht T, Yang YH, Johnson JD, Kieffer TJ. Reversal of diabetes with insulin-producing cells derived in vitro from human pluripotent stem cells. Nat Biotechnol. 2014 Nov.

57. Rix I, Nexøe-Larsen C, Bergmann NC, et al. Glucagon Physiology. [Updated 2019 Jul 16]. In: Feingold KR, Anawalt B, Blackman MR, et al.,

editors. Endotext [Internet]. South Dartmouth (MA).

58. Rogers JK, Yaroshinsky A, Pocock SJ, Stokar D, Pogoda J. Analysis of recurrent events with an associated informative dropout time: Application of the joint frailty model. Stat Med. 2016.

59. Rubino DM, Greenway FL, Khalid U, et al. Effect of Weekly Subcutaneous Semaglutide vs Daily Liraglutide on Body Weight in Adults With Overweight or Obesity Without Diabetes: The STEP 8 Randomized Clinical Trial. JAMA. 2022.

60. Ruder K. As Semaglutide's Popularity Soars, Rare but Serious Adverse Effects Are Emerging. JAMA.

61. Sizar O, Podder V, Talati R. Empagliflozin. [Updated 2023 May 29]. In: StatPearls [Internet]. Treasure Island (FL): StatPearls Publishing; 2023 Jan.

62. Soliman A, De Sanctis V, Alaaraj N, Hamed N. The clinical application of metformin in children and adolescents: A short update. Acta Biomed. 2020 Sep 7.

63. Takahashi K, Yamanaka S. Induction of pluripotent stem cells from mouse embryonic and adult fibroblast cultures by defined factors. Cell. 2006 Aug 25.

64. Tasanen K, Varpuluoma O, Nishie W. Dipeptidyl Peptidase-4 Inhibitor-Associated Bullous Pemphigoid. Front Immunol. 2019 Jun.

65. Taylor SI. The High Cost of Diabetes Drugs: Disparate Impact on the Most Vulnerable Patients. Diabetes Care. 2020 Oct.

66. Tirzepatide versus Semaglutide Once Weekly in Patients with Type 2 Diabetes, New England Journal of Medicine.

67. Unnikrishnan AG, Kalra S, Purandare V, Vasnawala H. Genital Infections with Sodium Glucose Cotransporter-2 Inhibitors: Occurrence and Management in Patients with Type 2 Diabetes Mellitus. Indian J Endocrinol Metab. 2018 Nov-Dec.

68. UpToDate editors. (2023). Insulin Action.

69. Varshavski, M. (2023, February 14). How to lose weight and keep it off [Video]. YouTube.

70. Vilsbøll T, Lindahl CØ, Nielsen NF, Tikkanen CK. Real-world impact of once-weekly subcutaneous semaglutide after 2 years of follow-up: Results from a nationwide observational study in people with type 2 diabetes. Diabetes Obes Metab. 2023 Jun.

71. Wadden TA, Bailey TS, Billings LK, Davies M, Frias JP, Koroleva A, Lingvay I, O'Neil PM, Rubino DM, Skovgaard D, Wallenstein SOR, Garvey WT; STEP 3 Investigators. Effect of Subcutaneous Semaglutide vs Placebo as an Adjunct to Intensive Behavioral Therapy on Body Weight in Adults With Overweight or Obesity: The STEP 3 Randomized Clinical Trial. JAMA. 2021 Apr.

72. Wegovy® Dosing Schedule | Wegovy® (semaglutide) Injection 2.4 mg. (n.d.). https://www.wegovy.com/taking-wegovy/dosing-schedule.html

73. Wilding JPH, Batterham RL, Calanna S, Davies M, Van Gaal LF, Lingvay I, McGowan BM, Rosenstock J, Tran MTD, Wadden TA, Wharton S, Yokote K, Zeuthen N, Kushner RF; STEP 1 Study Group. Once-Weekly Semaglutide in Adults with Overweight or Obesity. N Engl J Med. 2021 Mar.

74. Zell, (2021, March 19) [review about Ozempic].

75. Zhao X, Wang M, Wen Z, Lu Z, Cui L, Fu C, Xue H, Liu Y and Zhang Y (2021) GLP-1 Receptor Agonists: Beyond Their Pancreatic Effects. Front. Endocrinol. 12:721135.

76. Zheng.Z, Bao.S, Dongsheng.Y, Chunsheng.Z Gut Microbiota: An Important Player in Type 2 Diabetes Mellitus Frontiers in Cellular and Infection Microbiology VOLUME 12 2022.