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Analyzing The Effects Of Semaglutide (Ozempic/Wegovy) On Metabolism: Investigating Correlations With Weight Reduction

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Abstract:

Background: Ozempic and Wegovy are brand names of Semaglutide, a GLP1 receptor agonist. Semaglutide mimics the actions of the incretin hormone GLP-1 found in the body resulting in increased release of insulin from pancreatic beta cells postprandially, inhibition of glucagon release, and prolongation of gastric emptying. While the FDA approved Wegovy for weight loss, Ozempic is FDA approved for managing blood glucose in patients diagnosed with Type 2 Diabetes Mellitus. In the years following approval of Ozempic for glycemic control, various trials utilizing differing dosage regimens demonstrated consistent weight loss in patients regardless of their diabetic status. From this data, chronic weight management was added as an approved indication for Ozempic. Hereinafter, both Ozempic and Wegovy will be referenced as Semaglutide, the primary active ingredient in both drugs.

Objective: This study aims to conduct a network meta-analysis and systematic literature review to assess the efficacy of subcutaneous Semaglutide injection in promoting weight loss and improving metabolism in obese patients with and without comorbidities.

Methods: Relevant research studies published between 2018 to 2023 were collected from the Pubmed database using a keyword search. Results were streamlined to focus on clinical studies including patient populations suffering from obesity with or without the diagnosis of Type 2 Diabetes Mellitus and use of subcutaneous Semaglutide only. A total of twenty-one studies including randomized control trials, retrospective cohort studies, and clinical trials were chosen and the outcomes were analyzed such as weight management from baseline, hemoglobin A1c, blood glucose levels, and other associated biomarkers.

Findings: In numerous studies reviewed, a positive correlation was observed between weight loss and overweight/obese patients receiving scheduled Semaglutide. Semaglutide demonstrated efficacy in reducing HbA1c levels, making it a powerful tool for practitioners in glycemic control (De Lucas et. al., 2022). Comparative analysis of HbA1c and weight loss results between oral and subcutaneous Semaglutide administration routes revealed little difference. Patients without prior GLP-1 receptor agonist treatment showed greater effects in HbA1c, weight, and insulin reduction. Continuous treatment with Semaglutide over 48 weeks led to greater weight loss compared to patients who switched to a placebo part way through treatment (Rubino et. al., 2021). In adolescents, weekly 2.4mg Semaglutide injections demonstrated greater weight loss of 5% of their body weight compared to the placebo group (odds ratio, 14.0; 95% CI, 6.3 to 31.0; $P<0.001$) (Weghuber et. al., 2022). In patients with obesity and PCOS who faced challenges in losing weight with lifestyle modifications, weekly Semaglutide injections were able to help them lose weight; the overall mean weight loss after 6 months was 11.5 kg with 80% of responsive patients resulting in normalized menstrual cycles with minimal side effects (Carmina et. al., 2023). In addition, Semaglutide significantly reduced perceived hyperglycemia with no perceived hypoglycemia between treatments. Semaglutide further aids weight loss by decreasing patients' food cravings (Wharton et al., 2023). Patients on Semaglutide showed improvement in overall health including CRP levels and alleviations of symptoms associated with heart failure and obesity (Mikhail N Kosiborod et. al., 2023).

Interpretation: Analysis of relevant research studies indicate a positive correlation between Semaglutide and weight loss, with additional benefits to metabolic health including but not limited to glycemic control and lipid profiles. Furthermore, studies demonstrated a positive relationship between dosing and amount of weight lost. Lastly, of note, weight regain was found to occur upon treatment cessation thus affecting the degree of long-term effectiveness of Semaglutide.

Introduction:

Diabetes mellitus is wildely recognized as a group of metabolic disorders characterized by consistently high blood sugar levels. There are two types of diabetes mellitus: type 1 is marked by the insufficient production of insulin in the pancreas, while type 2 diabetes is identified by the development of cellular insulin resistance, particularly from fat, liver, and muscle cells. The hormone insulin regulates glucose uptake from the bloodstream into cells, thus maintaining blood glucose at physiologically optimal levels. Persistent elevated blood sugar levels, a hallmark of diabetes, can result in sustained organ impairment, deterioration, and eventual organ failure over time. It affects especially the nerves, eyes, kidneys, heart, and blood vessels. This can manifest as diabetic neuropathy, retinopathy, nephropathy, and an increased risk of cardiovascular disease. Moreover, diabetes mellitus can compromise the immune system making patients more susceptible to infections. (Cole & Flores, 2020)

Obesity is a medical condition with excessive accumulation of body fat resulting from an imbalance between caloric intake and energy expenditure. In order to diagnose and measure obesity, the Body Mass Index (BMI) scale is used and categorizes obesity as Class 1 (BMI of 30 to < 35), Class 2 (BMI of 35 to < 40), or Class 3 (BMI of 40 or higher). The accumulation of fat in obesity poses a significant risk for numerous chronic diseases, including metabolic diseases such as type 2 diabetes, cardiovascular diseases such as heart disease and stroke, and musculoskeletal disorders such as osteoarthritis (Lincoff et al., 2023). For type II diabetes, the excess visceral fat contributes to the development of insulin resistance which triggers the pancreas to increase its output of insulin, and results in elevated insulin levels in the blood. As the pancreatic beta-cells become increasingly overburdened, their capacity to produce insulin declines, culminating in type 2 diabetes. Obesity and diabetes collectively pose a substantial public health challenge due to their high prevalence, the severity of associated complications, and the economic burden they impose. Obesity and diabetes exacerbate health complications and create a considerable pressure on healthcare globally. The management and prevention of these conditions involve multifaceted approaches including pharmacotherapy, lifestyle modifications, and in some cases, surgical interventions. The increasing prevalence and the complex interplay between obesity and diabetes underscore the urgent need for effective therapeutic strategies to address this dual epidemic. (Banerjee et al., 2019)

Ozempic, brand name for Semaglutide, acts as a glucagon-like peptide-1 (GLP-1) receptor agonist. Patients with type 2 diabetes use ozempic to reach blood sugar control. Ozempic was approved by the U.S. Food and Drug Administration (FDA) in 2017 for use in the treatment of type 2 diabetes. Semaglutide at a different dosage under the brand name Wegovy, was approved by the FDA in June 2021. Wegovy contains a higher dose of semaglutide, specifically 2.4 mg once weekly, compared to Ozempic, which generally prescribes up to 1 mg weekly. Wegovy is specifically indicated for weight control in individuals dealing with obesity or excessive weight, accompanied by at least one related health issue such as type 2 diabetes, hypertension, or elevated cholesterol levels. Wegovy is prescribed alongside a calorie restricted diet and increased physical exercise. The future of Wegovy in healthcare appears promising, especially considering the increasing prevalence of obesity and obesity-related health issues. Its potential extends beyond mere weight reduction; it could play a critical role in comprehensive health management, including cardiovascular health, diabetes management, and overall quality of life improvements for individuals struggling with obesity. (Singh et al., 2022)

It is important to distinguish between the two brand names and their FDA-approved uses, even though they contain the same active ingredient, Semaglutide. The approval for weight management came after clinical trials demonstrated significant weight loss in participants using the drug compared to those using a placebo. Ozempic was initially introduced to enhance blood sugar control in adults with type 2 diabetes, in conjunction with lifestyle modifications involving dietary and exercise changes. Semaglutide's mechanism of action is to mimic the functions of the incretin

hormone GLP-1. It boosts the release of insulin from the pancreatic beta-cells in response to glucose, inhibits the unwarranted release of glucagon, and decelerates the process of gastric emptying. Semaglutide This mechanism moderates postprandial blood glucose levels, contributing to overall glycemic control. In type 2 diabetes mellitus, insulin resistance or insufficient insulin production is present, Ozempic aids in stabilizing blood sugar levels by increasing insulin secretion in response to meals and decreasing the hepatic glucose output. This not only helps in lowering fasting and postprandial glucose levels but also contributes to a reduction in glycosylated hemoglobin (HbA1c) levels, a marker for long-term glycemic control. Though originally approved for diabetes, emerging research has shown that Ozempic's effectiveness in weight loss is a benefit, particularly in patients with type 2 diabetes who are often overweight or obese. It is thought to assist in reducing weight by suppressing appetite and decelerating the rate at which the stomach processes and empties food. (Corne, 2020)

It is important to note that while Semaglitide has benefits, its accessibility and affordability are contingent upon several factors, including healthcare policies, individual insurance plans, and socioeconomic status, which can affect a patient's ability to obtain this medication. It is imperative to maintain the ongoing research of Ozempic as a weight loss pharmacotherapy to identify gaps in the current understanding or conflicting results from previous studies. To determine whether Semaglutide is a valuable form of pharmacotherapy exclusively for weight loss, a comprehensive analysis of available data on its efficacy in both diabetic and non-diabetic patients is essential. (Elder & Ashjian, 2023)

Method:

The primary source for accessing relevant studies in this article was PubMed, available at www.pubmed.gov. This was the only database used to search for and retrieve relevant published literature. Specific keywords were employed to investigate studies associated with the hypothesis. Various search techniques, such as employing keywords, were put into action to refine and reduce the volume of search outcomes. This paper systematically reviews studies to analyze the effects of Semaglutide (Ozempic/ Wegovy) on metabolism: investigating correlations with weight reduction. Keywords used in the search included but were not limited to (Ozempic) AND (Weight), (Wegovy) AND (Weight), (Ozempic) AND (Weight reduction), (Wegovy) AND (Weight reduction), (Semaglutide) AND (Weight reduction), (Subcutaneous Semaglutide) AND (Weight reduction), (Ozempic) AND (Obesity), (Wegovy) AND (Obesity), (Semaglutide) AND (Obesity), (Subcutaneous Semaglutide) AND (Obesity). Other keywords used also included: (Ozempic) AND (Weight loss), (Wegovy) AND (Weight loss), (Semaglutide) AND (Weight loss), (Subcutaneous Semaglutide) AND (Weight loss).

The studies of interest centered on examining the impact of Semaglutide (Ozempic/ Wegovy) on individuals with obesity, regardless of whether they had diabetes mellitus or not. This research was developed by relying solely on a single database to gather information from the internet and literature. For instance, the specific database used by the study include: PubMed. Studies that encompassed populations involving both young and elderly adults, including males and females, were also considered. The study was limited to specific databases that addressed scientific topics on Analyzing the Effects of Semaglutide (Ozempic/Wegovy) on Metabolism: Investigating Correlations with Weight Reduction**.** Studies failing to address any of these specific areas of interest were excluded from consideration in this review.

An additional approach to the search strategy included implementing filters that align with the predefined inclusion and exclusion criteria. Articles were chosen based on particular inclusion criteria, which included the following: had full text available and written in English, published within the last 5 years (2018-2023) (relatively recent reports), research findings disseminated and available through medical journals, randomized control trials, clinical trials, following rigorous research methodologies that incorporate both experimental and control groups, conducted by qualified authors affiliated with reputable institutions, and devoid of any

indication of unreported bias or result manipulation. Lastly, selected articles needed to contain a sufficient amount of relevant information to meet the objectives of this paper. The exclusion criteria included literature in languages other than English, publications older than five years, materials not freely accessible to the general public, those lacking robust research methodologies and control groups, and any secondary literature such as meta-analyses, literature reviews, etc.

A meta analysis was conducted, integrating the findings and conclusions relevant to the main topic of our research. The details are illustrated in Figure 1 of the PRISMA flow chart, which is available in the appendix of this paper.

After a meticulous review of research papers identified through the outlined methodology in the respective database sections, particular focus was directed towards articles directly pertinent to the variables and subject matter under consideration. These articles underwent a systematic inclusion and exclusion process, adhering to the criteria established in the methodology section. This step-by-step exclusion process aimed to refine the number of papers, retaining only those directly relevant to our topic of interest. Following a thorough analysis, a total of twenty-one papers were ultimately chosen.

Upon the initial retrieval of search records, duplicate entries were eliminated, leading to a reduction in the total number of papers. Following this, a thorough examination of abstracts led to the exclusion of additional articles that did not align with the eligibility criteria and were deemed irrelevant to the objectives of this review. A comprehensive evaluation of each paper resulted in further exclusions as certain sections did not meet the specified eligibility criteria.

The focus of the studies of interest was Analyzing the Effects of Semaglutide (Ozempic/Wegovy) on Metabolism: Investigating Correlations with Weight Reduction**.** Twenty-one relevant quantitative studies published within the last five years were selected for review in this paper. Table 1 in the appendix provides a summary of the studies along with their respective study designs. The evidence table, designated as Table 2 in the appendix, was formulated based on the twenty-one chosen studies. Information from the materials and methods as well as the results sections of each study was utilized to populate the columns of the table. Table 2 illustrates that the selection of studies was guided by a set of inclusion and exclusion criteria, which were classified based on factors such as the first author, date of publication, population of study and outcomes/results.

Results:

The primary PubMed database search yielded 216 results within the time frame of 2018-2023. The set inclusion criteria then gave a result of 216 articles and subsequently, 0 duplicates were removed. 108 articles were excluded from this study based on the eligibility criteria. 108 articles were assessed for full text review where another 87 articles were removed for being outside the scope of the inclusion criteria. In total, 21 articles met the inclusion criteria and were included in this systematic analysis.

An observational, retrospective clinical study conducted by De Lucas et al., with multi-health center data sought to understand the therapeutic potential of Semaglutide in the diabetic population. The purpose was to observe Semaglutide's effects over time on patient HbA1c and total body weight in diabetics with a weekly injection. There were 166 total participants who were further subdivided into 2 groups: a group that was GLP-1 receptor agonist (GLP-1RA) naive and a group that switched from another GLP-1RA. Dosing was progressively increased to a maximum of 1mg of Semaglutide per week. After 24 months of follow-up, the reductions in HbA1c were -0.91 ± 0.7% ($p<0.001$) in the total cohort, -1.13 ± 1.38% ($p<0.019$) for GLP-1RA-naïve participants, and -0.74 ± 0.9% ($p<0.023$) for GLP-1RA-experienced participants. Body weight reductions were -12.42 ± 9.1% in GLP-1RA-naïve participants vs. -7.65 ± 9.7% in GLP-1RA-experienced participants ($p<0.001$). In the total cohort, 77.1% reached the objective of an HbA1c level <7%, and 12.7% reached between 7.1% and 7.5%. Additionally, 66.9% achieved a weight reduction of ≥5%. These promising results for glycemic control and weight management support the addition of Semaglutide to the list of available tools medical practitioners have for

combating diabetes progression in their patients (De Lucas et al., 2022).

In addition, another retrospective observational study further looked at the effects of subcutaneous Semaglutide in a diabetic cohort. The specific parameters of interest in this study were HbA1c, fasting blood glucose (FBG), body weight, blood pressure, lipid profile, renal function, and beta-cell function (HOMA-B). 594 patients participated in the study with the vast majority being GLP-1RA naive. Every patient started with a Semaglutide prescription of .25 mg which was then titrated up to .50mg. Follow-up visits were performed at the 3-month, 6-month, and 12-month mark. Overall, HbA1c in these patients "decreased by -0.9% (95% C.I. -1.04; -0.76, $p < 0.0001$) after 6 months and the reduction was sustained after 12 months (-0.96%; 95% C.I. -1.09; -0.82, $p < 0.0001$); FBG decreased by -26.24mg/dl (95% C.I. -32.25; -20.23, $p < 0.0001$) after 6 months and the reduction was sustained after 12 months (-25.76 mg/dl; 95% C.I. -31.57; -19.94, $p < 0.0001$); body weight was reduced by -3.43 kg (95% C.I. -4.51; -2.34, $p < 0.0001$) after 6 months and benefit was substantially maintained after 12 months (-3.68 kg; 95% C.I.-4.93; -2.44, $p < 0.0001$). A unique and significant finding was the improvement in Beta-cell function and insulin resistance at 6 months through the index of secretory function HOMA-B (+17.53; 95% C.I. 14.21; 20.85, $p < 0.0001$). Lastly, eGFR and ACR measurements did not change within the 12 months studied. The breadth of diabetic biomarkers Semaglutide was shown to positively influence in this study indicate the possibility of a multi-organ system therapeutic effect over time. In addition, the lack of change in the renal parameters indicate a favorable renal safety profile (Cesare C Berra, 2023).

Another cohort study, conducted at a referral center for weight management, utilizing data collected from patients in the Mayo Clinic Health System prescribed Semaglutide. 175 patients were included and Semaglutide dosing was either 0.25, 0.5, 1, 1.7, or 2.4 mg depending on the patient. Weight change was analyzed at 3 and 6-month visits. "At 3 months, 175 patients achieved a mean (SD) weight loss of 6.7 (4.4) kg, equivalent to a mean (SD) weight loss of 5.9% (3.7%) ($P < .001$ from baseline). At 6 months, 102 patients had a mean (SD) weight loss of 12.3 (6.6) kg, equivalent to a mean (SD) weight loss of 10.9% (5.8%) ($P < .001$ from baseline)." The weight loss data was further analyzed by comparing the amount of weight lost between the patient's diabetes status, obesity class, and the varied dosages mentioned. Patients with type 2 diabetes had a lower mean (SD) percentage weight loss compared with those without type 2 diabetes at 3 months (3.9% [3.1%] vs 6.3% [3.7%]; $P = .001$) and at 6 months (7.2% [6.3%] vs 11.8% [5.3%]; $P = .005$). Obesity classes were divided into class 1 (BMI, 30 to <35), class 2 (BMI, 35 to <40), and class 3 (BMI, 40).17 Patients with class 3 obesity had similar mean (SD) weight loss outcomes when compared with patients with overweight or classes 1 and 2 obesity at 3 months (7.1 [5.0] kg [n = 89] vs 6.3 [3.6] kg [n = 86]; $P = .27$), equivalent to mean (SD) weight loss of 5.3% (3.8%) vs 6.5% (3.6%) ($P = .03$) and at 6 months (−12.6 [7.9] kg [n = 51] vs −12.1 [5.0] kg [n = 51]; $P = .70$), equivalent to mean (SD) weight loss of 9.2% (5.9%) vs 12.6% (5.2%) ($P = .002$). Finally, 77 patients (44.0%) received the highest current doses of subcutaneous Semaglutide (1.7 and 2.4 mg), while 98 (56.0%) received lower doses (0.25, 0.5, and 1 mg). At 3 months, patients who received the highest doses achieved a mean (SD) weight loss of 6.9% (3.9%) (95% CI, −7.8% to −6.0% [n = 77]) compared with a mean (SD) weight loss of 5.1% (3.4%) (95% CI −5.8% to −4.4% [n = 98]) for patients receiving lower doses ($P = .002$). At 6 months, patients receiving the highest doses achieved a mean (SD) weight loss of 12.1% (5.9%) (95% CI, −13.6% to −10.6% [n = 60]) compared with a mean (SD) weight loss of 9.2% (5.2%) (95% CI, −10.9% to −7.6% [n = 42]) for patients receiving lower doses ($P = .01$)." While the study limited follow up data to only 6 months, observing such statistically significant improvements in weight management in such a short period accentuates the effectiveness Semaglutide possesses in weight loss (Wissam Ghusn, 2022).

A clinical trial crossover created by Rune V. Overgaard et. al. conveyed the correlation between Semaglutide and reductions in body weight and HbA1C, in addition to the little difference in route of administration. Two

clinical trials were examined, PIONEER vs. SUSTAIN, to determine their positive or negative effects. The PIONEER study concluded that of the 703 patients given once a day oral 3, 7 or 14 mg Semaglutide with a mean HbA1c of 8.0% in the 26 week trial, reductions of -0.6% (3 mg), -0.9% (7 mg), and -1.1 (14mg) and body weight reductions of -0.1 kg (3mg), -0.9 kg (7 mg), and -2.3 kg (14 mg) were seen. Across SUSTAIN trial 1-5 injectable Semaglutide, significant reductions of HbA1C and bodyweight were concluded. To compare SUSTAIN and PIONEER clinical trials, subjects with higher HbA1c baseline had a higher reduction in HbA1c (>9.1 HbA1c reduction of 3% vs. <7.5 HbA1c reduction of 1%), body weight reductions were higher in females and subjects with higher baseline HbA1c had less weight loss. Comparison of route of administration was also examined, oral vs. subcutaneous (s.c) and the results are as follows; HbA1c reductions of -1.58% (oral) vs -1.62% (s.c), and body weight changes of -3.77 (oral) vs -3.48% (s.c). Of this, there is little difference in route of administration with reductions in HbA1c and weight loss which further represented the positive correlation of subcutaneous Semaglutide and weight loss (Rune V. Overgaard et al., 2023).

To further, a clinical open-label trial was created to see the effects of adding subcutaneous Semaglutide to Diabetes Mellitus type 2 patients previously on insulin (with or without oral antidiabetics) to see the effects of the plasma glucose concentration over-time. In this trial, 117 patients were followed for 53 weeks. Of the 117, 17 dropped out due to adverse effects or adherence issues. Results showed a significant drop of HbA1c of 0.74%, a weight reduction of 3.61 kg and total insulin use per injection 15.88 IU (all values had a 95% CI with $p<0.05$) from baseline measurements. Patients without prior GLP-1 receptor agonist treatment had a significantly greater reduction of HbA1c, weight, and insulin use while those with pre-treatment of GLP-1 receptor agonist medication only had a decrease in weight (Ares-Blanco J et al., 2022).

An exposure and response model was created to determine the relationship between glucagon-like peptide analogue Semaglutide and weight reduction. Three trials were analyzed to determine the relationship between the two; one 52-week trial dose ranging trial of 0.05-0.4 mg of once daily subcutaneous Semaglutide , and two 68 week, once a week injection of 2.4 mg Semaglutide. Of this, a population pharmacokinetic was developed in people with overweight/obesity, with or without type 2 diabetes. Population pharmacodynamics were created and categorized into Step 1-5. A total of 3818 participants were included, of those having a mean BMI of 37.5 kg/m2. The key finding was a correlation between weight loss and overweight/obese participants receiving a weekly injection of 2.4 mg of Semaglutide (Anders Strathe et al., 2023).

Another huge finding in a study conducted by John P. Wilding et al., showed a relationship between weight loss and subcutaneous Semaglutide. The 68 week double-blinded placebo trial enrolled 1961 participants; one group was given once weekly 2.4 mg subcutaneous Semaglutide and the other only underwent lifestyle modifications. The results showed the experimental group lost -14.9% mean body weight while the placebo (no Semaglutide) lost only -2.4% mean body weight (95% confidence interval [CI], -13.4 to -11.5; $P<0.00$). More participants achieved body weight reductions of 5% or more in the experimental group than the control group as well. The total change in weight was -15.3 kg as compared to the placebo with a loss of -2.4 kg at week 68 (-12.7 kg; 95% CI, -13.7 to -11.7). These findings are massively important to diabetic disease management as doctors and patients can readily see weight loss in type two diabetics (John P.H. Wilding et al., 2021).

Many studies were conducted on not only diabetic patients but obese and overweight individuals. A study was conducted involving 803 overweight or obese participants with 79% being women with an average age of 46 and an initial average weight of 107.2kg. Participants were given once-weekly subcutaneous Semaglutide, 0.25 mg, increased every 4 weeks to the maintenance dose of 2.4 mg once weekly and at week 20, participants were double-blind selected to either continue Semaglutide or switch to a placebo for 48 weeks. The participants initially lost an average of 10.6% of their body weight over 20 weeks using Semaglutide. Those who continued with Semaglutide experienced an additional average weight loss of 7.9%, whereas

those who switched to the placebo gained an average of 6.9%. Additionally, improvements were observed in waist circumference, blood pressure, and physical functioning scores among those who continued Semaglutide, all with statistical significance. However, gastrointestinal issues were more common in the Semaglutide group (49.1%) compared to the placebo group (26.1%). The study concluded that continual treatment with Semaglutide after initial weight loss leads to further weight loss over 48 weeks compared to switching to a placebo (Domenica Rubino et al., 2021).

Furthermore, a study was conducted involving Semaglutide 2.4mg versus a placebo group in treating overweight or obese participants. Amongst the participants, 92.8% of them completed the trial, 77.6% were female, 93.1% were white, mean age of 47.3 +/- 11 years, BMI of 38.5 mgm-2, and weight of 106 kg. In regards to weight loss, participants in the Semaglutide group (n=152) loss a mean of 15.2% from baseline to week 104. In contrast, the placebo group (n=152) lost 2.6%. This resulted in a substantial estimated difference of 12.6%. Additionally, a higher proportion of participants in the Semaglutide group achieved weight loss of ≥5% from baseline at week 104 compared to the placebo group (77.1% vs. 34.4%). Other benefits in the Semaglutide group include greater reductions in waist circumference, systolic blood pressure, diastolic blood pressure, and improvements in glycated hemoglobin, fasting plasma glucose and total cholesterol. Overall, compared to the placebo group, the Semaglutide treatment led to a substantial and sustained weight loss and health improvements over 104 weeks (W. Timothy Garvey et al., 2021).

While subcutaneous injections of Semaglutide have been utilized for adult weight loss, there has not been a lot of study into its effects on adolescents. A double-blind parallel-group placebo-controlled trial looked to evaluate a once-weekly 2.4mg subcutaneous dose of a glucagon-like peptide 1 receptor agonist in adolescents for a duration of 68 weeks. The adolescents who receive the once weekly Semaglutide injection had an average weight loss of 16.1% while the placebo group had an average weight loss of 0.6% (95% confidence interval [CI], -20.3 to -13.2; P<0.001). They also demonstrated improved cardiovascular and metabolic factors. At the conclusion of the trial, adolescents who received the weekly injection lost 5% of their body weight compared to the placebo group (odds ratio, 14.0; 95% CI, 6.3 to 31.0; P<0.001). The outcome of this trial proved that a once a week injection of 2.4mg Semaglutide displayed better outcomes for weight loss (Weghuber et al., 2022).

The addition of a once-weekly subcutaneous Semaglutide injection was studied for its efficacy in patients with Type 2 diabetes. This trial looked to establish the difference between a Semaglutide injection individually or in combination with another oral antidiabetic drug (OAD) versus an oral antidiabetic drug in the time span of 56 weeks. The HBA1c (baseline 8.1%) decreased with both Semaglutide injections as compared with the oral antidiabetic medication group (1.7% and 2.0% vs 0.7%, ETD vs OAD -1.08% and -1.37%, both P<.0001). In total, an HbA1c concentration less than 7.0% was reached in over 80% of participants in the injection groups . Additionally, with the drastic reduction in HbA1c in these participants, those who took part in the Semaglutide injection groups resulted in a weight loss of >5% in the 0.5mg injection group and >10% in the 1.0mg injection group as compared to the OAD group . Factors such as BMI and waist circumference were also reduced in the Semaglutide injection groups as compared to the OAD group. A Semaglutide weekly injection has once again shown a substantial decrease in BMI (Kaku et al., 2018).

A double-blind parallel-group trial conducted over the span of 13 weeks looked at the pharmacodynamics, pharmacokinetics, and safety of a 0.5mg and 1.0mg Semaglutide injection in 22 Japanese men and 22 Caucasian men. Both Semaglutide groups demonstrated weight reduction. The 0.5mg Semaglutide group and 1.0mg Semaglutide group for Japanese men had a p>0.05 and both groups for Caucasian men had the same effect as compared to the placebo groups . Specifically, the average weight decreased by 1.4kg in the 0.5mg Semaglutide injection group and 5.0kg in the 1.0mg Semaglutide injection group in Japanese men where the placebo group had a 1.1kg increase. In

Caucasian men, average weight decreased by 3.6kg in the 0.5mg Semaglutide injection group and 7.5kg in the 1.0mg Semaglutide injection group respectively as compared to a 0.7kg increase in the placebo group. Both Japanese and Caucasian men ended up losing weight with either option of the Semaglutide injection, where Caucasian men lost more but started with a higher initial BMI. This result proved that the subcutaneous Semaglutide injection shows results in decreasing BMI, but most importantly tends to work more effectively on people with an already higher starting BMI (Ikushima et al., 2018).

Looking into the STEP 2 clinical study of overweight and obese patients, diagnosed with Type 2 Diabetes injected with once weekly subcutaneous Semaglutide 2.4 mg vs placebo, the results show a clinically significant decrease in body weight in patients given Semaglutide. After the 68 week endpoint, change in mean bodyweight from baseline was -9.6% with Semaglutide 2.4 mg and -3.4% with placebo. A higher number of patients taking Semaglutide 2.4 mg also attained at least 5% weight reduction [68.8%, 267/388] compared to the placebo group [28.5%, 267/388]. Receiving a weekly Semaglutide injection has proven to decrease an individual's overall body weight and provide them a route to a healthier BMI (Davies et al., 2021).

A Semaglutide once weekly injection has been studied as an option for those who fail lifestyle modifications. Obese patients with a diagnosis of PCOS who failed to lose body weight after a lifestyle modification program were treated with SQ Semaglutide 0.5mg once weekly. After a three month trial, results showed a significant improvement in weight reduction. About 80% of patients enrolled had a weight loss of at least 5% with low dose Semaglutide. The patients who responded well continued another three month regimen. After 6 months the overall mean weight loss was 11.5 kg, mean BMI reduced from 34.4 to 29.4, and 80% of responsive patients normalized menstrual cycles with minimal side effects. Patients who have tried to utilize lifestyle modifications for weight loss and failed are candidates for a Semaglutide injection and this study demonstrates the benefit of the injection for weight loss within this patient population. (Carmina et al., 2023).

Another relationship that further solidifies the correlation between subcutaneous Semaglutide and weight loss was studied; Semaglutide and postprandial glucose and lipid responses. It is important to consider the pathophysiological factors that lead to weight loss in patients receiving Semaglutide injections. A randomized, double-blinded clinical trial was created after a 12-week treatment period, with initial glucose, lipid, and peptide (PYY) measured. The treatment group received weekly 1.0mg Semaglutide injections while the control did not receive any medications. Results showed that Semaglutide lowered fasting glucose and glucagon with a treatment ratio: 0.95 [95% confidence interval: 0.91, 0.98] compared to the placebo. First hour gastric emptying was delayed with AUC0-1h, estimated treatment ratio: 0.73 [0.61, 0.87] and PYY and fasting were lower with ($P = .0397$ and $P = .0097$, respectively) vs. placebo. Another key detail the study measured was weight loss as an average of 5 kg was reportedly lost during the 12 week trial in the experimental group. Weight loss increasingly impacts the insulin sensitivity in patients thus this domino effect was seen with lipid and glucose responses as weight loss helped lessen these key factors. Overall, postprandial glucose, lipid responses and peptides were lowered and impacted by weight loss in patients receiving the Semaglutide treatment (Julie B Hjerpsted, 2018).

A study reveals a notable enhancement in overall treatment satisfaction from the initial assessment to the conclusion of treatment across various trials, predominantly with Semaglutide compared to other treatments or placebo, as evidenced in the SUSTAIN 2-5 trials ($P < 0.05$). The use of a Semaglutide subcutaneous injection developed an improvement that was more pronounced in individuals attaining weight loss and glycaemic goals, with Semaglutide 1.0 mg showing superior outcomes in these categories. Higher doses of Semaglutide injections expectantly provide a greater reduction in weight loss. Contrastingly, in the SUSTAIN 7 trial, Semaglutide and dulaglutide demonstrated comparable effects on treatment satisfaction, unaffected by weight loss or glycaemic control. Notably, this improvement was more substantial

in patients who achieved their treatment objectives. The Semaglutide injection provided a reduction in weight loss more specifically at the 1.0mg dosage (Jendle et al., 2019).

Another interesting study focuses on analyzing the effect and evaluating the impact of once-weekly subcutaneous Semaglutide, in conjunction with behavioral therapy and a low-calorie diet. This study was conducted at 41 sites across the United States from August 2018 to April 2020, this phase 3a study involved 611 non-diabetic adults, who were with at least one comorbidity or were obese. Participants were divided in a 2:1 ratio to either the Semaglutide group (407 participants) or the placebo group (204 participants). For the first 8 weeks, participants were subjected to a low-calorie diet as well as 68 weeks of intensive behavioral therapy consisting of 30 counseling sessions. The primary focus of this study revolves around the percentage change in body weight and the proportion of participants achieving varying weight loss percentages from 5%, 10%, 15% or more from baseline. The results were notable. At the end of the 68 weeks, the Semaglutide group showed a mean weight reduction of 16.0% from baseline, compared to a 5.7% reduction in the placebo group. This marked a significant difference of 10.3 percentage points. Additionally, a substantially higher percentage of the Semaglutide group achieved weight loss of at least 5%, 10%, and 15% compared to the placebo group. In conclusion, in this study when Semaglutide was used alongside intensive behavioral therapy and a low-calorie diet, there was significant weight loss in adults who were overweight or obese over the 68-week period (Wadden, 2021).

Reduction in weight has been well established to aid individuals in decreasing weight related health risks. This comprehensive analysis underscores the critical role of obesity as a chronic disease, intricately linked to numerous health complications. The article focuses on elucidating the role of glucagon-like peptide 1 receptor agonists (GLP-1RAs) in weight management. Initially developed for type 2 diabetes, GLP-1RAs like liraglutide and Semaglutide have shown promise in obesity treatment, with their efficacy in weight reduction and maintenance being explored in clinical trials. The article aims to guide primary care providers in understanding the mechanism, efficacy, safety, and considerations of adverse effects in employing these pharmacotherapies for obesity management, emphasizing the potential need for long-term treatment strategies (Ards et al., 2021).

Significant variations in weight loss were clinically observed across different BMI subgroups, indicating a trend towards greater absolute weight reduction with higher initial BMI levels. In general, subjects taking Semaglutide at 0.5 mg and 1.0 mg reported nausea or vomiting at rates of 15.2% to 24.0% and 21.5% to 27.2%, respectively, compared to 6.0% to 14.1% for those using comparators. Notably, only a minimal portion (0.07 to 0.5 kg) of the observed treatment difference between Semaglutide and comparators could be attributed to nausea or vomiting (indirect effects). Across SUSTAIN 1 to 5 trials, Semaglutide consistently led to more significant weight loss compared to the comparator groups, irrespective of the participants' initial BMI. The impact of nausea or vomiting on this weight reduction was minimal. With the addition of Semaglutide, participants consistently demonstrated a significant weight loss (Ahren et al., 2018).

In adults with obesity, the administration of Semaglutide 2.4 mg demonstrated enhanced regulation of eating habits over both the short and extended durations, aligning with significant weight reduction. A study involving participants who completed the Control of Eating Questionnaire (Semaglutide group, n = 88; placebo group, n = 86), there was a notable difference in mean body weight changes between the two groups. Specifically, those in the Semaglutide group experienced a substantial reduction of -14.8%, while the placebo group exhibited a comparatively smaller decrease of -2.4%. Furthermore, the scores related to Craving Control and Craving for Savory domains demonstrated significant improvement with Semaglutide as opposed to placebo at weeks 20, 52, and 104 ($p < 0.01$). Similarly, Positive Mood and Craving for Sweet domains exhibited significant improvement at weeks 20 and 52 ($p < 0.05$), while hunger and fullness scores were notably enhanced at week 20 ($p < 0.001$). It's

worth noting that the improvements in craving domain scores were found to be positively correlated with reductions in body weight from baseline to week 104 in the Semaglutide group. At the 104-week mark, the scores for desire to eat salty and spicy food, cravings for dairy and starchy foods, difficulty in resisting cravings, and control of eating were significantly lower with Semaglutide compared to the placebo (all $p < 0.05$). Semaglutide injections correlate to a deceased body mass most notably due to the effect that it has on food cravings (Wharton et al., 2023).

Lastly, the KCCQ-CSS exhibited a mean change of 16.6 points when treated with Semaglutide compared to 8.7 points with a placebo. The estimated difference was 7.8 points, with a 95% confidence interval of 4.8 to 10.9 ($P<0.001$). Additionally, the mean percentage change in body weight was -13.3% for Semaglutide and -2.6% for placebo, resulting in an estimated difference of -10.7 percentage points (95% CI, -11.9 to -9.4; $P<0.001$). The 6-minute walk distance demonstrated a mean change of 21.5 m with Semaglutide and 1.2 m with placebo, yielding an estimated difference of 20.3 m (95% CI, 8.6 to 32.1; $P<0.001$). In the hierarchical composite endpoint analysis, Semaglutide achieved more wins than placebo (win ratio, 1.72; 95% CI, 1.37 to 2.15; $P<0.001$). The mean percentage change in CRP level was -43.5% with Semaglutide and -7.3% with placebo, showing an estimated treatment ratio of 0.61 (95% CI, 0.51 to 0.72; $P<0.001$). Serious adverse events were reported in 13.3% of participants in the Semaglutide group and 26.7% in the placebo group, totaling 35 and 71 individuals, respectively. Among individuals experiencing heart failure with preserved ejection fraction and obesity, the administration of Semaglutide (2.4 mg) resulted in more significant alleviation of symptoms and physical limitations, enhanced exercise function, and more substantial weight loss when compared to the effects observed with a placebo (Mikhail N Kosiborod et. al, 2023).

As you can see, the various articles summarized showed a significant correlation between weight and HbA1C reductions and Semaglutide. No matter the amount of subcutaneous medication given, an observed effect was seen throughout the various time ranges. It is valuable to utilize this information when treating those with Diabetes Mellitus and weight/HbA1C issues.

Discussion:

Following the recognition of obesity as a disease by the American Medical Association in 2013, tools available for prevention and management have steadily become more expansive and diverse. While traditional methods such as diet and exercise continue to be the initial approaches to weight management, innovative pharmaceutical treatments such as Semaglutide have demonstrated promising results effective enough to warrant strong consideration in early healthcare implementation. Utilizing a systematic literature review, this study provides evidence supporting the effectiveness of once-weekly Semaglutide in the weight management of obese patients with notable additional positive effects on eating behaviors and the biomarkers for other correlated chronic diseases. Moreover, our findings suggest that, holistically, Semaglutide's impact on obesity management consistently yields robust and safe results throughout the treatment timeline.

Beginning with prominent early hurdle weight loss treatments possessing effective balancing safety and early significant results, Semaglutide was found to deliver a multi-kilogram weight loss in patients soon after treatment initiation with minimal adverse effects. Specifically, within just 3 months of treatment commencement, once-weekly Semaglutide was found to deliver a mean weight loss of 4.4 kg. Adverse effects reported correspond with those demonstrated in clinical trials (Davies et al., 2021) primarily consisting of minor gastrointestinal symptoms. This strong start to the treatment timeline was followed up with a further mean 2.2kg weight loss observed by the 6-month follow-up (Ghusn et al., 2022). This continued significant weight loss serves as an important subsequent data point in trend establishment. Additionally, it as positive reassurance for patients early into their weight loss journey of treatment effectiveness.

On the other end of the treatment timeline, the prevention of lost weight regained while on treatment or after treatment cessation is also factored into the equation when determining

the overall long-term effectiveness. In this regard, patients taking once-weekly Semaglutide injections were found to still have continued weight loss two years after the start of treatment. Garcia de lucas et al. (2022) demonstrated a mean 9.7kg weight loss across a GLP-1RA naive and experienced cohort after a 24-month follow-up, supporting a trend of sustained efficacy lasting multiple years. However, another study found the cessation of treatment to result in a mean weight regain of 11.6% in their Semaglutide arm versus 1.9% in the placebo (Wilding et al., 2022). Together, these results indicate significant positive weight management while actively taking Semaglutide but a high risk for weight regain should the treatment be stopped voluntarily or due to one of the rare adverse health effects. In order to avoid this outcome, patients with higher BMIs who require greater weight loss by their healthcare provider may need to be on Semaglutide for much longer. With this in mind, since 2 years is the longest patient follow-up in this review, further studies following patients' outcomes across longer time periods are required. These studies will help to establish the degree of Semaglutide's persistent effectiveness and safety after more than 2 years. More long-term data will also be valuable in continuing the evaluation of these parameters as they relate to dosing differences since they can vary among patients when prescribed. Like most drugs, Semaglutide's relevant effects increase with increasing injection dosage but so do the risk of adverse effects.

With respect to the varying doses of Semaglutide studied, this review found that higher Semaglutide doses (maximum of 2.4mg) were directly correlated with greater amounts of weight loss among patients. Dosing of the weekly injection ranged from .25 to 2.4mg in the studies included. Higher dosages were achieved through a carefully managed progressive titration from much lower doses. Patients who received and tolerated higher dosages, specifically labeled as 1.7mg and 2.4 mg, were found to have the greatest effect on direct obesity biomarkers (BMI) and closely associated obesigenic biomarkers including HbA1c, fasting blood glucose, lipid profile, blood pressure, and pancreatic beta-cell function. In regards to mean total weight loss, the difference was 2.9% at 6 months between dosing categories, with lower doses being considered as 0.25, 0.5, and 1 mg and higher doses being 1.7 and 2.4mg (Ghusn et al., 2022). These results corroborate the mean weight loss observed within a similar time frame in the STEP 4 clinical trials at 2.4mg (12.1% after 6 months by Ghusn et al vs. 10.4% at 20 weeks by Rubino et al). In conjunction with strong results from the direct treatment target of weight loss, Semaglutide's indirect effects on associated systems similarly reveal promising data.

To elaborate on the positive indirect effects of Semaglutide mentioned, the diabetic and cardiovascular biomarkers including HbA1c, fasting blood glucose (FBG), pancreatic beta-cell function, lipid profile, and blood pressure all showed improvement with Semaglutide treatment. After 1 year, HbA1c was found to have decreased by .74% in diabetic patients who had previously been on insulin therapy (Ares-Blanco et al., 2022). Similarly, a .96% decrease in HbA1c was observed in patients who had been on stable antihyperglycemic therapy for at least 3 months with oral hypoglycemic agents (OHA) and/or insulin (Berra et al., 2023). Also after 12 months of Semaglutide treatment, FBG was found to have decreased by 25.76 mg/dl (Berra et al., 2023). After 6 months of treatment, pancreatic beta cell function measured by HOMA-B (homeostatic model assessment for b-cell function) improved from 40.2% to 57.8%. Statistically significant improvements found in these 3 diabetic biomarkers act to solidify the addition of Semaglutide into the list of available tools for healthcare professionals for the management of diabetic patients. Examining the cardiovascular effects, the lipid profile and blood pressure measurements both experienced improvements. However, there was only a statistically significant improvement specifically in the systolic blood pressure and not the diastolic. Systolic blood pressure fell from a mean of 132.41 to 130.18mmHg after a year of treatment (Berra et al., 2023). On the other hand, the entire lipid profile of patients after a year of Semaglutide saw improvements. Total cholesterol fell from a mean of 167.07 to 157.99mg/dl, LDL fell from 91.13 to 84.69 mg/dl, HDL rose from 45.33 to 46.13mg/dl, and

triglycerides fell from 166.51mg/dl to 147.18 mg/dl. Since the measurement of cardiovascular health encompasses much more than simply these two biomarkers, further studies are required before Semaglutide can be considered as a cardiovascular health treatment option. Nevertheless, this does not take away from the extensive beneficial implications these mentioned multisystemic results have on obese patients taking Semaglutide.

This study has various limitations. To begin, the resultant data tracked capped out at a maximum time period of 2 years across all papers reviewed. Obesity and its downstream effects on important health biomarkers can take more than 2 years to correct, thus warranting extended efficacy and safety data. Having data on treatment for more than two years will allow healthcare providers to develop a better understanding of where Semaglutide may rank on their list of obesity treatment tools. Furthermore, another limitation of this study is the absence of weight loss compositional data among the studies reviewed. Specifically, the composition of the weight loss whether it consisted primarily of adipose tissue or not is not provided. This means that patient total weight loss data could have included contributions from muscle mass, total body water, and bone density losses. Significant losses in muscle mass and bone density are commonly seen as negative body compositional changes, as losses of these tissues could lead to numerous well-studied negative health outcomes. To better clarify this data, body composition measurement methods such as dual-energy X-ray absorptiometry (DEXA) can be used on study participants before and after Semaglutide treatment. Having more detailed information on Semaglutide's changes in body composition will provide healthcare professionals and patients with the ability to take the appropriate steps to better mitigate unwanted changes. Lastly, this study is limited by sponsorship bias with the majority of studies reviewed being funded by Semaglutide manufacturer Novo Nordisk.

Conclusion:

This comprehensive review shows that there is a positive correlation between the use of Semaglutide and weight loss, with effects showing as early as three months into treatment with an average of 5.9% weight loss (Ghusn et al., 2022). Our extensive analysis of both clinical trials and observational studies reveals that Semaglutide not only aids the glycemic control of patients with type 2 diabetes, but also helps weight loss in diabetic and non-diabetic patients. These observed effects underpin Semaglutide's usefulness as a tool in tackling two significant medical conditions: diabetes and obesity. Patients on Semaglutide also showed improvements in various metabolic parameters including HbA1c levels, fasting blood glucose, lipid profiles, and blood pressure. However, weight regained after treatment cessation is a factor to account for. With treatment cessation, patients treated with Semaglutide experienced a weight regain of 11.6% compared to a 1.9% regain observed in the placebo group (Wilding et. al). Patients with higher BMI may need to be on Semaglutide long-term to increase weight loss. In another study, a dose-dependent relationship was noted (Ghusn et al). With a higher dose of Semaglutide, there was a greater percentage of weight loss and metabolic improvements. This finding further supports the positive relation between Semaglutide and weight loss.

Future studies should look into the side effects associated with increased dosing and prolonged usage of Semaglutide to better maximize the therapeutic benefits and minimize the side effects. The studies should also focus on long-term outcomes of Semaglutide to better understand the sustained efficacy, safety, and additional benefits of Semaglutide; this will be especially useful for patients with high-BMI who may require prolonged treatment.

In conclusion, Semaglutide represents a significant advancement in metabolic health care, providing an additional treatment option for patients that have been struggling with weight management and metabolic disorders. Further research regarding its efficacy, benefits and side effects will better help our healthcare system maximize the potential of this medication. By integrating Semaglutide in weight loss treatment, patients can have a significant improvement on their struggles with obesity and its associated complications.

Appendix

Table 1. Summary of study designs

Study design	Number of studies
Randomized Controlled Trial (RCT)	**12**
Clinical Trials/ Cross over	**4**
Retrospective Cohort study	**4**
Case series	**1**

Figure 1: Inclusion and Exclusion upon Search:

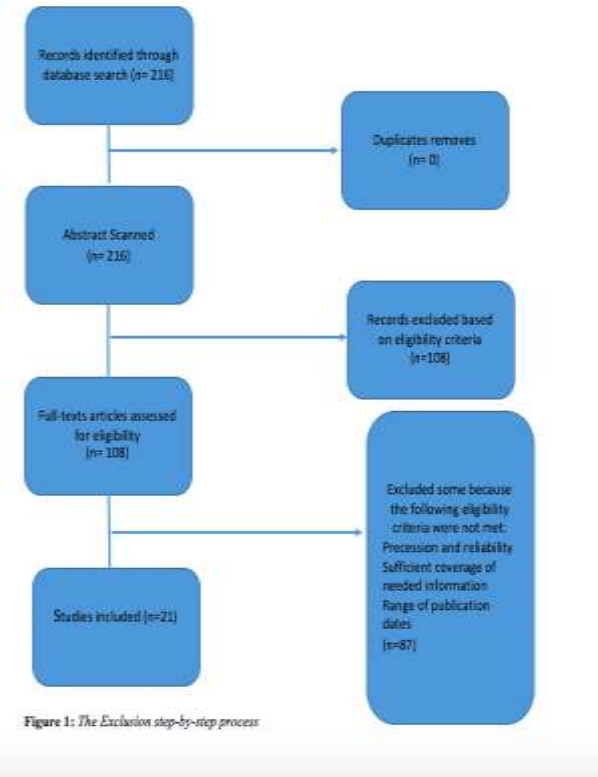

Figure 1: *The Exclusion step-by-step process*

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First Author	Date of Publication	Population of study	Outcome/Results
Maria Dolores Garcia de Lucas (Gabe)	**September 16, 2022**	**Multicenter retrospective observational clinical study**	**Outcome** Examining the outcome of once weekly Semaglutide injections in patients with diabetes yielded results where body weight reductions were -12.42 ± 9.1% in

			GLP-1RA-naïve participants vs. -7.65 ± 9.7% in GLP-1RA-experienced participants (p<0.001). In the total cohort, 77.1% reached the objective of an HbA1c level <7%, and 12.7% reached between 7.1% and 7.5%. Additionally, 66.9% achieved a weight reduction ≥5%.
Cesare C Berra (Gabe)	**January 18, 2023**	**A Retrospective, cohort study**	**Outcome** Overall, HbA1c in these patients "decreased by -0.9% (95% C.I. -1.04; -0.76, p < 0.0001) after 6 months and the reduction was sustained after 12 months (-0.96%; 95% C.I. -1.09; -0.82, p < 0.0001); FBG decreased by -26.24mg/dl (95% C.I. -32.25; -20.23, p < 0.0001) after 6 months and the reduction was sustained after 12 months (-25.76 mg/dl; 95% C.I. -31.57; -19.94, p < 0.0001); body weight was reduced by -3.43 kg (95% C.I. -4.51; -2.34, p < 0.0001) after 6 months and benefit was substantially maintained after 12 months (-3.68 kg; 95% C.I.-4.93; -2.44, p < 0.0001).
Wissam Ghusn (Gabe)	**September 1, 2022**	**Retrospective Cohort Study**	**Outcome/ Results** 75 patients were included and Semaglutide dosing was either 0.25, 0.5, 1, 1.7, or 2.4 mg depending on the patient. Weight change was analyzed at 3 and 6-month visits. "At 3 months, 175 patients achieved a mean (SD) weight loss of 6.7 (4.4) kg, equivalent to a mean (SD) weight loss of 5.9% (3.7%) (P < .001 from baseline). At 6 months, 102 patients had a mean (SD) weight loss of 12.3 (6.6) kg, equivalent to a mean (SD) weight loss of 10.9% (5.8%) (P < .001 from baseline)."

			The weight loss data was further analyzed by comparing the amount of weight lost between the patient's diabetes status, obesity class, and the varied dosages mentioned. Patients with type 2 diabetes had a lower mean (SD) percentage weight loss compared with those without type 2 diabetes at 3 months (3.9% [3.1%] vs 6.3% [3.7%]; P = .001) and at 6 months (7.2% [6.3%] vs 11.8% [5.3%]; P = .005.
Rune V. Overgaard (Allie)	**September 3rd, 2023**	**Clinical Trial, Cross-Over**	**Results- comparison of two clinical trials (pioneer vs sustain)** The PIONEER study concluded of the 703 patients given once a day oral 3, 7 or 14 mg semaglutide with a mean HbA1c of 8.0% in the 26 week trial, reductions of -0.6% (3 mg), -0.9% (7 mg), and -1.1 (14mg) and body weight reductions of -0.1 kg (3mg), -0.9 kg (7 mg), and -2.3 kg (14 mg) were seen.
Ares-Blanco J (Allie)	**July 8th, 2022**	**Retrospective, open-label (not blinded) clinical trial**	**Results: significant loss of weight, HbA1C and insulin with injection** Results showed a significant drop of HbA1c of 0.74%,a weight reduction of 3.61 kg and total insulin use per injection 15.88 IU (all values had a 95% CI with $p<0.05$) from baseline measurements.
Anders Strathe (Allie)	**July 9th 2023**	**Exposure/Response-Case control study**	**Results:** A total of 3818 participants were include, of those having a mean BMI of 37.5 kg/m2. The key finding was a correlation between weight loss and overweight/obese participants receiving a weekly injection of 2.4 mg of

			Semaglutide.
John P.H. Wilding (Athena)	**March 18, 2021**	**Randomized, double-blind, placebo-controlled trial**	In a study, overweight or obese participants were given either 2.4mg of Semaglutide weekly or a placebo. The Semaglutide group experienced significant weight loss, averaging 14.9% compared to 2.4% in the placebo group. The treatment also improved heart and metabolic health, as well as physical functioning. However, some participants discontinued treatment due to gastrointestinal side effects.
Domenica Rubino (Athena)	**April 13, 2021**	**Randomized clinical trial**	In a study with 803 overweight or obese participants (79% women, average age 46, initial weight 107.2kg), Semaglutide was administered for 20 weeks, resulting in an average weight loss of 10.6%. After 20 weeks, participants were either continued on Semaglutide or switched to a placebo for 48 weeks. Those who stayed on Semaglutide experienced an additional 7.9% weight loss, while those on the placebo gained 6.9%. Continuation with Semaglutide also showed improvements in waist circumference, blood pressure, and physical functioning, with higher rates of gastrointestinal issues (49.1%) compared to the placebo group (26.1%). Discontinuation rates due to adverse effects were similar. Overall, the study concluded that ongoing Semaglutide treatment leads to sustained weight loss over 48 weeks compared to switching to a placebo.
W Timothy Garvey (Athena)	**October 2022**	**Randomized controlled trial**	A study compared Semaglutide 2.4mg to a placebo in overweight or obese participants. The Semaglutide group (n=152)

			showed a significant mean weight loss of 15.2% from baseline to week 104, while the placebo group (n=152) lost only 2.6%. The estimated difference was 12.6%, with a higher proportion of Semaglutide participants achieving ≥5% weight loss compared to the placebo group (77.1% vs. 34.4%). Semaglutide also led to additional health benefits, including reduced waist circumference, blood pressure, and improvements in glycated hemoglobin, fasting plasma glucose, and total cholesterol. Overall, Semaglutide resulted in substantial and sustained weight loss and health improvements over the 104-week study period compared to the placebo group.
D. Weghuber (Alexia)	**December 15th, 2022**	**Double-blind, parallel-group, randomized, placebo-controlled trial**	**Outcome/Results** The adolescents who receive the once weekly Semaglutide injection have an average weight loss of 16.1% while the placebo group had an average weight loss of 0.6% (95% confidence interval [CI], -20.3 to -13.2; P<0.001). They also demonstrated improved cardiovascular and metabolic factors. At the conclusion of the trial, adolescents who received the weekly injection lost 5% of their body weight compared to the placebo group (odds ratio, 14.0; 95% CI, 6.3 to 31.0; P<0.001).
K. Kaku (Alexia)	**January 8th, 2018**	**Phase III, open label clinical trial**	**Outcome/Result** In total, an HbA1c concentration less than 7.0% was reached in over 80% of participants in the injection groups. Additionally, with the drastic reduction in HbA1c in these participants, those who took part in the Semaglutide

			injection groups resulted in a weight loss of >5% in the 0.5mg injection group and >10% in the 1.0mg injection group as compared to the OAD group.
I. Ikushima (Alexia)	**March 13th, 2018**	**Randomized control trial**	**Outcome/Results** The 0.5mg Semaglutide group and 1.0mg Semaglutide group for Japanese men had a p>0.05 and both groups for Caucasian men had the same effect as compared to the placebo groups. The average weight decreased by 1.4kg in the 0.5mg Semaglutide injection group and 5.0kg in the 1.0mg Semaglutide injection group in Japanese men where the placebo group had a 1.1kg increase. In Caucasian men, average weight decreased by 3.6kg in the 0.5mg Semaglutide injection group and 7.5kg in the 1.0mg Semaglutide injection group respectively as compared to a 0.7kg increase in the placebo group.
Melanie Davies (Tarrone)	**March 13, 2021**	**Randomized, Double Blind, Phase 3 Clinical Trial**	**Outcome/Results** In a STEP 2 clinical study, Semaglutide 2.4 mg injected once weekly demonstrated a notable reduction in body weight among overweight and obese patients with Type 2 diabetes compared to a placebo. At the 68-week endpoint, the mean bodyweight change from baseline was -9.6% with Semaglutide 2.4 mg, while it was -3.4% with placebo. Overall, A higher percentage of patients (68.8%) treated with Semaglutide 2.4 mg achieved at least a 5% weight reduction compared to the placebo group (28.5%).
Enrico Carmina (Tarrone)	**September 12, 2023**	**Open Label Clinical Trial**	**Outcome/Results** Patients diagnosed with PCOS,

			who did not achieve weight loss through a lifestyle modification program, were treated with a weekly dose of 0.5mg SQ Semaglutide. The three-month trial yielded significant improvements, with approximately 80% of participants experiencing a weight loss of at least 5%. Overall, the average weight loss was 11.5 kg, mean BMI decreased from 34.4 to 29.4, and 80% of responsive patients normalized their menstrual cycles, all with minimal side effects.
Julie B Hjerpsted Anne Flint (Tarrone)	**March 20, 2018**	**Randomized, double-blind, placebo-controlled, 2-period, Crossover trial**	In obese adults, weekly injections of 1 mg SQ Semaglutide improved fasting and postprandial glucose levels, as well as lipid metabolism, compared to a placebo. Overall,gastric emptying did not differ significantly from the placebo. The study suggests that the one-hour postprandial gastric delay might contribute to the slower entry of glucose into circulation and lower postprandial glucose concentrations with Semaglutide.
Johan Jendle (Princess)	**July 12th, 2019**	**Randomized Control Trial**	**Results/Conc:** Improvement was more pronounced in individuals attaining weight loss and glycaemic goals, with Semaglutide 1.0 mg showing superior outcomes in these categories.
Thomas A Wadden (Princess)	**February 24th, 2021**	**Randomized Control Trial**	At the end of the 68 weeks, the Semaglutide group showed a mean weight reduction of 16.0% from baseline, compared to a 5.7% reduction in the placebo group. This marked a significant difference of 10.3 percentage points. Additionally, a

			substantially higher percentage of the Semaglutide group achieved weight loss of at least 5%, 10%, and 15% compared to the placebo group.
Jamy Ard (Princess)	**May 11th, 2021**	**Randomized Control Trial**	This study explores the effectiveness of weekly-administered Semaglutide, a glucagon-like peptide-1 receptor agonist, in enhancing treatment satisfaction among participants in the SUSTAIN clinical trials. Using the Diabetes Treatment Satisfaction Questionnaire, the research assessed patient perspectives on treatment efficacy, with a focus on hyperglycemia and hypoglycemia. Overall, In conclusion, Semaglutide is associated with greater improvements in treatment satisfaction, particularly among patients meeting specific treatment goals.
Bo Ahrén (Roman)	**June 12th, 2018**	**Clinical Trial, Cross-Over**	The study found that weight loss varied significantly across different BMI subgroups, with higher initial BMI levels showing greater absolute weight reduction. Overall, Semaglutide consistently led to more significant weight loss across multiple trials, regardless of participants' initial BMI, and the impact of nausea or vomiting on this weight reduction was minimal.
Sean Wharton (Roman)	**January 18th, 2023**	**Clinical Trial, Cross-Over**	In a study comparing Semaglutide and placebo groups, participants receiving Semaglutide showed a substantial -14.8% reduction in body weight compared to the placebo group's -2.4%. Overall, Semaglutide 2.4 mg demonstrated effective regulation of eating habits and significant weight reduction in adults with

			overweight/obesity over both short and extended durations.
Mikhail N Kosiborod (Roman)	**September, 21st 2023**	**Clinical Trial, Cross-Over**	In a study involving individuals with heart failure and preserved ejection fraction combined with obesity, treatment with Semaglutide (2.4 mg) demonstrated notable improvements over a placebo. Overall, Semaglutide demonstrated superior efficacy in alleviating symptoms, improving exercise function, and inducing weight loss in this specific patient population.