Long-Term Control of Type II Diabetes Mellitus and Weight Through Roux-En-Y Gastric Bypass Surgery versus Weight Loss Medication

by

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Abstract

Type II diabetes mellitus (T2DM) affects hundreds of millions of individuals in the United States and is only becoming more common. The disease can damage organs all throughout the body and even lead to death. The goal of treatment is to lower blood glucose, but since T2DM tends to be associated with obesity, another common goal in treatment is weight loss. However, this is difficult for many people to achieve, and intense medical treatment is sometimes needed. Since T2DM is a lifelong disease, interventions must be considered in the long term. The purpose of this project is to compare long-term efficacy of Roux-en-Y gastric bypass surgery and several antidiabetic medications that result in weight loss in type II diabetics who have failed to achieve goals through first line treatment of diet, exercise, and metformin. A literature review was completed using the electronic search database PubMed using a variety of MeSH terms and keywords which yielded 2,954 results. Filters and other criteria further narrowed down the search to 16 studies selected for review. Research showed strong evidence that surgery was superior to medications in reducing HbA_{1C} and weight. However, it is not a viable option for many individuals. The antidiabetic medications studied were also shown to decrease HbA_{1C} and weight superiorly to placebos and other classes of antidiabetic medications. However, research must be continued to study these medications over a longer interval as the medications remain on the market for a longer period of time. Studies that directly compare antidiabetic medications that result in weight loss to determine whether one is superior to others in the long term are also needed.

Keywords: diabetes mellitus type II, long term, gastric bypass, weight loss medication

Introduction

Diabetes mellitus is a metabolic disorder that was described as early as the year 1500 BCE by the ancient Egyptians, who described frequent urination and weight loss in those afflicted. It was named for the sweet tasting urine of those afflicted by the disease by a Greek physician named Aretaeus sometime between the years 80 and 138 CE. However, little was known about the pathogenesis or treatment of diabetes mellitus for thousands of years, and until the discovery of insulin in 1923, it was typically fatal within months of the onset of disease (Polonsky, 2012).

When a person eats, food is typically broken down into glucose which enters the blood stream. Insulin, which is made by the beta islets of the pancreas, is released in response to raised blood glucose, and it initiates a chain of reactions that delivers glucose into cells to provide energy necessary for cellular functions. In those with diabetes mellitus, insulin either does not function properly, or is not secreted at all. As a result, glucose is unable to enter cells properly and instead builds up in the blood, where the kidneys eventually filter out excess blood glucose and excrete it through the urine. The excess glucose in the blood leads to damage throughout many organs of the body, most notably the kidneys, eyes, nerves, heart, and blood vessels (Galicia-Garcia et al., 2020).

In 1936, it was first proposed that there are two different forms of the disease: insulin deficiency and insulin resistance (Polonsky, 2012). The insulin deficiency form is likely what the ancient Egyptians and Greeks described, and it is now known as type I diabetes mellitus. It is an autoimmune disorder that leads to destruction of pancreatic beta cells that results in the inability to produce insulin. These patients require lifelong treatment with insulin. The insulin resistant form is now known as type II diabetes mellitus (T2DM). Due to a multitude of factors including

age, genetics, and lifestyle, tissues such as the liver and muscle lose their ability to respond properly to insulin. This is called insulin resistance, and the pancreatic beta cells begin to produce less insulin, and over time, glucose begins to build up in the blood stream.

Patients with T2DM are commonly characterized as overweight or obese, and it is believed that adipose tissue creates inflammatory mechanisms that lead to insulin resistance. As the world has seen a rise in high calorie diets, sedentary lifestyles, and rates of obesity, incidence and prevalence of T2DM has risen dramatically. T2DM now accounts for approximately 90% of the cases of diabetes (Galicia-Garcia et al., 2020). The International Diabetes Federation reported that T2DM resulted in 4.2 million deaths in 2019 and estimated that 463 million adults between the ages of 20 and 79 live with T2DM. That number is expected to grow to 700 million by the year 2045 (Galicia-Garcia et al., 2020). While those numbers are staggering, there are a variety of treatment options for T2DM, and it is possible for the disease to be completely reversed or at least significantly improved. The standard initial treatment for T2DM is to encourage lifestyle changes such as exercise and nutritional alterations that will lead to weight loss because loss of adipose tissue improves insulin sensitivity and can help to prolong beta cell function. A medication called metformin helps to inhibit hepatic glucose function, reduce intestinal glucose absorption, and increase insulin sensitivity through increased peripheral glucose uptake. Metformin is started in conjunction with lifestyle changes for nearly all patients who are diagnosed with T2DM.

While weight loss through diet and exercise is important in managing or treating T2DM, it is extremely difficult to achieve for most people. That plus the use of metformin is often not enough to control T2DM, and other options must be considered. There are several other classes of medications that can be used to lower blood glucose, and many antidiabetic medications that

have entered the market recently have also been shown to result in weight loss. Bariatric surgery in obese individuals has also been shown to serve as an incredibly useful tool in the treatment of T2DM (Koliaki et al., 2017).

T2DM diagnosis and monitoring is often done through a blood test called glycated hemoglobin (HbA_{1C}) which measures the amount of glucose that is bound to a hemoglobin molecule. Increased glucose in the blood leads to a higher amount of glucose that is bound to a hemoglobin molecule. Hemoglobin molecules are a component of red blood cells which have a lifespan of two to three months, so the HbA_{1C} lab test gives a picture of the average blood glucose over that two-to-three-month period and serves as a good objective measurement of glycemic control. For this reason, HbA_{1C} is used as a measurement for control of T2DM in this project.

Statement of the Problem

While there are studies proving the efficacy of the available medications and Roux-en-Y gastric bypass surgery (RYGB), the majority of studies are done over a condensed period of time. T2DM is typically a lifelong disease so it is important to think about the long-term efficacy of a treatment during clinical decision making. It is not uncommon for patients to regain the weight they lost in the years following RYGB. A 10-year study noted that 41% of post-RYGB patients regained more than 15% of their lowest post-operative weight, with youngest patients being at highest risk of weight regain, which raises the question of what happens to diabetic control following the weight regain (Monaco-Ferreira & Leandro-Merhi, 2017). Additionally, there is no clear picture of whether one medication approved for diabetes control and weight loss is superior to another, so studying the long-term efficacy of options available is important to assist with guidance in clinical selection.

Research Question

In patients with type 2 diabetes mellitus who have failed to achieve blood glucose control through diet, exercise, and metformin, does Roux-en-Y gastric bypass surgery or addition of weight loss medication improve long-term HbA_{1C} more effectively?

Research Methods

A literature review was completed using articles from the electronic search database PubMed. The search was completed using the MeSH terms "glycated hemoglobin" and "diabetes mellitus, type 2," and keywords "long term," "gastric bypass," or "weight loss medication." This yielded 2,954 results. The filters "clinical trial," "randomized controlled trial," and "in the last five years" were applied, reducing the search results to 302. Articles were also found in the "similar articles" feature in PubMed and in a meta-analysis that was not used in this project. Articles were examined and selected based on relevance to the research question. Studies using participants with uncontrolled T2DM at baseline were selected under the assumption that uncontrolled meant diet, exercise, and metformin, the first line treatments of T2DM, had failed. Only articles that studied Roux-en-Y gastric bypass or FDA approved medications for weight loss and/or diabetes treatment were selected. Studies under 52 weeks in length were excluded to fulfill the long-term aspect of the research question, excluding many of the search results. Studies that did not measure HbA_{1C} as an outcome were also excluded as this did not fit the research question. Finally, studies that used participants under 18 years of age, participants with type 1 diabetes mellitus, or were not written in English were excluded. Sixteen studies met the final criteria.

Literature Review

Long-term HbA1C in patients who had Roux-en-Y gastric bypass surgery

Schauer et al. (2017) set out to study long-term results of bariatric surgery in patients with T2DM, with a primary goal of determining whether they could achieve an HbA_{1C} of 6% or lower after 5 years. This was a randomized, controlled, nonblinded study of 134 obese patients who had T2DM. Demographically, 66% of the participants were women, the mean (SD) age was 49 (8) years; the average body mass index (BMI) was 37 (3.5), and the initial mean HbA_{1C} was 9.2 (1.5) %. The participants were randomly assigned (1:1:1) to one of three interventions: Roux-en-Y gastric bypass (RYGB) (n = 49), sleeve gastrectomy (n = 47), and a control group of intensive medical therapy alone (n = 38). Each member of the medical therapy group was prescribed medications based on their individual needs; the medication types were not specified in the article. The article did not break down the demographics of each group. In the RYGB group, 28.6% of patients were able to achieve the goal of an HbA_{1C} of 6% or below, making this group significantly more likely to achieve the goal than those on medical therapy alone (p = 0.03). While 23.4% of patients who received sleeve gastrectomy achieved the goal HbA_{1C} of 6% or below, they were not statistically significantly more likely to achieve the goal than the medical therapy group (p = 0.07). A secondary finding of the study is that HbA_{1C} was significantly lowered in both surgical groups after 5 years compared to the medical therapy only group, with those in the RYGB group lowering HbA_{1C} by 2.1 (1.8) % (p = 0.003) and the sleeve gastrectomy group by 2.1 (2.3) % (p = 0.003). The study also found that at the end of the 5 year period, RYGB and sleeve gastrotomy significantly reduced body weight; RYGB by -23.2 (9.6) kg and sleeve gastronomy by -18.6 (7.5) kg compared to -5.3 (- 10.8) kg in the medical therapy group (p = 0.003; p = 0.003, respectively), as well as triglycerides (p = 0.03; 0.04 respectively), and

increased HDL cholesterol ($p = 0.012$; $p = 0.016$ respectively) and quality of life (assessed by a 36-item health survey) ($P < 0.05$ for both) compared to medical therapy alone. This study showed that Roux-en-Y gastric bypass significantly improved control of HbA_{1C} compared to intense medical therapy alone in type two diabetics over a period of 5 years. In the future, similar studies with a larger population and longer duration would be beneficial to continue studying the long-term effects of bariatric surgery. Strengths of this study include that it was randomized and controlled, and most variables were measured objectively. A weakness is that this study could not monitor for adherence to medications, nor account for factors that could cause the participants to be unable to adhere to the medical therapy, such as cost, side effects, or other barriers.

Almby et al. (2021) aimed to observe long-term metabolic and neuroendocrine changes after RYGB. This study is a follow-up of a single center, randomized, non-blinded study. In the initial study, patients were randomly placed into a control group ($n = 6$) where they continued usual care, or a RYGB surgery group ($n = 13$). The RYGB group consisted of 10 females and 3 males with a mean age of 51 years at the start of the study; other demographics such as race/ethnicity were not published. After 24 weeks of follow-up, the usual care group could elect to receive RYGB, which many did. This study measured the RYGB group 104 weeks after the procedure and compared them to a control group of nondiabetic, healthy individuals ($n = 22$) who were matched to the post-RYGB patients for age, sex, and BMI. The formal primary endpoint of the study was a change of HbA_{1C} by more than 1% following the surgery. Body weight and many other inflammatory and hormonal markers were also studied. At 104 weeks, the average (SD) HbA_{1C} of 6.0 (0.4) % was significantly lower in patients post RYGB compared to the mean baseline of 7.2 (1.1) % ($p < 0.001$), and 9 of the subjects were able to discontinue

their antidiabetic treatment. However, HbA_{1C} was still significantly higher than the average HbA_{1C} of 5.4 (0.3) % in the control group of nondiabetic subjects ($p < 0.001$). The average body weight of 76.9 (10.1) kg and body fat percent of 33.7 (9.3) % were significantly lower than baseline averages of 99.8 (13.7) kg and 42.8 (7.5) %, respectively, at the 104-week mark ($p < 0.001$, 0.001, respectively), and were not significantly different than the control group of nondiabetic subjects, which averaged 81.2 (11.2) kg and 31.8 (6.6) %, respectively. Morning serum insulin was found to be significantly reduced compared to baseline, lowering from approximately 30 to 10 mU/L over the 104-week period ($p < 0.001$). Overall, this study showed that 2 years after RYGB surgery, participants had substantial reductions in body fat, inflammation, and HbA_{1C} levels; however, hyperglycemia was still slightly increased compared to the nondiabetic control group. While this study was interesting, there were several weaknesses. Most notably, the n value was very low; a study with a larger group of participants would be helpful to corroborate the findings of this study. Additionally, there was a large difference in the number of males versus females in this study, and there was no mention of consideration of race/ethnicity in the groupings which would help identify which subpopulations this information is helpful for. While two years is a longer time-period than many studies, the same study over an even longer period would give better long-term results. Finally, following the control group of the initial participants who continued usual diabetic treatment probably would have been more helpful than comparing the patients to only a nondiabetic control group after the 104 weeks.

Mingrone et al. (2021) studied 10-year outcomes of metabolic surgery in comparison to medical therapy and lifestyle interventions for the treatment of advanced T2DM. This prospective, open label, randomized controlled trial's primary endpoint was diabetes remission,

defined as an HbA1C of < 6.5% and fasting glycemia of < 100 mg/dL without ongoing medication for at least one year, at 2 years. Sixty participants were randomly assigned (1:1:1) to receive RYGB (n = 20), biliopancreatic diversion (BPD) (n = 20), or medical therapy (n = 20). The average age (SD) was 43.9 (7.6), 43.6 (8.2) and 43.5 (7.3) years; average weight was 128.7 (11.4) kg, 128.0 (10.0), and 137.0 (16.5) kg; mean baseline HbA_{1C} was 8.6 (1.4) %, 8.9 (1.7) %, and 8.5 (1.2) %; male gender made up 40%, 50%, and 50% in the respective groups. The medication and lifestyle treatments were individualized for each patient by a team of diabetologists, dieticians, and nurses; with a target of achieving weight loss and blood glucose control through decreased energy and fat intake and increased physical activity; drugs included oral antihyperglycemic agents, insulin, GLP-1 analogues, and SGLT2 inhibitors. The study found that 10 participants who received BPD and 5 who received RYGB maintained remission throughout the 10-year period, while no patients who received medical therapy where able to do so; there was no statistically significant difference in achievement rates between the two surgical groups (p = 0.19). There were also several secondary outcomes measured. The mean HbA_{1C} after 10 years was reduced significantly in the metabolic surgery groups compared to medical therapy; the BPD group changed by -2.4 (1.6) % (estimated treatment difference [ETD] -1.6 95% [confidence interval (CI) -2.8, -0.4]; p < 0.0001); the RYGB group by -1.9 (1.6) % (ETD -1.0 [CI -2.2, 0.2]; p = 0.0097), and medical therapy by -0.8 (1.0) %. Significantly more weight was lost in the metabolic surgery groups compared to medical therapy, with 42.2 (21.5) kg lost in BPD (ETD -35.7 [CI -49.7, -21.6]; p < 0.0001), 37.3 (14.5) kg lost in RYGB (ETD -11.4 [CI -21.9, -1]; p < 0.0001), and 6.5 (12.9) kg lost in medical therapy groups. The total number of diabetes medication requirements was also significantly different between the metabolic surgery groups and medical therapy group; patients who received BPD surgery used 73.3 (36.4) % less

medication (ETD -91.1 [CI -129.7, -52.5]; $p < 0.001$), RYGB used 27.5 (61.2) % less medications (ETD -45.3 [CI -83.9, -6.7]; $p < 0.001$), and the medical therapy group required 17.8 (35.3) % more antidiabetic medication. The metabolic surgery groups also had a significantly lower incidence of diabetes-related complications that the medical therapy groups; each metabolic surgery group had one patient with a diabetes-related complication, while the medical therapy group had 13. Members of the BPD group experienced more serious adverse events compared to the medical therapy group (estimated odds ratio [EOR] 2.7 [CI 1.3-5.6]), while members of the medical therapy group had a higher incidence of serious adverse events than the RYGB group (EOR 0.7 [CI 0.3-1.9]). The results of this study showed that in the long-term control of T2DM, metabolic surgery is more effective than medical and lifestyle interventions as significantly more patients in the surgery groups achieved T2DM remission, lowered HbA_{1C} concentration, and had fewer diabetes-related complications, among other factors. Interestingly, weight changes did not predict diabetes remission or relapse following the surgery. Additionally, none of the patients who did not go into remission after the first two years post-surgery went into remission during the ten-year period. The highest risk of diabetes relapse appears to be within five years of the surgery; the risk declines significantly afterward. This study had several weaknesses including a relatively low n-value and the fact that it had to be open-label as it is impossible to mask who received the procedures and who received medical therapy; the type of procedure also had to be disclosed to patients to accurately inform them of risks and benefits of the surgeries. There were also strengths of this study; they were able to maintain a high follow-up rate over the long 10-year period this trial was carried out over. According to the article, the long-term results of the medical therapy in this are consistent with larger trials.

Long-term HbA1C in patients taking semaglutide

In a 52-week clinical trial, oral semaglutide, a glucagon-like peptide 1 receptor agonist (GLP-1RA) medication, was found to reduce HbA_{1C} and body weight compared to other common anti-diabetic medications. In an extension of that trial, Buse et al. (2020) aimed to evaluate the long-term efficacy and safety of oral semaglutide with flexible dose adjustment after 104 weeks of treatment, and to study the safety and efficacy of switching from sitagliptin to oral semaglutide compared with continuing use of sitagliptin, a common dipeptidyl peptidase-4 (DPP-4) inhibitor medication. This was a prospective, open-label, randomized trial. Participants who had been randomized to receive oral semaglutide in the initial trial continued the same regimen (n = 253); average age of this group was 57 (10) years, 42.7% of patients were female, 77% white, 9% black, 13% Asian, and 1% other. Average baseline HbA_{1C} was 8.3 (0.6) % and average baseline body weight was 88.9 (19.6) kg. The remaining participants from the initial study were randomly selected to switch from sitagliptin to oral semaglutide therapy (switch group) (n = 100) or continue use of sitagliptin 100 mg (n = 98). In the switch group, the average age was 58 (10) years, 43% were female, 77% white, 6% black, and 17% Asian; the mean baseline HbA_{1C} was 7.4 (1.0) %, and bodyweight was 85.8 (15.4) kg. The sitagliptin group's average age was 58 (10) years, 43.9% were female, 73% white, 10% black, and 17% Asian; average baseline HbA_{1C} was 7.5 (0.9) % and body weight 86.9 (20.4) kg. Oral semaglutide dose was available at 3, 7, and 14 mg doses. It was started at 3 mg and adjusted every 8 weeks based on HbA_{1C} ($< 7\%$, dose was unchanged and $\geq 7\%$, dose increased) and adverse effects. As this was an extended clinical trial, there was no primary endpoint, but secondary endpoints included changes in HbA_{1C} and body weight. The study found that after 104 weeks of oral semaglutide treatment, HbA_{1C} was lowered by 1.3 (1.0) %, and body weight was reduced by 3.7 (5.2) kg. The

patient group who remained on sitagliptin during the extension period maintained HbA_{1C} through the extension phase; between weeks 52 and 104, HbA_{1C} increased by 0.1%, while the switch group saw a decrease of 0.3% between weeks in that time. This difference did not show oral semaglutide to be superior to sitagliptin (p=0.0791). However, when use of rescue medication (insulin) was corrected for in statistical analysis, oral semaglutide decreased HbA_{1C} by 0.4% versus an increase of 0.2%; this difference was found to be significant (p=0.0021). Loss of body weight was also significantly increased in the switch group when accounting for use of rescue medication, with a loss of 2.9 kg versus the average 1.0 kg lost in the sitagliptin group (p=0.0176). More patients complained of adverse effects on oral semaglutide compared to those on sitagliptin, and six patients in the switch group prematurely discontinued the study. The most common complaints were nausea, diarrhea, and vomiting. Only one participant in the 104-week semaglutide treatment group discontinued treatment during the extension trial, however, 9.1% of patients taking oral semaglutide in the initial trial discontinued prematurely due to gastrointestinal (GI) side effects. Discontinuation correlated with the dose escalation every eight weeks. This trial showed that continued use of oral semaglutide with flexible dosing over two years continued to improve HbA_{1C} goals and further success in weight loss. It remained well tolerated, with most discontinuation of the medication due to adverse effects occurring before 52 weeks of using the medication. After an initial increase, oral semaglutide decreased patients' HbA_{1C} to levels lower than sitagliptin. While this was not significant in the raw data, it was significant when rescue insulin was accounted for during analysis, indicating that there may have been greater rescue insulin use in the sitagliptin group. Oral semaglutide also resulted in increased weight loss compared to sitagliptin. Adverse reactions of the group switching to oral semaglutide were similar to those observed in the patients taking oral semaglutide in the initial

trial. Strengths of this study include a flexible dosing strategy which makes this information relevant to clinical practice, high treatment completion, it was performed in a variety of countries on individuals of multiple races, and the fact that this was a longer-term study. Weaknesses include that it was an open-label study, a relatively low N value of the patients in the sitagliptin and switch to oral semaglutide groups, and this article has high potential to be biased as the funder of the study was heavily involved in development of the journal article, from the designing of the study to the writing of the report.

Rosenstock et al. (2021) set out to assess the efficacy of oral semaglutide at 3, 7, or 14 mg doses compared with sitagliptin in addition to metformin with or without sulfonylurea in patients with uncontrolled T2DM. This was a prospective, randomized, double-blind, double-dummy study. The primary endpoint of the study was a change in HbA_{1C} after 26 weeks of medication use, and the confirmatory secondary endpoint was a change in body weight at that time. Additional secondary endpoints included change in HbA_{1C} and weight at 52 and 78 weeks. Patients were randomized (1:1:1:1) to oral semaglutide at 3 (n = 466), 7 (n = 466), or 14 (n = 465) mg doses or sitagliptin 100 mg/d (n = 467) groups. Groups were parallel for country of origin, demographics, and background medication (metformin ± sulfonylurea). Participants continued to receive background metformin with or without sulfonylurea at a stable dose throughout this trial. 52.8% of participants were male, 71.1% were white, the mean age was 58 years, average HbA_{1C} was 8.3% and mean body weight was 92.2 kg. At the primary endpoint of 26 weeks, HBA_{1C} was decreased by 0.6%, 1.0%, and 1.3% for 3, 7, and 14 mg/d oral semaglutide, respectively, and 0.8% for sitagliptin. The 7 and 14 mg/d semaglutide resulted in significantly decreased HbA_{1C} compared to sitagliptin (ETD -0.3 [CI -0.4, -0.1] $p < 0.001$, ETD -0.5 [CI -0.6, -0.4] $p < 0.001$, respectively). The 3 mg/d did not achieve a lower HbA_{1C} compared

to sitagliptin, however, it was not statistically demonstrated to be inferior to sitagliptin treatment (ETD 0.2 [CI 0.0, 0.3]; p = 0.09). Weight change at week 26 was -1.2 kg, -2.2 kg, and -3.1 kg for semaglutide 3, 7, and 14 mg/d, and -0.6 kg for sitagliptin. Doses of 7 and 14 mg/d oral semaglutide significantly increased weight loss compared to sitagliptin (ETD -1.6 [CI -2.0, -1.1] p < 0.001; ETD -2.5 [CI -3.0, -2.0] p < 0.001, respectively). Superiority with respect to weight loss at the 3 mg/d dose of oral semaglutide versus sitagliptin was not tested because of the noninferiority finding in respect to HbA_{1C}. At week 78, HbA_{1C} reductions were 0.6, 0.8, 1.2, and 0.8% for 3, 7, and 14 mg/d semaglutide and sitagliptin, respectively. The 14 mg/d semaglutide significantly decreased HbA_{1C} compared to sitagliptin (ETD -0.4 [CI -0.6, -0.3]; p < 0.001). The 7 mg/d dose significantly deceased HbA_{1C} compared to sitagliptin only when uses of rescue medication (insulin) or trial product discontinuation was accounted for through statistical analysis (ETD -0.3 [CI -0.4, -0.1] p < 0.001). Average weight loss was 1.8, 2.7, 3.1, and 1.0 kg in 3, 7, and 14 mg oral semaglutide, and sitagliptin, respectively. Weight loss was significantly greater with all 3, 7, and 14 mg/d doses of semaglutide compared to sitagliptin (ETD -0.8 [CI -1.5, -0.1] p = 0.02; ETD -1.7 [CI -2.3, -1.0] p < 0.001; ETD -2.1 [CI -2.8, -1.5] p < 0.001, respectively). Adverse effects were most frequently reported in the 14 mg semaglutide group, with the most common complaints being related to GI symptoms, especially nausea. Most adverse effects were mild or moderate in severity; proportions of serious adverse effects during treatment were similar across all treatments. GI related adverse events were the most common reason for discontinuation of treatment in all groups, and in the 7 and 14 mg semaglutide groups, the adverse effects correlated with the dosage-escalation period. This paper showed that addition of 7 and 14 mg/d semaglutide to metformin with or without sulfonylurea showed increased reductions of HbA_{1C} and weight loss at 26 weeks and 72 weeks compared to sitagliptin and is

associated with less use of rescue insulin in the control of T2DM. It also showed that 3 mg/d semaglutide results in more weight loss than sitagliptin at both time periods and was noninferior to sitagliptin. Side effects were more common in semaglutide, especially at the 14 mg/d dose, with the most commonly observed ones including nausea, vomiting, or diarrhea. Strengths of this trial included a double-blind design with a double-dummy approach to ensure comparison of products was unbiased. This study also had a larger n value and a high retention rate. The authors of this study considered the length to be a strength, though future studies that extend over an even longer period would be beneficial. Other weaknesses include that adherence to treatment was not formally measured, which could have affected results. Additionally, while DPP-4 inhibitors were widely used at the start of the study because they are usually well-tolerated, they have modest glucose-lowering effects and minimal effect on body weight compared to other medications available, so the two may not be the most comparable. One final weakness is that Novo Nordisk, the funder of the study and the pharmaceutical company that produces the brand name of forms semaglutide, was heavily involved in the study including analysis, interpretation, and review of the manuscript which could cause the findings to be biased.

Zinman et al. (2019) aimed to study the efficacy and safety of oral semaglutide in addition to insulin with or without metformin. This was a prospective, randomized, double-blind trial that observed a 52-week treatment period. Patients were randomly placed into groups that received 3 (n = 184), 7 (n = 182), or 14 (n = 182) mg oral semaglutide, or a placebo pill (n = 184); randomization was stratified based on country of origin, background treatment, and other demographic factors to make parallel groups. Overall demographics were 54.0% male gender, 51.4% white, 36.0% Asian, and 6.7% black, mean age of 61 years, mean baseline HbA_{1C} of 8.2%, and mean body weight of 85.9 kg. Background metformin was used by 67.2% of patients.

At the start of the trial participants were instructed to reduce total daily insulin dosage by 20% for eight weeks; in weeks 8-26, insulin could be altered so long as it didn't exceed the pre-randomization dosage, and in weeks 26-52, daily insulin was freely adjustable based on the investigator's discretion. Insulin dosage could be reduced as needed at any time throughout the trial. Glucose-lowering rescue medication was available to patients who had a fasting plasma glucose of 200 mg/dL or above from week 16 onward or and/or an HbA_{1C} > 8.5% from week 26 and on. Primary endpoint and confirmatory secondary endpoints were a change in HbA_{1C} and body weight at week 26, and supportive secondary endpoints included changes from baseline in HbA_{1C} and body weight at week 52. At the primary endpoint of 26 weeks, change from baseline HbA_{1C} was significantly greater at all three doses of oral semaglutide compared to the placebo, with a mean change of -0.6% (ETD -0.5 [CI -0.7, -0.3]; p < 0.0001), -0.9% (ETD -0.9 [CI -1.1, -0.7]; p < 0.0001), -1.3% (ETD – 1.2 [CI -1.4, -1.0]; p < 0.0001), and -0.1% for 3, 7, and 14 mg semaglutide and placebo, respectively. Body weight changes on oral semaglutide at 26 weeks was also significantly greater compared to the placebo, with a change in body weight of -1.4 kg (ETD -0.9 [CI -1.8, 0.0]; p = 0.0392), -2.4 kg (ETD -2.0 [CI -3.0, -1.0]; p = 0.0001), -3.7 kg (ETD -3.3 [CI -4.2, -2.3]; p < 0.0001), and -0.4 kg for 3, 7, and 14 mg semaglutide and placebo, respectively. At week 52, change in mean HbA_{1C} from baseline was still significantly increased compared to the placebo, with changes including -0.6% (ETD -0.4 [CI -0.6, -0.2]; p = 0.0004), -0.8% (ETD -0.6 [CI -0.8, -0.4]; p < 0.0001), -1.2% (ETD -0.9 [CI -1.1, -0.7]; p < 0.0001), and -0.2% for 3, 7, and 14 mg semaglutide and placebo, respectively. Weight loss was also significantly higher at week 52 on all three doses of semaglutide compared to placebo, with body weight changes of -0.8 kg (ETD -1.3 [CI -2.4, -0.3]; p = 0.0101), -2.0 kg (ETD -2.5 [CI -3.6, -1.4]; p < 0.0001), -3.7 kg (ETD -4.3 [CI -5.3, -3.2]; p < 0.0001), and 0.5 kg in the 3, 7, and 14

mg semaglutide and placebo, respectively. Number of adverse effects was similar in all 4 treatment groups, with 74.5%, 78.5%, 83.4%, and 75.5% of patients in the 3, 7, and 14 mg semaglutide and placebo groups, respectively, experiencing any side effects, and 13.6%, 10.5%, 6.6%, and 9.2% of patients in the 3, 7, and 14 mg semaglutide and placebo, respectively, experiencing serious adverse effects. Most common adverse effects were gastrointestinal symptoms in the 7 and 14 mg semaglutide groups, while infection and infestations were more common in the 3 mg semaglutide and placebo groups. This trial showed that after 52 weeks, 3, 7, and 14 mg oral semaglutide significantly reduced HbA_{1C} and body weight at dose-dependent rate compared to placebo in patients with T2DM inadequately controlled with insulin with or without metformin. 52.4% of patients on semaglutide were able to achieve a HbA_{1C} of < 7%, which means that over the course of the study, their T2DM was considered well-controlled. Strengths of this study included a placebo-controlled and double-blind design, parallel patient populations between groups, and a relevantly diverse patient population. Weaknesses include a fairly low n-value, and another possible conflict of interest as this study was also funded by Novo Nordisk who was again involved in the trial.

Visaria et al. (2021) conducted a retrospective study to examine the association between the use of the injectable once weekly (OW) semaglutide and changes in HbA_{1C} levels using real world data over an extended period. The data was sourced using medical and pharmacy administrative claims data and clinical laboratory test results from the HealthCore Integrated Research environment; no patient identifiers were included in this data, to comply with the Health Insurance Portability and Accountability Act (HIPAA). Everyone who qualified for this study was considered the intention-to-treat (ITT) group (n = 1888). A subgroup of the ITT group called the persistent population (PP) (n = 595) included patients who continued use of OW

semaglutide for more than 90 days after their initial use of OW semaglutide. The groups were also broken further into GLP-1RA naïve patients who had not used a GLP-1RA in the 12 months before this trial, and GLP-1RA experienced patients. Patients with an HbA_{1C} of > 9% at the start of OW semaglutide were also evaluated separately. Overall, the mean age was 54.3 (9.1) years and 50.5% were female. Demographics such as ethnicity were not discussed. Demographics were similar between the GLP-1RA naïve and experienced groups and were also similar in the PP subgroup. The median time on OW semaglutide in the ITT group was 197 days, and in the PP subgroup, median time was 218 days. In the ITT and PP groups, the change in HbA_{1C} from baseline was -0.9% (CI -0.96, -0.82; $p < 0.001$), and -1.1% (CI -1.15, -0.96; $p < 0.001$), respectively. In the GLP-1RA naïve groups ITT's change was -1.2% (CI -1.26, -1.06; $p < 0.001$) in ITT, and -1.3% (-1.53, -1.26; $p < 0.001$) in PP. In the GLP-1 experienced groups, the change was -0.6% (CI -0.61, -0.42; $p < 0.001$) in ITT and -0.6% (CI -0.76, -0.53; $p < 0.001$). In the subgroup with an HbA_{1C} of > 9%, the change in HbA_{1C} was even greater, with change from baseline of -2.2% (CI -2.4, -2.05; $p < 0.001$) in ITT overall, -2.4% (CI -2.7, -2.24; $p < 0.001$) in PP overall, -2.5% (CI -2.66, -2.24; $p < 0.001$) in ITT GLP-1 naïve, -2.8 (-3.05, -2.49; $p < 0.001$) in PP GLP-1 naïve, -1.8% (CI -2.04, -1.45; $p < 0.001$) in ITT GLP-1 experienced, and -1.9% (CI -2.25, -1.49; $p < 0.001$) in PP GLP-1RA experienced. Sensitivity analyses found that HbA_{1C} changes were not meaningfully different between groups. The absolute increase in patients who attained an HbA_{1C} < 7% after the start of OW semaglutide was 25.3%; 23.3% of patients in this trial had an HbA_{1C} < 7% at baseline. Of the patients in the HbA_{1C} > 9% subgroup, 26.9% were able to achieve the target goal of <7%, and 49.2% achieve < 8%. The number of patients achieving target HbA_{1C} goals was significant in all groups ($p < 0.001$ in all). This study showed that clinically meaningful changes in HbA_{1C} occurred with the use of OW semaglutide across a

variety of patient populations, and a significant number of people were able to achieve the American Diabetes Association's (ADA) recommendation of an $HbA_{1C} < 7\%$. Strengths of this study include that it is applicable to the real world and reflects what is seen clinically, where patients tend to be less compliant with their medications than in clinical trials. Weaknesses include that it is retrospective, there is no control group, the database the information is attained from may have coding errors, and race/ethnicity and socioeconomic data were not available and therefore not included in the study. Also, some of the authors of the study are employees and shareholders of the Novo Nordisk, the pharmaceutical company that sells the name-brand forms of semaglutide, and the study was funded by the same pharmaceutical company, leading to possibility of bias in this study.

Long-term HbA1C in patients taking liraglutide

Mirabelli et al. (2020) studied the long-term clinical effectiveness of liraglutide 1.2 or 1.8 mg in the management of weight and glycemic control in overweight/obese individuals with T2DM who were previously naïve to GLP-1RAs. This was a retrospective study done on a population of Southern Italian subjects who received liraglutide, another GLP-1RA medication, for 60 months, alone or in combination with other antidiabetic medications (n = 40). Data was collected from an electronic health record and stored anonymously in a database for analysis. The primary outcome was to measure the long-term effectiveness of liraglutide for weight management with a goal of a change in body weight of > 5% after 60 months of treatment. Secondary outcomes included changes in HBA_{1C} and several other metabolic and cardiovascular measures. All subjects were Caucasian. Of the participants, 20 used 1.2 mg/day and 20 used 1.8 mg/day dosage, 55% of participants were women, mean age was 57.5 (6.6) years. In total, body weight decreased by 5.0 (7.0) kg ($p < 0.001$). The weight loss that occurred in the first six

months of therapy was maintained at the end of the five-year study period. Dosage was not correlated with weight change. HbA_{1C} was reduced from 7.9 (0.9) % at baseline to 7.0 (0.7) % after five years of treatment ($p < 0.001$). The proportion of patients who achieved the ADA's target for glycemic control ($HbA_{1C} < 7\%$) increased from 17.5 to 50% after five years ($p = 0.007$). These results showed that five-year treatment with liraglutide combined with one or more other antidiabetic medication(s) induced and sustained weight loss over a 5-year period, especially in the female gender and in individuals with a higher baseline body weight. It is also able to lower HBA_{1C} to achieve or move toward glycemic control in type 2 diabetics. This study has several weaknesses including a retrospective observational design, lack of drug comparison as a control, lack of diverse the patient population, and a very low sample size. Strengths include the length of the study, and its retrospective design may be more representative of real-life medication use compared to prospective clinical trials where medication compliance can be higher than normal due to increased check-ins for the study.

Tack et al. (2019) investigated the long-term efficacy of liraglutide based on insulin use at baseline. This was a post hoc, double-blind, randomized, placebo-controlled trial. Patients were randomized 1:1 to receive liraglutide (n = 4668) or placebo (n= 4672) in addition to the standard of care treatment (intensified treatment at investigator's discretion for individuals who did not achieve an HBA 1C < 7% with any glucose lowering therapy except for GLP-1, DPP-4, or pramlintide); these groups were further broken down into subgroups based on insulin use: basal-only insulin (n = 3159), other insulin (n = 1010), or no insulin (n = 5171). Participants were followed for 3 to 5 years. The primary endpoint was the time to first occurrence of a major adverse cardiovascular event (MACE); secondary endpoints included metabolic parameters such as change in HBA_{1C}, body weight, and more. Baseline characteristics and demographics were

balanced between randomized treatment groups to create parallel groups, but data was not shown. Liraglutide was shown to reduce the risk of first MACE compared with placebo in the patients who were not treated with insulin at baseline (hazard ratio 0.81, CI 0.68, 0.98), and in general but the risk of MACE with liraglutide versus placebo was not significantly different based on basal insulin dose ($p = 0.62$). Patients on liraglutide had decreased HbA_{1C} and body weight compared to the placebo group in all three insulin-use groups, with a change of -0.48% (CI -0.57, -0.39; $p < 0.001$) and -2.3 kg (CI -2.5, -2.0; $p < 0.001$), -0.37% (CI -0.54, -0.21; $p < 0.001$) and -2.5 kg (CI -2.9, -2.1; $p < 0.001$), and -0.36% (CI -0.43, -0.29; $P < 0.001$) and -1.9 kg (CI – 2.3, -1.6; $P < 0.001$) in basal-only insulin, other insulin, or no insulin subgroups, respectively. This data showed that adding liraglutide to insulin treatment with T2DM improves glycemic control and reduces body weight for at least 36 months. Cardiovascular safety of liraglutide is maintained regardless of insulin use or dose at baseline. These results reflect results of other clinical trials measuring similar factors over a period of 6-12 months, and support using combined treatment of insulin and liraglutide. Strengths of this study include a large sample size and a placebo-controlled double-blinded design. Weaknesses include that this was a post-hoc analysis which can create a bias in results and statistical analysis, and the research was funded by the pharmaceutical company who sells this medication, which may also lead to bias in interpretation of results.

Pratley et al. (2019) aimed to compare the efficacy and safety of liraglutide with oral semaglutide in patients with T2DM that is uncontrolled with background metformin with or without an SGLT2 inhibitor. The randomized, double-blind, double-dummy, active-controlled and placebo-controlled study was done over a 52-week period. Participants were randomized (2:2:1) to receive subcutaneous liraglutide 1.8 mg (n = 284), oral semaglutide 14 mg (n = 285),

or placebo (n = 142) in addition to a stable dose of background metformin with or without an SGLT2 inhibitor. Baseline demographic and clinical characteristics were similar between groups; overall, 48% of participants were female, mean age (SD) was 56 (10) years, mean baseline HbA_{1C} was 8.0 (0.7) %, mean baseline bodyweight of 94.0 (21.0) kg, with 73% of participants describing race as white, 4% as black or African American, 13% Asian, 2% other, and 7% not available; 94% reported non-Latino ethnicity. The primary endpoint was a change in HbA_{1C} from baseline to week 26, and the confirmatory secondary endpoint was a change in body weight over that time. Supportive secondary endpoints included change in HbA_{1C} and bodyweight from baseline to week 52, achievement of an HbA_{1C} of 7% or less, and more. At week 26, mean change in HbA_{1C} (SD) was -1.1 (0.1) % for liraglutide, -1.2 (0.1) % for oral semaglutide, and -0.2 (0.1) % for placebo. There was no significant difference in reduction of HbA_{1C} between liraglutide and oral semaglutide ([ETD 0.1%, 95% CI -0.3, 0.0; $p < 0.001$ for non-inferiority). Change in bodyweight at week 26 was -3.1 (0.2) kg for liraglutide, -4.4 (0.2) kg for oral semaglutide, and -0.5 (0.3) kg for placebo; weight loss was significantly higher with oral semaglutide compared to liraglutide with ETD of -1.2 kg (CI -1.9, -0.6; $p = 0.0003$), and was also significantly higher compared to placebo with ETD of -3.8 (CI -4.7, -3.0; $p < 0.0001$). At week 52, HbA_{1C} changed from baseline by -0.9% for liraglutide, -1.2% for oral semaglutide, and -0.2% for placebo. Oral semaglutide resulted in significantly greater reductions in HbA_{1C} compared to both liraglutide and placebo, with an ETD of -0.3 (CI -0.5, -0.1; $p = 0.0002$) and ETD -1.0 (CI -1.2, -0.8; $p < 0.0001$), respectively. Change in body weight at 52 weeks was -3.0 kg for liraglutide, -4.3 kg for oral semaglutide, and -1.0 kg for placebo. Oral semaglutide resulted in significantly more reduction in bodyweight compared to liraglutide and placebo, with ETA of -1.3 (CI -2.1, -0.5; $p = 0.0019$) and -3.3 (CI -4.3, -2.4; $p < 0.0001$), respectively. 55.0% of

patients on liraglutide were able to achieve an HbA_{1C} of < 7% at week 52 compared to 60.7% on oral semaglutide; this was not significantly different between the groups with an estimated odds ratio (EOR) of 1.33 (CI 0.93, 1.91; p = 0.1193); oral semaglutide was significantly more likely to achieve this goal compared to the 15.0% of the placebo group who reached an HbA_{1C} of < 7% (EOR 11.36, CI 6.40, 20.19; p < 0.0001). Superiority of liraglutide over placebo was not calculated for change in HbA_{1C}, bodyweight, or achieving goal HbA_{1C} < 7%. Adverse reactions were reported in 74% of liraglutide patients, 80% of oral semaglutide patients, and 67% of placebo group, with most common events being gastrointestinal-related, notably nausea and diarrhea. Slightly more participants discontinued treatment due to adverse effects in the oral semaglutide group (11%) compared to liraglutide (9%) and placebo (4%) groups. Overall, oral semaglutide showed a significantly greater reduction in HbA_{1C} at week 52 compared to liraglutide and placebo, and it showed greater reduction in bodyweight at weeks 26 and 52 compared to the groups. Liraglutide resulted in increased reduction in HbA_{1C} and bodyweight at weeks 26 and 52 compared to placebo, but differences were not calculated so it cannot be determined if the differences were statistically significant. Improvement of HbA_{1C} was more rapid with liraglutide compared to oral semaglutide, and fewer patients discontinued liraglutide compared to oral semaglutide, where the most common complaint in both medications was nausea. Strengths of this study include the double-blind, dummy-dummy, and placebo-controlled design and the comparison of two different GLP-1RA medications. Weaknesses include funding and involvement in the study from the manufacturers of oral semaglutide, which could create bias in interpretation of results. A similar longer-term study with larger sample sizes would be helpful in future studies.

Long-term HbA1C in patients taking empagliflozin

Rodbard et al. (2019) studied efficacy and safety of empagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, compared to oral semaglutide in patients with T2DM that was uncontrolled with metformin. This was a prospective, open-label, multi-national study. Patients were randomized (1:1) to receive oral semaglutide 14 mg (n = 412) or empagliflozin 25 mg (n = 410) in addition to a stable dose of metformin for 52 weeks. Demographic characteristics were well balanced between the two groups; overall 49.5% were female, mean age was 58 (10) years, average baseline HbA_{1C} was 8.1 (0.9) %, and average body weight was 91.6 (20.3) kg. 86.2% of patients were white, 7.2% black or African American, 6% Asian, and 0.6% other race, and 24.2% identified as Latino ethnicity. The primary endpoint was a change in HbA_{1C} from baseline to week 26, and confirmatory secondary end point was change in body weight from baseline to week 26. Other secondary endpoints included changes in HbA_{1C} and body weight from baseline to week 52, among other measurements. At week 26, it was found that oral semaglutide provided superior reduction in HbA_{1C} compared to empagliflozin, with a change in HbA_{1C} by -1.3% in the former and 0.9% in the latter groups (ETD -0.4 [CI -0.6, -0.3] $p < 0.0001$). Change in body weight between baseline and week 26 was not significantly higher in one group over the other with weight change of -3.8 kg in semaglutide and -3.7 kg in empagliflozin (ETD -0.1 kg [CI -0.7, 0.5] $p = 0.7593$). Change in HbA_{1C} at week 52 showed very similar results to 26 weeks, where change in HbA_{1C} was still -1.3% in semaglutide and -0.9% in empagliflozin (EDT -0.4 [CI -0.5, -0.3] $p < 0.0001$). Change in weight at 52 weeks was not significantly different between semaglutide and empagliflozin, with change of -3.8 kg and -3.6 kg, respectively (ETD -0.2 kg [CI -0.9, 0.5]; $p = 0.6231$), but when discontinuation of therapy and use of rescue medication was statistically accounted for, there was a significantly greater reduction in body weight with

oral semaglutide compared with empagliflozin, with a change of -4.7 kg versus -3.8 kg, respectively (ETD -0.9 kg [CI -1.6, -0.2]; p = 0.0114). The number of adverse effects were similar in both groups, with 70.5% of patients on oral semaglutide reporting adverse events and 69.2% on empagliflozin reporting an adverse event; the majority were classified as mild to moderate. Adverse events were more commonly reported as the reason for discontinuing therapy in the oral semaglutide treatment group (10.7%) compared to the empagliflozin group (4.4%). The most common events in the oral semaglutide group included gastrointestinal events such as nausea, vomiting, and abdominal pain, while UTIs and genital infections were more commonly reported in the empagliflozin group. The study showed that oral semaglutide treatment achieved more meaningful reductions in HbA_{1C} compared to empagliflozin, while changes in body weight was comparable between the two groups unless product discontinuation and rescue medication use is factored in. Though the number of adverse events was similar between the two groups empagliflozin was discontinued due to adverse events less frequently than oral semaglutide, indicating it was more tolerable to patients. A strength of this study is that it is clinically relevant and helpful as it is a head-to-head comparison of two medication classes that are typically added whenT2DM is uncontrolled by metformin. Well-balanced, randomized groups is another strength. Weaknesses include the open-label design and the fact that this was funded by the manufactures of oral semaglutide.

Inzucchi et al. (2020) aimed to study how baseline cardio-metabolic risk factors are affected after empagliflozin 10 or 25 mg is added as second line therapy to metformin in patients with T2DM. This was a prospective, randomized, placebo-controlled, double-blind trial. Patients were randomized (1:1:1) to receive empagliflozin 10 mg (n = 217), empagliflozin 25 mg (n = 213), or placebo (n = 207) once daily in addition to a background stable dose of metformin.

Groups were further subdivided based on HbA_{1C} (</> 8.5%), weight (< 80kg, 80-90 kg, > 09 kg), and systolic blood pressure (SBP) (<130 mmHg, 130-140 mmHg, >140 mmHg), which will not be discussed in this literature review. This was an extension trial for an initial study whose primary end point was a change from baseline HbA_{1C} after 24 weeks, the secondary endpoint investigated in this trial is a change from baseline HbA_{1C} after 76 weeks. Treatment groups were parallel and comparable demographically and clinically. Compared to the placebo, empagliflozin significantly reduced HbA_{1C}, body weight, and systolic blood pressure of both subgroups at both 24 and 76 weeks. At week 24, compared to placebo the 10 mg empagliflozin dose changed HbA_{1C} by -0.51% (CI -0.67, -0.35; $p < 0.0001$) and -0.73% (CI -1.01, -0.46; $p < 0.0001$) in the <8.5% and ≥8.5% subgroups, respectively; weight changed by -1.37 (0.33) kg (CI -2.02, -0.73; $p < 0.0001$), -1.81 (0.59) kg (CI -2.95, -0.66; $p = 0.0021$), and -2.11 (0.46) kg (CI -3.02, -1.21; $p < 0.0001$) in the < 80kg, 80-90 kg, and > 90 kg subgroups, respectively. The 25 mg empagliflozin dose changed HbA_{1C} by -0.52% (CI -0.68, -0.36; $P < 0.0001$) and -0.97% (CI -1.26, -0.68; $P < 0.0001$) in the <8.5% and ≥8.5% subgroups, respectively; weight changed by -1.41 (0.34) kg (CI -2.08, -0.74; $p < 0.0001$), -2.54 (0.54) kg (CI -3.30, -1.81; $p < 0.0001$), and -2.93 (0.47) kg (CI -3.85, -1.21; $p < 0.0001$) in the < 80kg, 80-90 kg, and > 90 kg subgroups, respectively. By week 72, patients on the 10 mg empagliflozin saw changes of HbA_{1C} by -0.55% (CI -0.73, -0.38; $p < 0.0001$) and -0.78% (CI -1.08, -0.47; $p < 0.0001$) in the <8.5% and ≥8.5% subgroups, respectively. Weight changed by -1.29 (0.40) kg (CI -2.08, -0.50; $p = 0.0014$), -1.88 (0.72) kg (CI -3.29, -0.47; $p = 0.0089$), and -3.35 (0.57) kg (CI -4.46, -2.23; $p < 0.0001$) in the < 80kg, 80-90 kg, and > 90 kg subgroups, respectively. The 25 mg empagliflozin dose changed HbA_{1C} by -0.64% (CI -0.81, -0.46; $p < 0.0001$) and -0.99% (CI -1.31, -0.68; $p < 0.0001$) in the <8.5% and ≥ 8.5% subgroups, respectively. Weight changed by -1.27 (0.42) kg (CI -2.09, -0.45; $p = 0.0025$), -

1.83 (0.66) kg (CI -3.13, -0.53; p = 0.0059), and -4.93 (0.58) kg (CI -5.36, -3.10; p < 0.0001) in the < 80kg, 80-90 kg, and > 90 kg subgroups, respectively compared to the placebo at week 76. The most common adverse effect was urinary tract infection (UTI); UTI events were reported similarly in frequency between the placebo and empagliflozin groups; genital infections were reported more frequently in the 10 and 25 mg doses of empagliflozin than the placebo. This study shows that empagliflozin added onto metformin results in significantly greater reductions in HbA_{1C} and body weight compared to the placebo, and higher starting variables results in increased change. SBP is not significantly lowered compared to the placebo. Strengths include a large n-value, randomized, placebo-controlled, parallel group, double-blind study design, and the long-term nature of the study. Weaknesses include the fact that data for demographics of participants was not included, so it is tough to tell which populations this best applies to, and n-values of the subgroups were not published either.

Ridderstråle et al. (2018) aimed to study the long-term efficacy and safety of empagliflozin compared with the sulfonylurea glimepiride as an add-on to fixed metformin therapy to patients with T2DM. This was a prospective, randomized, active-controlled, double-blind, parallel group trial that was a 104-week extension-phase trial to an initial 104-week trial, totaling 204 weeks in total duration. In the initial trial, patients were randomized (1:1) to receive empagliflozin 25 mg (n = 765) or glimepiride 1 to 4 mg (n = 780) once daily in addition to metformin and diet and exercise counseling. Patients who completed the initial trial and opted to continue the study received the same treatment of empagliflozin (n = 576) or glimepiride (n = 549) in the extension phase in a double-blind manner. Besides race and region, the demographic and clinical characteristics between groups were parallel, but demographics were not broken down in this article. Rescue therapy (any medication except a sulfonylurea or SGLT2 inhibitor,

chosen at digression of the investigator) could be initiated if a patient had a fasting blood glucose of > 240 mg/dL during weeks 1-12, > 200 mg/dL in weeks 12 to 28, or > 180 mg/dL or HbA_{1C} > 8% after week 28. All endpoints at week 208 were exploratory, and included changes from baseline HbA_{1C}, body weight, proportion of patients who achieved ADA's recommendation of HbA_{1C} < 7% when it had been above that number at baseline, percentage who received rescue therapy over the 208-week period, confirmed hypoglycemic adverse events, and more. Mean HbA_{1C} reductions were greater with empagliflozin, where patients on empagliflozin saw HbA_{1C} change by an additional -0.16% (CI -0.28, -0.03; p = 0.0129) compared to glimepiride treatment. Weight changes on empagliflozin occurred early and were sustained over the 208-week trial; the mean difference versus glimepiride in weight change from baseline was -4.92 kg (CI -5.52, -4.31; p < 0.0001). There was no significant difference in proportion of patients who achieved an HbA_{1C} < 7% after a baseline of > 7% with empagliflozin (22%) and glimepiride (21%). Rescue therapy was used at a significantly higher proportion for patients on glimepiride (34%) compared to empagliflozin (23%) (odds ratio 0.56 [CI 0.45, 0.71]; p < 0.0001). Hypoglycemic events were more common in glimepiride (28%) than empagliflozin (3%) (odds ratio 0.08 [CI 0.05, 0.13]; p < 0.0001). The most common adverse effects in patients treated with empagliflozin included urinary tract infection and genital infection. This study showed that 208 weeks of empagliflozin therapy was associated with a slightly more desirable change in HbA_{1C}, less use and more delay of rescue therapy initiation, increased weight loss and maintenance of that weight loss, and much lower hypoglycemia risk compared to glimepiride. This indicates that there would be a clinical advantage to using empagliflozin over glimepiride. Strengths of this study include a double-blind, placebo, parallel group design, and a long study time. Researchers disclosed that there was missing data values at week 208 but did not clarify which values were missing; this may have

altered the results and is therefore a major weakness of the study. Another weakness is this research project was funded by the pharmaceutical company that makes empagliflozin, which may create bias toward positive findings for that medication.

Long-term HbA1C in patients taking dapagliflozin

Kohan et al. (2014) aimed to examine the efficacy and safety of dapagliflozin, another SGLT2 inhibitor, in patients with T2DM and moderate renal impairment. This was a double-blind, placebo controlled, long-term extension of an initial 24-week trial. Of the 252 patients initially randomized (1:1:1) into placebo, 5mg dose, and 10 mg dose of dapagliflozin groups, 53, 59, and 59 patients, respectively, continued to the final extension period, and 43, 45, and 51 patients, respectively, completed the full 104-week study. Demographics of the placebo, 5mg, and 10 mg dapagliflozin included average age of 67 ± 8.8, 66 ± 8.9, and 68 ± 7.7 years, respectively; men made up 63.1%, 66.3%, and 65.9% of the groups, respectfully; white race reported in 82.1%, 78.3%, and 90.6% of patients, respectfully; African American race reported in 1.2%, 8.4%, and 4.7%, respectively; Asian race was reported in 7.1%, 4.8%, and 3.5%, respectively, and other race was reported as 9.5%, 8.4%, and 1.2%, respectfully. Pre-enrollment antidiabetic therapy was parallel between groups. The primary endpoint was a mean change in HbA_{1C} excluding data after glycemic rescue. At week 104, HbA_{1C} changed (SD) from baseline by -0.67 (0.41) % (CI -1.98, 0.63), -1.21 (0.38) % (CI -2.10, -0.32), and -0.75 (0.22) % (CI -1.25, -0.25) in the placebo, 5mg, and 10 mg dapagliflozin groups, respectively. Change in HbA_{1C} on dapagliflozin compared to the placebo was not statistically significant (p-value not reported). The dapagliflozin groups did experience mean weight loss compared to the placebo group, with a change of 2.63 (0.79) kg (CI 1.07, 4.19), -0.34 (0.75) kg (CI -1.82, 1.15), and -2.20 (0.74) kg (-2.56, -0.36) in the placebo, 5mg, and 10 mg dapagliflozin groups, respectively. The change in

glomerular filtration rate (GFR) from baseline to week 104 was similar between the dapagliflozin 5 mg (-1.71 [1.23] ml/min per 1.73m^2), dapagliflozin 10 mg (-3.50 [1.02] ml/min per 1.73m^2) and placebo (-2.38 [1.01] ml/min per 1.73m^2) groups. Serious adverse effects were seen in similar proportions between the dapagliflozin and placebo groups throughout the 104-week treatment period. There was a higher incidence of genital infections in dapagliflozin patients compared to placebo, and UTIs were experienced in similar proportion between the two groups. In the 104-week period, 7.7% of patients in the dapagliflozin groups reported a bone fracture, compared to zero in the placebo group. While 104 weeks of dapagliflozin treatment reduces weight in patients with T2DM and moderate renal impairment, it does not impact glycemic control compared to the placebo. This is likely because dapagliflozin's ability to inhibit renal glucose reabsorption declines as GFR decreases. Strengths of this study include a double-blind and placebo-controlled study design. Weaknesses include a low n-value, and lack of racial diversity. Additionally, this study focuses on a subset of the general population with T2DM and is only applicable to renally impaired patients.

Müller-Wieland et al. (2018) aimed to determine how dapagliflozin alone or in combination with saxagliptin, a DPP-4 inhibitor compared in efficacy and safety to glimepiride, a sulfonylurea, added onto metformin in patients with T2DM. This was a prospective, parallel-group, double-blind, dummy-dummy, active controlled study performed over a 52-week treatment period. Patients receiving a stable dose of metformin were randomized (1:1:1) to receive dapagliflozin 10 mg (Dapa 10 mg), n = 314; dapagliflozin 10 mg plus saxagliptin 5 mg (Dapa 10 mg + Saxa 5 mg), n= 312; and glimepiride 0-6 mg (Glim 0-6 mg), which was started at 1 mg and was titrated as needed, n = 313. The primary end point was a change in HbA_{1C} from baseline to the endpoint of the study. Secondary endpoints included proportion of patients with

hypoglycemic episodes (defined as typical symptoms of hypoglycemia with blood glucose < 70 mg/dL) throughout the treatment period, changes in bodyweight from baseline to endpoint, and more. Baseline demographics included mean (SD) age of 58.4 (8.6) years, 63.9% male gender, 98.9% Caucasian, mean body weight was 96.8 (18.1 kg), baseline HbA_{1C} was 8.3 (0.7) %. At week 52, the mean change in HbA_{1C} from baseline was -0.82% Dapa 10 mg, -1.20% Dapa 10 mg + Saxa 5 mg, and -0.99% for glim 0-6 mg. The change in HbA_{1C} was significantly greater in dapagliflozin plus saxagliptin group compared to glimepiride (P = 0.001). The proportion of patients who experienced hypoglycemic episodes was low across all groups; it occurred in 0% of Dapa 10 mg patients (mean difference -4.2; 95% CI -6.6, -2.0), 0.3% of Dapa 10 mg + Saxa 5 mg patients (mean difference -3.9; 95% CI -6.2, -1.6), and 4.2% of glimepiride patients (P < 0.001; P < 0.001, respectively). Change in body weight was increased in both dapagliflozin groups compared to glimepiride, with weight change of -3.5 (0.2) kg (ETD -5.3, CI -5.9, -4.7) in Dapa 10 mg; -3.2 (0.2) kg (mean difference -4.9 CI -5.5, -4.3) in Dapa 10 mg + Saxa 5 mg; and 1.8 (0.2) kg in Glim 0-6 mg. This study showed that while dapagliflozin 10 mg did not lead to significant reductions in HbA_{1C} compared to glimepiride, dapagliflozin plus saxagliptin did. Both medications containing dapagliflozin lead to increased loss of body weight after 52 weeks, and they both resulted in fewer hypoglycemic episodes compared to glimepiride. Strengths of study include the parallel group, double-blind, dummy-dummy study design, and the titration of glimepiride which mirrors real-world practice. Weaknesses include a lack of diversity in race/ethnicity in the patient population. Groups sizes and length of study were moderate in size, but similar research with a larger n-value and over a longer period of time would be helpful.

Bailey et al. (2013) performed a 102-week prospective, double-blind, placebo-controlled, multicenter study on adults with T2DM who failed to reach adequate glycemic control on

metformin therapy alone. The purpose of this study was to determine whether dapagliflozin as an add-on to metformin effectively helps to achieve glycemic control. The study started as a 24-week study with 546 participants who were placed into 4 parallel groups at a ratio of 1:1:1:1. It was extended by 78 weeks to assess long-term effects; 476 participants remained in the extension in their originally assigned groups. Of 339 participants who completed the 102-week study, 73 were in a control group which received metformin plus a placebo drug, 82 were in a group that received metformin plus 2.5 mg dapagliflozin once daily (DAPA 2.5), 89 were in a group that received metformin plus 5 mg dapagliflozin once daily (DAPA 5), and 95 were in a group that received metformin plus 10 mg dapagliflozin once daily (DAPA 10). The primary outcome of this study was a change from the baseline HbA_{1C} at 24 weeks. At baseline (SD), HbA_{1C} was 8.12 (0.96) % in placebo, 7.99 (0.90) % in DAPA 2.5, 8.17 (0.96) % in DAPA 5, and 7.92 (0.82) % in DAPA 10. At week 102, HbA_{1C} changed by +0.02% (CI -0.20 to 0.23%), -0.48% (CI -0.68 to -0.29%), -0.58% (CI -0.77 to -0.39%) and -0.78% (CI -0.97 to -0.52%) respectively. Patients who received the 5 and 10 mg doses of dapagliflozin had significantly decreased HbA_{1C} compared to those who received the placebo ($p < 0.0001$). Exploratory objectives also included a goal of HbA_{1C} <7.0% at week 102 and change in body weight from baseline. At week 102, 15.4% (CI 9.5 to 21.3%) of patients in the placebo group achieved an HbA1c below 7.0%, while 20.7% (CI 14.0 to 27.3%) in DAPA 2.5, 26.4% (CI 19.4 to 33.4%) in DAPA 5, and 31.5% (CI 23.7 to 39.3%) in DAPA 10 did so. The DAPA 5 and 10 groups had a statistically significant increase in participants who were able to achieve the goal HbA_{1C} of <7% compared to the control group only when use of rescue insulin was statistically accounted for ($P = 0.2380$, 0.0176, and 0.0011 respectively). Baseline body weight (SD) was 87.74 (12.24) kg in placebo group, 84.90 (17.77) kg in DAPA 2.5, 84.73 (16.26) kg in DAPA 5, and 86.28 (17.53) in DAPA 10. This changed by

+1.36 kg (CI 0.53 to 2.20%), -1.10 kg (CI -1.91 to -0.29%), -1.70 kg (CI -2.48 to -0.91%), and -1.74 kg (CI -2.51 to -0.96 %) respectively. All three groups who received any dose of dapagliflozin lost significantly more weight compared to the placebo group ($p = <0.0001$ in all groups). This study effectively showed that dapagliflozin in use with metformin resulted in improved glycemic control and modest weight reduction in patients whose T2DM is not controlled by metformin alone. However, it did not show that achievement of an HbA_{1C} below 7.0% is significantly increased. Strengths of this study include the fact that it was double blinded, placebo controlled, and used objective measurements. While it would be difficult to overcome, one issue with this study is that in order to ensure that patients received quality care for their T2DM, study guidelines stated that patients whose HbA_{1C} exceeded 7.5% 50 weeks or 7.0% at 76 weeks received rescue therapy of pioglitazone. While the number was not specified, a number of patients in the placebo group needed this therapy, which may have limited the statistical interpretation.

Discussion

Selecting effective methodology to achieve long-term weight loss and control of HbA_{1c} in people with T2DM requires consideration of many different factors. Available literature helped to provide insight and considerations in selecting between gastric bypass surgery or weight loss medication for this population.

Multiple studies observed the long-term control of HbA_{1C} and weight change following RYGB versus medical therapy. The studies reviewed did not specify the type of medication patients received in the medical therapy groups; it was prescribed based on each individual patients' needs, so while it is likely that some of the patients in the control groups received diabetic medications that have also been shown it result in weight loss, it is impossible to know

and therefore directly compare antidiabetic weight loss medications to RYGB. The studies reviewed all agreed that RYGB resulted in significantly greater reduction in HbA_{1c} and body weight in the long term compared to medical therapy (Schauer et al., 2017; Almby et al., 2021; and Mingrone et al., 2021). Each of the three studies also found that at the end of the respective trial periods, patients were able to take fewer antidiabetic medications than they were required to before the surgery with some no longer needing any antidiabetic medication, indicating that RYGB can reduce the severity of T2DM and in some cases reverse it. Mingrone et al. (2021) also reported lower incidence of diabetes-related complications such as retinopathy, neuropathy, and nephropathy. Almby et al. (2021) reported that the number of antihypertensive medications was reduced after receiving gastric bypass surgery. While measuring slightly different outcomes besides change in body weight and HbA_{1C}, the studies overall showed that RYGB improved clinical outcomes in patients with T2DM.

The Mingrone et al. (2021) study observed the relationship between weight loss and diabetes control and found that the amount of weight change after the surgery was not predictive of diabetes remission or relapse. It also noted that if patients did not go into remission of diabetes within two years of the surgery, they were unlikely to do so, and the highest risk of diabetes relapse was within five years of the surgery, with the risk significantly decreasing after that period (Mingrone et al., 2021).

While the studies on RYGB showed promising numbers for weight loss and control of HbA_{1c}, there are factors that need to be considered clinically that the research did not discuss. One issue is the risk versus benefit of surgery; it is a major surgery where the patient risks adverse reactions to anesthesia, infections, and excessive bleeding as well as long-term complications such as nutritional deficiencies due to decreased absorption. Some people will be

too high risk to receive the surgery, and there is often an upper and lower weight limit to receive surgery which limits the number of people who RYGB will be a good option for. Another factor the studies did not consider is the cost; many insurances consider gastric bypass an elective surgery and if they do cover the procedure, it is often only partial coverage which some people still cannot afford to pay. There are also usually qualifications a person must meet before qualifying for bariatric surgery such as documented failure of other methods of weight loss, psychological preparation, and several other factors which can exclude someone from being a candidate for RYGB. Since surgery is not an option for everyone, diabetic medications for weight loss should still be considered.

Semaglutide, liraglutide, empagliflozin, and dapagliflozin were all studied as options for antidiabetic weight loss medications. Pratley et al. (2019) studied effects of liraglutide and oral semaglutide and found that semaglutide reduced HbA_{1C} and body weight significantly more than liraglutide did. This would indicate that oral semaglutide may have a higher efficacy compared to liraglutide, but since there was no other study to corroborate these findings, that cannot be definitively stated. Rodbard et al. (2019) compared empagliflozin and oral semaglutide and found that patients on oral semaglutide saw significantly greater reductions in HbA_{1C} compared to patients on empagliflozin. This may indicate that oral semaglutide is more effective at lowering HbA_{1C} than empagliflozin, but again, that cannot be determined from one study alone. The study also showed that there was no significant difference in weight loss between patients on oral semaglutide or empagliflozin until discontinuation of therapy and use of rescue medication were accounted for; after that was done, patients on oral semaglutide saw significantly more weight loss than those on empagliflozin. Besides those two, all studies reviewed were compared to a placebo or antidiabetic medications from different classes, so it is difficult to directly

compare medication types and determine if one is definitively better than the others, but insight was still gained on the efficacy of the medications.

Two studies compared the long-term change in HbA_{1C} and body weight between patients taking oral semaglutide and sitagliptin. Buse et al. (2020) used flexible dosing in the trial and found that oral semaglutide did not significantly reduce HbA_{1C} or body weight compared to sitagliptin. Rosenstock et al. (2021) divided participants taking oral semaglutide into 3, 7, and 14 mg dose groups and found that compared to sitagliptin, the 3 and 7 mg semaglutide doses did not significantly decrease HbA_{1C}, but the 14 mg dose did. All three dosage groups saw a significant decrease in weight compared to the sitagliptin group. These findings seem to indicate that while oral semaglutide does lower HbA_{1C} and body weight, it does not do so significantly more than sitagliptin unless at higher doses. Zinman et al. (2019) observed that patients on a 3, 7, and 14 mg dose of oral sitagliptin all saw significant reductions in HbA_{1C} and body weight. Visaria et al. (2021) observed that patients who took once weekly injectable semaglutide also saw a significant reduction in HbA_{1C} from baseline, but body weight was not measured in this study. These studies indicate that starting semaglutide does significantly decrease HbA_{1C} from baseline. The long-term studies reviewed on semaglutide show that HbA_{1C} decreased by 0.925% and body weight by 2.54 kg on average.

Tolerability of medications should always be considered in medication selection as a person is more likely to discontinue use if the medication is not well tolerated. Buse et al. (2020), Rosenstock et al. (2021), and Zinman et al. (2019) all observed that patients taking oral semaglutide most commonly experienced side effects that were GI in nature, such as nausea and diarrhea, and the latter two studies observed that adverse effects appeared to be dose dependent.

Mirabelli et al. (2020) performed a retrospective study that observed the change in HbA_{1C} and body weight from baseline to 60 months of using liraglutide and found that both were reduced significantly after treatment. Tack et al. (2019) observed that change from baseline HbA_{1C} and body weight after 36-60 months of liraglutide use was significant with or without basal insulin use compared to placebo. These studies seem to indicate that liraglutide does result in reduction of HbA_{1C} and body weight, but they do not show whether it reduces those numbers more significantly than other medications. As previously discussed, Pratley et al. (2019) found that semaglutide reduced HbA_{1C} and body weight significantly more than liraglutide. No conclusions can be made from this study alone, but this finding may indicate superiority of oral semaglutide over liraglutide in controlling HbA_{1C}. The study also found that patients on liraglutide reported fewer adverse reactions than those on semaglutide, but the most common adverse events were also nausea and diarrhea (Pratley et al., 2019). The three studies done on liraglutide saw an average reduction in HbA_{1C} of 0.602% and body weight of 2.94 kg, which supports the Pratley et al. (2019) finding that patients on liraglutide see a smaller change in HbA_{1C} and a similar change in body weight.

Inzucchi et al. (2020) found that after 18 months, HbA_{1C} and body weight were significantly lowered in patients on background metformin who took empagliflozin compared to a placebo. Patients on a higher dose of empagliflozin saw greater changes in HbA_{1C} and body weight, and patients with higher baseline HbA_{1C} and/or body weight greater changes than those with a lower HbA_{1C} or body weight. Ridderstråle et al. (2018) compared change in HbA_{1C} and body weight after 48 months of using either empagliflozin or glimepiride and found that both HbA_{1C} and body weight were significantly lower in patients on empagliflozin. As previously discussed, Rodbard et al. (2019) compared changes in HbA_{1C} and body weight in patients on

empagliflozin or oral semaglutide and found that oral semaglutide is superior to empagliflozin. These findings would indicate that while empagliflozin is effective in lowering HbA_{1C} and body weight, it may not be as effective as semaglutide. In the three studies pertaining to empagliflozin that were reviewed, the average HbA_{1C} change was -0.69% and body weight -2.88 kg, falling somewhere between semaglutide and liraglutide in change in HbA_{1C} and body weight. All three studies found that the most common adverse events observed with this medication were UTIs and genital infection (Inzucchi et al., 2020; Ridderstråle et al., 2018; Rodbard et al., 2019). Rodbard et al. (2019) also noted that while the number of adverse events were similar between patients taking oral semaglutide and empagliflozin, the adverse effects caused patients to discontinue treatment with oral semaglutide more often.

Bailey et al. (2013) studied the change in HbA_{1C} and body weight after 24 months of dapagliflozin use or a placebo. It found that HbA_{1C} was significantly reduced with dapagliflozin use only after use of rescue insulin was accounted for. Body weight was significantly decreased after dapagliflozin use compared to the placebo. Müller-Wieland et al. (2018) studied the change in HbA_{1C} and body weight after 12 months of dapagliflozin, dapagliflozin plus saxagliptin, or glimepiride, and found that dapagliflozin alone did not significantly reduce HbA_{1C} compared to glimepiride, but the combination of dapagliflozin and saxagliptin did. Both the dapagliflozin and dapagliflozin/saxagliptin combination significantly reduced body weight compared to glimepiride. It was noted that patients on dapagliflozin had a smaller proportion of hypoglycemic episodes compared to patients on glimepiride, indicating it might be a safer option for people who are prone to hypoglycemic episodes. Kohan et al. (2014) looked at dapagliflozin's efficacy on renally impaired patients and found that HbA_{1C} and body weight were not significantly reduced after 24 months of dapagliflozin treatment compared to a placebo. The

change in GFR was similar between the dapagliflozin and placebo groups, indicating that as a person's GFR decreases, so does dapagliflozin's ability to inhibit renal glucose absorption. The study shows that dapagliflozin is likely not the best option to use in renally impaired diabetic patients.

Across the studies reviewed pertaining to dapagliflozin, the average change in HbA_{1C} was -0.83% and body weight -1.97 kg; when the dapagliflozin/saxagliptin combination was not taken in, the average change in HbA_{1C} was -0.77% and body weight was -1.76 kg. While there were multiple studies that found that dapagliflozin did not significantly decrease HbA_{1C} or body weight compared to the control, the average change of HbA_{1C} for patients on this medication was the second highest of the medication types studied. Average loss of body weight was the lowest of all medication groups studied. This seems to indicate that while dapagliflozin does decrease HbA_{1C} and body weight, there are other medications available that could work at a similar efficacy. Like the empagliflozin studies, Kohan et al. (2014) noted that there was a higher incidence of genital infections in the patients who took dapagliflozin, however, it found similar incidence rates of UTIs between those taking dapagliflozin or the placebo.

The culmination of the many studies on antidiabetic medications that can assist with weight loss helps to guide clinical selection medications. Semaglutide might be a good option for many people, but if the adverse effects are not tolerated, empagliflozin or dapagliflozin might be considered. The SGLT2 inhibitors may not be the best option for renally impaired patients. However, without more studies that directly compare the medications to one another, or at least studies that compare the medications to one common alternative, it is impossible to say if one is better than the others.

Going forward, as the medications discussed are on the market for a longer time, studies over a longer period of medication use is necessary. While two years of improved glycemic control and weight loss on an antidiabetic medication is great, will the affects be maintained for ten years or for the rest of the patient's life? The topic of long-term maintenance of glycemic control and weight loss should continue to be studied as new antidiabetic medications enter the market as well. A medication called tirzepatide was recently released and looks like an extremely promising new medication in achieving weight loss and glycemic control and there are likely more medications to come. It will be interesting to see how results are maintained over many years.

Conclusion

There are several different options to assist in lowering HbA_{1C} and body weight in the long-term in adults with uncontrolled T2DM. RYGB has shown superior long-term reductions in HbA_{1C} and body weight compared to medical therapy options, and even if patients regain part of the weight lost following the surgery, it is not predictive of HbA_{1C} increasing again.

In cases where surgery not an option, studies showed semaglutide, liraglutide, dapagliflozin, and empagliflozin all lowered HbA_{1C} and body weight compared to baseline. While it is difficult to directly compare the medications to one another because very few studies did so, it appears that semaglutide may result in greater reductions in HbA_{1C} and body weight than the other medications but is also more likely to be discontinued than dapagliflozin and empagliflozin due to the adverse effects of the medication. In cases where semaglutide is not tolerated by a patient, empagliflozin and dapagliflozin should also be considered. While there are no studies directly comparing the long-term efficacy of empagliflozin versus dapagliflozin, empagliflozin may be a first choice for a larger number of patients because dapagliflozin was

found to be ineffective in renally impaired patients, and one study found that independently, it was not significantly more effective than a placebo, so combination therapy should be considered with this medication.

While this information helps to shed light on factors that can guide clinical selection of medication or surgery, much more research is needed on the topic of long-term diabetes control. There are now several studies available on the long-term effects of RYGB in type 2 diabetic patients, but the studies are small; studies with larger populations to corroborate the findings discussed here would be helpful. Medications for T2DM and weight loss are relatively new, so additional research studying their effects over longer periods of time is necessary to truly determine their long-term effectiveness. To definitively determine if one medication reduces HbA_{1C} and body weight more significantly than the others, more long-term studies either directly comparing these medications or comparing them to one standard medication would also be necessary.

Application to clinical practice

These findings are best used to guide clinical decision making when treating adults who have not been able to achieve control of their T2DM through diet, exercise, and metformin. A patient's current physical state, insurance, financial state, side-effect tolerance, and comorbid conditions are some items on a long list of factors that will dictate which option is best for a patient. Knowing available options, their efficacy, and their strengths and weaknesses will assist in selecting the best option for an individual.

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