Current Research in Diabetes & Obesity Journal
ISSN: 2476-1435

Juniper Publishers
key to the Researchers

Review Article
Volume 17 Issue 1 - August 2023
DOI: 10.19080/CRDOJ.2023.17.555953

Curr Res Diabetes Obes J

Weight Loss in Diabetes: Pharmacological Management and Other Strategies

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Submission: August 08, 2023; **Published:** August 21, 2023

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Abstract

Diabetes and obesity are prevalent metabolic disorders that present a significant global public health challenge. This review article provides a comprehensive overview of pharmacological and surgical management strategies for weight loss in diabetes. Diabetes, characterized by high blood glucose levels, and obesity, resulting from excessive body fat accumulation, are closely linked, making effective management essential. Pharmacological interventions for weight loss in diabetes include metformin, which can lead to modest weight reduction in some patients. GLP-1 receptor agonists, such as Semaglutide, liraglutide, and exenatide, offer effective glycemic control and weight loss options. Dual GIP/GLP-1 agonists, particularly Tirzepatide, show promise in treating diabetes and obesity with significant weight loss and glycemic control observed in clinical trials. SGLT-2 inhibitors, like dapagliflozin and empagliflozin, not only manage diabetes but also offer cardiovascular benefits and weight reduction. Amylin mimetics, exemplified by pramlintide, regulate post-meal glucose levels, suppress glucagon secretion, and promote satiety, leading to sustained weight reduction in diabetic patients. Gastric bypass surgery, an option for select individuals with obesity and diabetes, shows significant weight loss and improved metabolic profiles. By understanding these treatment options, healthcare professionals can develop personalized management plans combining lifestyle modifications, pharmacotherapy, and surgery where appropriate. Such approaches can lead to better patient outcomes, including weight loss and improved metabolic control. Ongoing research is essential to explore the long-term efficacy and safety of these interventions to optimize diabetes and obesity management in diverse patient populations.

Keywords: Diabetes mellitus; Obesity, Weight loss; Pharmacological management; Surgical management; Metformin; GLP-1 receptor agonists; Semaglutide; Liraglutide; Exenatide; Dual GIP/GLP-1 agonists; Tirzepatide; SGLT-2 inhibitors; Dapagliflozin; Empagliflozin; Amylin mimetics; Pramlintide; Gastric bypass surgery

Abbreviation: DM2: Type 2 Diabetes Mellitus; GLP-1 RA: Glucagon-like Peptide 1 Receptor Agonist; FDA: U.S. Food and Drug Administration; CKD: Chronic Kidney Disease; SGLT2i: Sodium-Glucose Cotransporter 2 Inhibitors; T2DM: Type 2 Diabetes Mellitus; BMI: Body Mass Index; GLP-1: Glucagon-like Peptide 1; DPP-4: Dipeptidyl Peptidase-4; LRYGB: Laparoscopic Roux-en-Y Gastric Bypass; HDL - High-Density Lipoprotein

Introduction

Diabetes is a metabolic disorder characterized by high blood glucose levels due to inadequate insulin production or impaired insulin action. It can lead to severe complications affecting various organs and systems in the body, such as the heart, kidneys, nerves, and eyes. Obesity, in contrast, is a condition in which excessive body fat accumulates, leading to an increased risk of various health problems, including diabetes [1,2]. The risk factors for diabetes include genetics, sedentary lifestyle, unhealthy eating habits, obesity, and age. Type 2 diabetes mellitus (DM2), the most

common form, is closely linked to obesity, as excess body fat can lead to insulin resistance and impair the body's ability to regulate blood sugar levels [1-3]. The epidemiology of obesity and diabetes is concerning, with both conditions showing a significant increase worldwide. In the United States, approximately 34.2 million people have diabetes, representing about 10.5% of the population.

Obesity in the US is even higher, affecting around 42.4% of adults [3]. Diabetes and obesity rates also rise in other countries, contributing to a global public health challenge [4]. The pathogenesis of weight gain in diabetes is multifactorial. In type 2 diabetes, insulin resistance plays a key role, as the body's cells do not respond adequately to insulin, leading to decreased glucose uptake and increased fat storage. Moreover, certain medications used to treat diabetes, such as insulin and sulfonylureas, can promote weight gain by stimulating fat storage and reducing appetite control [5]. Complications of obesity in diabetes can be severe and affect various organ systems. Cardiovascular complications include an increased risk of heart disease, stroke, and high blood pressure. Diabetes-related obesity can also lead to complications such as diabetic retinopathy, diabetic neuropathy, kidney disease, and non-alcoholic fatty liver disease [4-6]. Treating obesity in diabetes involves a combination of lifestyle modifications, pharmacotherapy, and sometimes bariatric surgery.

Lifestyle changes, including a healthy diet, regular physical activity, and behavior therapy, are the cornerstone of management. Pharmacological interventions may include medications that promote weight loss or reduce appetite, such as GLP-1 receptor agonists and SGLT-2 inhibitors [1-8]. This article aims to provide a comprehensive overview of pharmacological management and other strategies for weight loss in diabetes. By understanding the definition, risk factors, epidemiology, pathogenesis of weight gain, complications, and treatment options for obesity in diabetes, healthcare professionals can develop practical approaches to managing these interconnected conditions and improve patient outcomes.

Metformin

Metformin is an oral anti-diabetic medication commonly prescribed for managing DM2. Its mechanism of action involves reducing hepatic glucose production, enhancing peripheral insulin sensitivity, and increasing glucose uptake by skeletal muscle. Metformin does not stimulate insulin secretion from the pancreas [9-11]. The typical dose ranges from 500mg to 2,000 mg per day, divided into two or three doses [10,11]. It is usually taken with meals to minimize gastrointestinal side effects. The duration of treatment is generally long-term, as metformin is considered a foundational therapy for type 2 diabetes [9-13]. Metformin is indicated for patients with type 2 diabetes, particularly those who have not achieved glycemic control with diet and exercise alone. It can be used as monotherapy or in combination with other oral anti-diabetic medications or insulin. The drug is generally well-tolerated, but common adverse effects include gastrointestinal disturbances such as nausea, diarrhea, and abdominal discomfort.

Metformin is contraindicated in patients with renal impairment, significant hepatic disease, or a history of lactic acidosis [11-13]. Regarding its efficacy for weight loss, metformin may lead to modest weight reduction in some individuals with type 2 diabetes, especially those who are overweight or obese. However, the extent of weight loss is generally mild, and it should not be prescribed solely for weight management [10,11]. The FDA approves metformin and has been widely used for many years. It is generally considered safe in pregnancy, but monitoring blood glucose levels closely during pregnancy is crucial, as the dosing may need adjustment. It is not typically used in children younger than 10 years old; safety and efficacy in pediatric populations require careful consideration [11]. In terms of cost, metformin is relatively affordable and available in generic formulations, making it a cost-effective option for diabetes management.

GLP-1 Agonists

Semaglutide

Semaglutide is a 31-amino acid peptide hormone that mimics native GLP-1. It resists degradation by dipeptidyl peptidase-4 (DPP-4) and has reduced renal clearance, leading to a prolonged plasma half-life. As a GLP-1 receptor agonist (GLP-1 RA), Semaglutide regulates glucose homeostasis by increasing insulin secretion and decreasing glucagon secretion in a glucose-dependent manner. It also delays gastric emptying and lowers both fasting and post-prandial blood glucose levels, resulting in weight reduction. Semaglutide activates sites in the hypothalamus to control energy intake and reduce food cravings. The recommended dose for weight management is 2.4mg injected subcutaneously once weekly. However, it carries a black box warning against use in patients with a history of medullary thyroid carcinoma or pancreatitis, and it should not be used during pregnancy [14,15].

Liraglutide

Liraglutide is a modified GLP-1 receptor agonist that binds to serum albumin non-covalently, leading to a longer half-life of 11 to 15 hours. It enables 24-hour glycemic control with once-daily dosing. Liraglutide improves fasting and post-prandial glycemic control through increased insulin secretion, reduced glucagon levels, and minor gastric emptying delays. Additionally, it reduces appetite and energy intake and has favorable effects on post-prandial lipid profiles. The FDA approved liraglutide for treating type 2 diabetes with a daily injectable dose of 1.8 mg and for chronic weight management with a 3.0 mg daily injectable dose. Liraglutide was found to reduce fasting blood glucose, hemoglobin A1c, and systolic blood pressure [16].

Exenatide

Exenatide is an incretin mimetic agent, a synthetic analog of GLP-1, derived from salivary secretions of the lizard Heloderma. As an adjunctive therapy for type 2 diabetes, exenatide improves

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glycemic control by stimulating glucose-dependent insulin secretion, suppressing elevated glucagon levels, delaying gastric emptying, and reducing food intake. It mainly undergoes elimination through glomerular filtration. The recommended dosing is 1.0 mg subcutaneously twice daily. Adverse events, including mild to moderate nausea, have been reported in clinical trials. Exenatide has shown significant improvements in glycemic control and modest weight loss in patients receiving add-on therapy with metformin or sulfonylurea [17,18]. Overall, these GLP-1 receptor agonists, including Semaglutide, liraglutide, and exenatide, offer effective options for the management of type 2 diabetes and weight reduction in appropriate patients, with varying dosing regimens and administration routes.

Dual GIP/GLP-1 Agonists

Tirzepatide

Tirzepatide is a synthetic peptide that acts as a dual gastric inhibitory polypeptide (GIP) and glucagon-like peptide 1 (GLP-1) receptor agonist. It consists of 39 amino acids and stimulates insulin release from the pancreas, reducing hyperglycemia in individuals with type 2 diabetes mellitus (T2DM). Additionally, it increases adiponectin levels and lowers appetite, making it more effective in controlling hyperglycemia and inducing weight reduction compared to GLP-1 agonists alone. The drug is administered via subcutaneous injection and is available in different dosages.

The standard dosing is once weekly, starting with an initiation dose of 5 mg/0.5 mL, which can be adjusted based on efficacy and adverse effects. The most common adverse drug reactions are gastrointestinal, such as abdominal discomfort and nausea, which may influence the dosing titration based on patient tolerance. Tirzepatide is FDA-approved for T2DM treatment but not for type 1 diabetes or pancreatitis. It can also be used off-label for obesity management, similar to GLP-1 medications like Semaglutide [19-21].

Regarding safety, Tirzepatide has been shown to be generally well-tolerated, with gastrointestinal adverse effects being the most common. Nausea, diarrhea, and decreased appetite are frequently reported, and constipation and vomiting are reported less frequently. It can also cause delayed gastric emptying, potentially affecting the absorption of other oral medications and leading to reduced efficacy of oral contraceptives. Other reported adverse effects include sinus tachycardia, acute kidney injury, hypersensitivity reactions at the injection site, and worsening of diabetic retinopathy in some patients. There is a risk of hypoglycemia, especially in patients on insulin therapy or sulfonylureas, and the drug is contraindicated in individuals with a personal or family history of medullary thyroid carcinoma or multiple endocrine neoplasia syndrome type 2 [22-29].

Tirzepatide offers significant potential in treating T2DM and obesity, with double-digit weight loss and glycemic control seen in clinical trials. A growing body of evidence from various clinical trial programs, such as SURPASS and SURMOUNT, supports the drug's efficacy and safety. Further research is needed to assess its long-term cardiovascular safety and effectiveness and its impact on other cardiometabolic complications in people with T2DM and obesity. The FDA has approved Tirzepatide as Mounjaro® for improving glycemic control in adults with T2DM. Still, it is not indicated for type 1 diabetes and is not recommended for use in children under 18 years old [30,31].

Regarding use during pregnancy and lactation, there is insufficient data to determine the drug-related risk for pregnant women, but animal data suggests that Tirzepatide may cause fetal harm. Therefore, its use in pregnant women is not recommended. As for breastfeeding, there is limited information on the clinical use of Tirzepatide during lactation. The drug is a large peptide molecule with low absorption potential in infants, but more data is needed to fully understand its safety during breastfeeding. Until further evidence becomes available, caution should be exercised when using Tirzepatide during breastfeeding, especially in nursing newborns or preterm infants [32].

SGLT-2 Inhibitors

Sodium-glucose cotransporter 2 inhibitors (SGLT2i) represent a novel class of hypoglycemic drugs that includes dapagliflozin, empagliflozin, canagliflozin, ertugliflozin, and Sotagliflozin. These drugs work by lowering the renal glucose threshold and increasing urinary glucose excretion, thereby improving glycemic control [33]. Besides their antidiabetic effects, SGLT2i has demonstrated benefits in cardiovascular conditions such as heart failure, myocardial infarction, hypertension, cardiomyopathy, and arrhythmia [34]. Moreover, evidence supports their use in diabetic individuals with chronic kidney disease (CKD) and non-diabetic populations with CKD [35,36].

The mechanism of action of SGLT2i involves their competitive binding to SGLT2 proteins in the proximal segments (S1) of the renal tubules. The drugs reduce glucose reabsorption by inhibiting these cotransporters, increasing urinary glucose excretion and decreasing plasma glucose levels. Unlike other antidiabetic medications, SGLT2i does not stimulate pancreatic β cells to secrete insulin, making them insulin-independent and associated with a low risk of hypoglycemia. However, it's worth noting that their efficacy may decrease in individuals with reduced renal function [37-39].

In addition to their antidiabetic effects, SGLT2i have shown beneficial effects on endovascular function by indirectly reducing oxidative stress and inhibiting proinflammatory mediators [40]. These drugs also improve myocardial metabolism by inhibiting sodium-hydrogen exchanger 1 isoform in the myocardium, reducing calmodulin-dependent kinase II activity, and enhancing mitochondrial calcium levels, ultimately improving cardiac efficiency [39-41]. Furthermore, SGLT2i have been found to

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improve renal function, reduce adipose-mediated inflammation and sympathetic overdrive, modulate the intrarenal renin-angiotensin system, and increase erythropoietin levels, which positively impacts vascular progenitor cells [41].

Sodium-glucose cotransporter 2 inhibitors have also demonstrated significant efficacy in promoting weight loss in addition to their antidiabetic and cardiovascular benefits. This weight loss effect is particularly advantageous for individuals with obesity or overweight, making SGLT2i a favorable option for those aiming to reduce body weight [42]. The weight loss mechanism of SGLT2i is attributed to their ability to increase urinary glucose excretion. As glucose is excreted in the urine, it leads to the loss of calories, resulting in a reduction in body weight [10]. Studies have shown that treatment with SGLT2i is associated with clinically meaningful weight loss in diabetic and non-diabetic patients with obesity [42,43].

In clinical trials, SGLT2 inhibitors, such as dapagliflozin and empagliflozin, have significantly reduced body weight compared to other antidiabetic medications or placebo [43,44]. This weight loss effect can be particularly beneficial for individuals with type 2 diabetes who often struggle with overweight or obesity, as it can contribute to improved glycemic control and reduced cardiovascular risk factors [42,43]. The combination of glycemic control, cardiovascular benefits, and weight loss makes SGLT2i a valuable therapeutic option for patients with type 2 diabetes and obesity. However, it's essential to consider individual patient characteristics and potential side effects when determining the most suitable treatment approach.

Close monitoring and personalized management are crucial to optimize the outcomes and safety of SGLT2 inhibitors in diverse patient populations [43-45]. Overall, SGLT2 inhibitors have proven to be promising medications not only for the management of diabetes but also for their beneficial effects on cardiovascular, renal, and weight loss conditions. Their unique mechanisms of action set them apart from other antidiabetic drugs and offer potential advantages in terms of safety and cardiovascular risk reduction. Further research is ongoing to explore their full potential and role in treating various metabolic and cardiovascular disorders.

Amylin Mimetics

Pramlintide

The drug is a synthetic analog of amylin, a peptide hormone produced by the pancreas. It differs from native amylin in three amino acid substitutions and is a stable and soluble analog administered via subcutaneous injection at mealtime. Pramlintide regulates post-meal blood glucose levels by slowing gastric emptying, suppressing abnormal postprandial glucagon secretion, and promoting satiety, which leads to reduced caloric intake [46-50]. The glucose-dependent mechanism of pramlintide prevents hypoglycemia without therapies that cause it and helps exogenous insulin therapy better match physiologic needs.

The drug is only approved for use in patients with type 1 and type 2 diabetes who are taking prandial insulin. Dosing varies depending on the type of diabetes, and patients may require adjustments in pre-meal insulin doses to achieve euglycemia. The primary adverse events associated with pramlintide are nausea, vomiting, and anorexia, which are more common in patients with type 1 diabetes and tend to diminish over time. There is an increased risk of severe hypoglycemia, especially in patients with type 1 diabetes, when pramlintide is started at full doses without reducing insulin doses. Pramlintide has also been associated with migraine-like symptoms, likely due to the activation of amylin-responsive receptors in various body parts [47-54].

One significant benefit of pramlintide therapy is its association with weight loss. Clinical studies have shown that improved glycemic control with pramlintide is correlated with sustained and significant reductions in body weight. The drug induces satiety and decreases caloric intake, possibly contributing to weight loss. In combined data from pramlintide clinical trials, patients with type 1 diabetes experienced weight reductions of approximately 1.5 kg at 25 weeks, while patients with type 2 diabetes saw reductions of 1.2 kg compared to placebo-treated patients, who had slight weight gains.

Weight reductions were sustained for up to 52 weeks in long-term trials for both types of diabetes [50-56]. Regarding lactation, pramlintide has a high molecular weight and a short half-life, making it unlikely to pass into breast milk in clinically significant amounts. Additionally, it is a peptide likely to be digested in the infant's gastrointestinal tract, further reducing the potential for reaching clinically important levels in the infant's serum. However, since there is limited information on using pramlintide during breastfeeding, an alternate drug may be preferred to ensure the safety of the nursing infant [57,58].

Gastric Bypass Surgery

Gastric bypass surgery involves creating a small stomach reservoir and a gastrojejunoanastomosis using a defunctionalized Roux Y loop to alter digestion. It is recommended as an option for the treatment of type 2 diabetes in selected surgical candidates with a BMI ≥40 kg/m^2 (or ≥37.5 kg/m^2 in Asian individuals) and in adults with BMIs between 35.0 and 39.9 kg/m^2 (or 32.5–37.4 kg/m^2 in Asian Americans) who have not achieved lasting weight loss or improvement in comorbidities with non-surgical methods. Metabolic surgery may also be considered for adults with a BMI of 30.0–34.9 kg/m^2 (or 27.5–32.4 kg/m^2 in Asian American individuals) who have not succeeded with non-surgical methods [59]. While there are no absolute contraindications to bariatric surgery, relative contraindications exist. These include severe heart failure, unstable coronary artery disease, end-stage lung disease, active cancer treatment, portal hypertension, drug/alcohol dependency, impaired intellectual capacity, and Crohn's

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disease, in the case of LRYGB. Additionally, gastric bypass surgery is generally contraindicated in patients with uncontrolled medical conditions such as severe cardiovascular disease, uncontrolled hypertension, or uncontrolled diabetes. Patients with active substance abuse and severe mental health disorders may not be suitable candidates due to hindrances in post-operative recovery and adherence to lifestyle changes. Pregnant or planning pregnant women, individuals with previous gastrectomy or bowel resection, young adolescents, and patients at high surgical risk may also not be ideal candidates for the procedure [60].

Studies have demonstrated the efficacy of gastric bypass surgery in weight loss for individuals with a BMI greater than 35 kg/m^2 and those with a lower BMI. Randomized clinical trials and observational studies have shown significant weight loss in gastric bypass groups compared to non-surgical treatment groups. The surgery has also been associated with superior glycemic control, cardiovascular risk reduction, decreased incidence of microvascular diseases, improved quality of life, and reduced risk of cancer and other associated risks. Gastric bypass surgery has been found to lower triglyceride levels, increase high-density lipoprotein (HDL) cholesterol, and reduce the need for insulin in type 2 diabetes patients [61-64]. In some cases, metabolic surgery has shown potential benefits for individuals with type 1 diabetes, but larger and longer studies are needed to confirm its role in these cases. Despite the high initial costs, some analyses have suggested that metabolic surgery may be cost-effective for people with type 2 diabetes, depending on assumptions about its long-term efficacy and safety [65]. Overall, gastric bypass surgery appears to be a valuable treatment option for selected individuals with obesity and type 2 diabetes, offering significant weight loss, improved metabolic profiles, and reduced cardiovascular risks [66].

Conclusion

The treatment of weight loss in individuals with diabetes requires a comprehensive approach. Pharmacological interventions, such as metformin, GLP-1 receptor agonists, SGLT-2 inhibitors, and amylin mimetics, can play a significant role in weight reduction and glycemic control. Additionally, dual GIP/GLP-1 agonists, such as tirzepatide, demonstrated significant potential in treating type 2 diabetes and obesity, offering considerable weight loss and glycemic control. However, further research is needed to assess their long-term cardiovascular safety and the impact on other cardiometabolic complications.

Gastric bypass surgery is a valuable treatment option for selected individuals with obesity and type 2 diabetes, offering significant weight loss and improved metabolic profiles. It has been associated with superior glycemic control, cardiovascular risk reduction, and improved quality of life. However, it is essential to carefully select suitable candidates for surgery and consider potential contraindications and risks. Personalized treatment plans, lifestyle modifications, and continued research are needed to optimize outcomes and improve management strategies for weight loss in individuals with diabetes.

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How to cite this article: Mayra Rebeca Dominguez de R, Jhon Navarro G, Patricia V Visbal L, Felix Ricardo Bonilla B, Isaac Alberto Gomez H. Weight Loss in Diabetes: Pharmacological Management and Other Strategies. Curre Res Diabetes & Obes J 2023; 17(1): 555953.
DOI: 10.19080/CRDOJ.2023.17.555953

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