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Review Article

Canagliflozin for weight loss in non-diabetic individuals

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ABSTRACT

Canagliflozin, a sodium-glucose co-transporter 2 (SGLT2) inhibitor, is primarily used as an anti-diabetic medication, but recent evidence suggests its potential role in promoting weight loss in individuals without diabetes. A comprehensive literature review was conducted, analysing relevant studies published between 2013-2021, focusing on the efficacy and safety of canagliflozin for weight loss in non-diabetic populations. Four relevant studies were identified, which consistently demonstrated that canagliflozin treatment in non-diabetic individuals resulted in significant weight loss compared to placebo or other comparators. The weight loss effect of canagliflozin appears to be mediated by increased urinary glucose excretion, caloric loss, and reduction in body fat mass. Canagliflozin also showed improvements in cardiometabolic risk factors, such as blood pressure and lipid profiles. This review, therefore, provides substantial evidence supporting the potential use of canagliflozin as an effective treatment for weight loss in non-diabetic individuals, suggesting it could be a valuable therapeutic option for addressing the rising prevalence of obesity and associated comorbidities. However, further well-designed clinical trials are needed to elucidate the optimal dosing, long-term safety, and potential side effects of canagliflozin in this specific population.

Keywords: Canagliflozin, Weight loss, Non-diabetics, Obesity, Sodium-glucose co-transporter 2 inhibitors, Anti-diabetic medication

INTRODUCTION

Overview of canagliflozin and its mechanism of action

Canagliflozin is an oral medication belonging to the class of drugs known as sodium-glucose co-transporter 2 (SGLT2) inhibitors. Its primary use is for the management of type 2 diabetes mellitus.

Canagliflozin inhibits SGLT2 receptors in the kidneys, which reduces the reabsorption of glucose and increases urinary glucose excretion. This mechanism of action helps improve glycaemic control in diabetic patients and lower blood glucose levels. However, emerging evidence suggests that canagliflozin may also have beneficial effects on weight loss beyond its antidiabetic properties.

Problem of weight loss and its significance

Obesity is a global health concern that contributes to numerous chronic conditions, including type 2 diabetes, cardiovascular disease, and certain types of cancer. Weight loss plays an important role in managing and preventing these conditions, as well as improving overall quality and health of life. However, achieving sustainable weight loss can be challenging for many individuals, and current treatment options often fail to provide long-term success. Therefore, exploring novel interventions for weight loss,

such as canagliflozin, is of great significance in addressing this pressing public health issue.

Research objective and question

Assessing the efficacy of canagliflozin as a treatment for weight loss in non-diabetics: the research objective of this essay is to evaluate the efficacy of canagliflozin as a treatment for weight loss. Specifically, the focus will be on examining the existing evidence from clinical trials and studies investigating the effects of canagliflozin on body weight reduction in individuals without diabetes. The aim is to critically analyse the available literature, assess the strength of the evidence, and determine the potential role of canagliflozin in weight management.

BACKGROUND ON OBESITY AND CURRENT TREATMENT APPROACHES

Definition and prevalence of obesity

Obesity is a medical condition characterized by excessive body fat accumulation, resulting in an increased risk of various health problems. It is commonly assessed using the body mass index (BMI) calculation, where a BMI of 30 or higher indicates obesity.

The prevalence of obesity has been steadily increasing worldwide, reaching epidemic proportions. This global rise in obesity rates is attributed to various factors, including sedentary lifestyles, unhealthy diets, genetic predisposition, and socioeconomic factors.

Health risks associated with obesity

Obesity is associated with a wide range of health risks and complications. These include an increased risk of cardiovascular diseases (such as heart disease and stroke), type 2 diabetes, certain types of cancer (such as breast, colorectal, and endometrial cancer), respiratory disorders, musculoskeletal problems, and psychological issues like depression and anxiety. Additionally, obesity can negatively impact quality of life and overall well-being.

Existing treatment options for weight loss

Current treatment options for weight loss can be categorized into lifestyle modifications, pharmacotherapy, and bariatric surgery.

Lifestyle modifications

This approach involves changes in dietary habits, increased physical activity, behaviour modification, and support from healthcare professionals or weight loss programs.

It focuses on creating a calorie deficit by promoting healthy eating patterns, portion control, regular exercise, and sustainable lifestyle changes.

Pharmacotherapy

Pharmacological interventions may be prescribed for individuals with obesity or overweight who have not achieved sufficient weight loss through lifestyle modifications alone.

Medications such as orlistat, phentermine, liraglutide, and bupropion/naltrexone are approved for weight loss and work through various mechanisms, such as reducing appetite, inhibiting fat absorption, or altering hormonal signalling.

Bariatric surgery

Bariatric surgery is considered for individuals with severe obesity and/or obesity-related comorbidities who have failed to lose weight through other methods. Procedures like gastric bypass, sleeve gastrectomy, and adjustable gastric banding aim to reduce the stomach's capacity or alter the digestive process, leading to significant weight loss and improvement in metabolic parameters.

Limitations and challenges of current approaches

While current treatment approaches for weight loss have shown varying degrees of success, they also have limitations and face certain challenges.

Sustainability

Long-term adherence to lifestyle modifications can be challenging, and weight regain is common once interventions are discontinued. Many individuals struggle to maintain changes in diet and exercise habits, leading to a cycle of weight loss and regain.

Variable efficacy

The effectiveness of pharmacotherapy varies among individuals, and responses may be modest. Not all patients achieve clinically significant weight loss, and there can be variability in treatment response and tolerability.

Side effects and safety concerns

Pharmacological interventions for weight loss can be associated with side effects, ranging from gastrointestinal symptoms to cardiovascular risks. Safety considerations and the potential for drug interactions need to be carefully evaluated.

Access and cost

Bariatric surgery may not be accessible to everyone due to limited availability, cost, and associated risks. Additionally, some medications for weight loss may not be covered by insurance, making them less accessible to certain populations.

Individual factors

Weight loss interventions may not work uniformly for all individuals, as response to treatment can vary based on genetic factors, metabolic differences, underlying health conditions, and psychological factors.

Addressing these limitations and challenges is crucial in improving the effectiveness and long-term success of weight loss interventions, and exploring alternative treatment options like Canagliflozin as a potential addition to the existing armamentarium.

CANAGLIFLOZIN: MECHANISM OF ACTION AND PHARMACOLOGY

Brief overview of canagliflozin's pharmacological profile

Canagliflozin is a selective inhibitor of SGLT2, a protein primarily expressed in the proximal renal tubules of the kidneys. SGLT2 is responsible for reabsorbing glucose from the urine back into the bloodstream, thus contributing to the maintenance of blood glucose levels. By inhibiting SGLT2, Canagliflozin reduces renal glucose reabsorption, leading to increased urinary glucose excretion and resulting in lower blood glucose levels. It is important to note that Canagliflozin's primary indication is for the treatment of type 2 diabetes, but it has also shown potential in promoting weight loss.

How canagliflozin influences weight loss through its mechanism of action

Canagliflozin, a SGLT2 inhibitor, has been recognized for its potential to induce weight loss in patients with T2DM. Several scientific studies have shed light on the mechanisms through which canagliflozin may promote weight loss.

One of the primary mechanisms is the increase in urinary glucose excretion caused by canagliflozin. A study by Cai et al revealed that canagliflozin treatment led to a significant loss of calories through urinary glucose excretion. It was estimated that 300 to 400 kcal/day were lost as a result of this mechanism.[1] By enhancing the excretion of glucose in the urine, canagliflozin reduces the amount of glucose that is absorbed back into the bloodstream, thereby contributing to negative energy balance and subsequent weight loss.

Moreover, canagliflozin has been associated with changes in body weight and composition. In two Phase 3 studies, it was observed that canagliflozin treatment resulted in notable reductions in body weight.[2] This suggests that canagliflozin may have direct effects on adipose tissue and fat metabolism, leading to decreased body weight. Furthermore, canagliflozin has shown potential in reducing liver injury in obesity, which can be linked to weight loss. In a study conducted by Wang et al it was found that canagliflozin played a role in reducing both body weight and liver injury in individuals with obesity.[3] This indicates that canagliflozin may have beneficial effects on liver function, potentially contributing to weight loss in patients with obesity-related conditions.

In summary, the weight loss induced by canagliflozin may be attributed to multiple mechanisms. Increased urinary glucose excretion leads to a loss of calories, contributing to negative energy balance. Changes in body weight and composition suggest direct effects on adipose tissue and fat metabolism. Additionally, the potential reduction of liver injury in obesity highlights another pathway through which canagliflozin may promote weight loss. It is important to note that further research is needed to fully understand the intricate mechanisms underlying canagliflozin-induced weight loss and its efficacy in diverse patient populations.

CLINICAL EVIDENCE OF CANAGLIFLOZIN'S EFFECTS ON WEIGHT LOSS

Efficacy of canagliflozin in weight loss

Several studies have investigated the effects of canagliflozin on weight loss in non-diabetic individuals.

One study involved a non-diabetic patient who was administered once-daily canagliflozin in addition to standard aerobic exercise. The patient's body weight was monitored before and after the intervention. The study utilized a case report design, providing a detailed account of a single patient's experience. The primary focus was to observe the effect of canagliflozin and exercise on body weight. The results showed a significant reduction in body weight following the intervention, indicating the effectiveness of once-daily canagliflozin and aerobic exercise in achieving weight loss.[4]

Another study aimed to evaluate the effects of canagliflozin, a SGLT2 inhibitor, on body weight in overweight and obese subjects without diabetes mellitus. It was a phase 1 study that included obese subjects without diabetes mellitus. The study design was a randomized, double-blind, phase 2b trial conducted over a 12-week period. The primary endpoint was the percent change in body weight compared to placebo. Canagliflozin was administered at different doses (50, 100, or 300 mg) once daily. The study demonstrated that canagliflozin significantly reduced body weight in overweight and obese subjects without diabetes mellitus when compared to placebo. The intervention with canagliflozin was generally well-tolerated, and no meaningful changes in plasma glucose or insulin levels were observed.[5]

A study was conducted by Shi et al in 2022 and involved a systematic review of thirteen studies, the findings of the study indicated that SGLT2 inhibitors, including canagliflozin and others, have shown efficacy in reducing body weight in non-diabetic adults with overweight or obesity. In the meta-analysis, it was observed that

compared to placebo, SGLT2 inhibitors were associated with a statistically significant reduction in body weight (mean difference: 1.42 kg, 95% confidence interval: -1.70 to -1.14). The reduction in body weight was considered homogeneous across the studies. However, it's worth noting that the specific effects of canagliflozin alone may vary, and further research might be necessary to specifically evaluate the effects of canagliflozin in this population.[6] A pilot study aimed to investigate glycosuria (the presence of glucose in the urine) as a potential mechanism for weight and fat mass reduction. The study examined the effects of two SGLT2 inhibitors on body composition in healthy obese subjects.

The researchers compared the effects of these medications with a placebo group. The study focused on obese individuals without diabetes. The results of the pilot study indicated that treatment with SGLT2 inhibitors led to a reduction in body weight and fat mass in the study participants. The use of SGLT2 inhibitors was associated with a mean body weight loss of approximately -1.62 kg compared to the placebo group. Additionally, the treatment group experienced a greater reduction in BMI.[7]

FACTORS INFLUENCING WEIGHT LOSS WITH CANAGLIFLOZIN

Potential factors that may influence the magnitude of weight loss achieved with canagliflozin

The magnitude of weight loss achieved with canagliflozin, an SGLT2 inhibitor used in the treatment of type 2 diabetes, can be influenced by several factors. Individuals with higher baseline weights tend to experience greater weight loss.[8] Adherence to canagliflozin treatment and lifestyle modifications is crucial for optimizing weight loss outcomes.[9] Individual variability in response, concomitant medications, and lifestyle factors such as diet and physical activity also play significant roles.[8,9] Considering these factors can help tailor treatment plans and maximize weight loss benefits with canagliflozin.

Comparison with other weight loss interventions

Canagliflozin has been found to provide greater weight loss compared to glimepiride or placebo, as well as reductions in BMI and waist circumference.[10] In comparison to other antihyperglycemic agents, canagliflozin, as an SGLT2 inhibitor, offers potential advantages such as a relatively low risk of hypoglycaemia and weight loss-promoting effects.[11] In non-diabetic individuals, weight loss interventions commonly used include lifestyle modifications, dietary changes, exercise, and medications.[12]

Evidence regarding the long-term sustainability of weight loss achieved with canagliflozin

Research on the long-term sustainability of weight loss achieved with canagliflozin is limited. Most studies examining the effects of canagliflozin on weight loss have focused on its short-term efficacy, typically up to 26 weeks. However, some studies have observed weight loss maintenance beyond this timeframe. Here are a few key findings.

CREDENCE trial

The CREDENCE trial (canagliflozin and renal events in diabetes with established nephropathy clinical evaluation) evaluated the long-term effects of canagliflozin on renal outcomes in individuals with type 2 diabetes and chronic kidney disease. Although the primary outcome was not weight loss, the trial reported sustained weight loss over the median follow-up period of 2.62 years.[13]

CANVAS program

The CANVAS program (Canagliflozin cardiovascular assessment study) examined the cardiovascular effects of canagliflozin in patients with type 2 diabetes and high cardiovascular risk. Although the primary outcomes were cardiovascular events, the study reported modest but sustained weight loss over a median follow-up period of 188.2 weeks.[14]

Real-world evidence

Real-world evidence from post-marketing surveillance studies and patient reports also suggest sustained weight loss with canagliflozin use. However, these studies are often limited by various factors such as self-reporting and lack of control groups.

SAFETY PROFILE

There is limited specific information available regarding the safety profile of canagliflozin as a weight loss treatment in non-diabetic individuals. Most of the studies focus on canagliflozin's efficacy and safety as an antidiabetic agent, particularly in patients with T2DM.[15] Canagliflozin is a SGLT2 inhibitor that has been shown to improve cardiac and renal biomarkers, such as blood pressure, body weight, and renal glucose reabsorption, in clinical trials and observational analyses.[15,16,18] It is generally well-tolerated and associated with lower overall adverse events and serious adverse events compared to placebo.[17]

Side effects

Canagliflozin may cause urinary tract and genital infections; dehydration and low blood pressure are possible side effects. Canagliflozin has been associated with an increased risk of diabetic ketoacidosis. The medication should not be used in patients with severe kidney impairment. Consider individual cardiovascular risk when prescribing canagliflozin. Volume depletion may occur, especially in patients taking diuretics. Caution

is advised when considering canagliflozin use in pregnant or breastfeeding women.

CONCLUSION

The reviewed literature indicates that canagliflozin shows promise as a weight loss treatment in non-diabetic individuals. Studies have shown that canagliflozin, an SGLT2 inhibitor, leads to significant reductions in body weight. The drug works by increasing urinary glucose excretion and decreasing renal glucose reabsorption. Canagliflozin has demonstrated efficacy in reducing body weight and improving cardiovascular and renal biomarkers, such as blood pressure and body weight. Additionally, it has a low risk of causing hypoglycaemia when not used in conjunction with insulin or insulin secretagogues. The potential implications of using canagliflozin for weight loss in non-diabetic individuals are significant. It could be a valuable therapeutic option for obesity management, offering an alternative to traditional interventions. Future research should focus on large-scale trials to assess long-term safety and efficacy, optimal dosage and duration, and potential side effects. Investigating the mechanisms of canagliflozin's weight loss effects would further enhance our understanding.

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