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Review

The Impact of Sodium-Glucose Co-Transporter-2 Inhibitors on Weight Loss in Obesity

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ABSTRACT

Obesity is a chronic medical condition characterized by excessive body fat accumulation, posing health risks. Obesity is influenced by genetic, environmental, behavioral, and socioeconomic factors, emphasizing its complexity. It is associated with numerous comorbidities, including type 2 diabetes, cardiovascular diseases, respiratory disorders, and certain cancers. Obesity management involves a multidisciplinary approach, including lifestyle modifications, behavioral therapy, pharmacotherapy, and bariatric surgery in severe cases. Studies highlight the weight loss effects of various sodium-glucose co-transporter 2 inhibitors (SGLT-2i) such as canagliflozin, dapagliflozin, and empagliflozin, in diabetic and non-diabetic obese individuals. Modest reductions in body weight have been observed, supporting the use of SGLT-2i as a weight management option. SGLT-2i, initially used for diabetes, have demonstrated additional benefits for managing obesity and related metabolic conditions. Clinical trials and real-world evidence consistently show significant weight loss in individuals treated with SGLT-2i, independent of their glucose-lowering properties. The weight loss observed is smaller than expected due to adaptive mechanisms that increase energy intake to counterbalance the loss. Combining SGLT-2i with appetite-suppressing drugs, such as GLP-1 analogs, may enhance weight reduction. However, further research is needed to optimize the weight-reducing effects and explore combination therapies. Despite these limitations, SGLT-2i remains valuable in managing obesity and offers benefits beyond glycemic control.

Keywords: Obesity, SGLT-2 inhibitors, weight loss, diabetes

INTRODUCTION

Obesity is a complex and chronic medical condition characterized by an excessive accumulation of body fat to the extent that it poses a health risk (1). It is commonly defined based on an individual's body mass index (BMI), which is calculated by dividing a person's weight in kilograms by the square of their height in meters (BMI = weight (kg) / height² (m²)).

The World Health Organization (WHO) and many health organizations worldwide use the following BMI classifications to define obesity:

- •BMI < 18.5: Underweight
- •BMI 18.5 - 24.9: Normal weight
- •BMI 25.0 - 29.9: Overweight
- •BMI ≥ 30.0: Obesity

Within the obesity category, there are further classifications based on BMI:

- •Class I Obesity: BMI 30.0 - 34.9
- •Class II Obesity: BMI 35.0 - 39.9
- •Class III Obesity (also known as severe or morbid obesity): BMI ≥ 40.0

It's important to note that while BMI is a useful screening tool, it has limitations and does not provide a complete picture of an individual's health. Other factors such as body composition, distribution of fat, and metabolic health should also be considered when assessing obesity.

Obesity is influenced by a combination of genetic, epigenetic, environmental, behavioral, and socioeconomic factors (2,3). Obesity is a complex condition influenced by various factors, and not solely a result of personal choices or lack of willpower.

Obesity has significant health implications and is associated with an increased risk of various comorbidities, including:

- •Type 2 diabetes
- •Cardiovascular diseases (e.g., hypertension, heart disease, stroke)
- •Respiratory disorders (e.g., sleep apnea, asthma)

•Musculoskeletal conditions (e.g., osteoarthritis)
•Certain cancers (e.g., breast, colorectal, prostate)
•Metabolic syndrome
•Non-alcoholic fatty liver disease
•Mental health issues (e.g., depression, anxiety)
•Reproductive disorders (e.g., polycystic ovary syndrome)

Obesity management involves a multidisciplinary approach that includes lifestyle modifications (such as adopting a healthy diet and increasing physical activity), behavioral therapy, pharmacotherapy, and, in severe cases, bariatric surgery. Successful management of obesity aims to improve overall health, reduce the risk of obesity-related complications, and enhance the quality of life for individuals affected by this condition. Moreover, clinicians must stay updated, especially regarding weight loss pharmacotherapies, before referring to an invasive intervention since bariatric interventions bear more complications compared to pharmacological interventions.

Sodium-glucose co-transporter-2 (SGLT-2) inhibitors (SGLT-2i) are a class of medications that inhibit sodium glucose co-transporter-2 protein localized in the brush border on S2 and S3 segments of proximal renal tubules and primarily used for the management of type 2 diabetes (4,5). SGLT-2i increase the excretion of glucose through urine, thereby lowering blood glucose levels (6). While initially developed for diabetes treatment, SGLT-2i have shown additional benefits beyond glycemic control. In recent years, they have gained attention for their potential use in managing obesity and related metabolic conditions (6,7).

Clinical trials and real-world evidence have consistently demonstrated significant weight loss in individuals treated with SGLT-2i (7,8). The weight loss is attributed to multiple factors, including calorie loss through glucosuria (glucose excretion in urine), reduction in fat mass, and decreased visceral adiposity. The weight loss effects are independent of the glucose-lowering properties of these medications, making them a valuable option for individuals with obesity, even in the absence of diabetes (8,9). Previous studies demonstrated some oral antidiabetics, as SGLT-2i can, result in weight loss.

•SGLT-2i: As mentioned earlier, SGLT-2i, such as canagliflozin, dapagliflozin, and empagliflozin, have been consistently associated with weight loss. These medications increase urinary glucose excretion, leading to calorie loss and reductions in fat mass (7-9).

•GLP-1 receptor agonists: While GLP-1 receptor agonists are usually administered via injection, there is an oral formulation available (semaglutide). GLP-1 receptor agonists, such as exenatide, liraglutide, and semaglutide, have been shown to promote weight loss. They work by slowing gastric emptying, increasing satiety, and reducing appetite (10-11).

•Metformin: Recent studies have provided emerging evidence supporting the notion that metformin-induced weight loss can be attributed to various mechanisms, including the modulation of hypothalamic appetite-regulatory centers, alterations in the gut microbiome, and the reversal of age-related effects. Furthermore, metformin is being investigated for its potential role in managing the complications associated with obesity, such as hepatic steatosis, obstructive sleep apnea, and osteoarthritis (12,13).

STUDIES ADDRESSING WEIGHT LOSS EFFECTS OF SGLT-2I IN DIABETIC AND NON-DIABETIC OBESE INDIVIDUALS

Weight Loss in SGLT-2i Studies

Weight loss effects of SGLT-2i were observed in many studies (14). The leading trials were listed below regarding this topic:

•The EMPA-REG OUTCOME trial: This landmark trial evaluated empagliflozin in patients with type 2 diabetes and established cardiovascular disease. It demonstrated significant weight loss in patients treated with empagliflozin compared to those receiving a placebo, with an average weight reduction of approximately 2 kg (15).

•The CANVAS Program: This study investigated the effects of canagliflozin in patients with type 2 diabetes and a high risk of cardiovascular events. It revealed that canagliflozin was associated with weight loss, with participants experiencing an average weight reduction of about 2-3 kg compared to the placebo group (16).

•Dapagliflozin trials: Various clinical trials, including the DECLARE-TIMI 58 trial, have shown that dapagliflozin leads to modest weight loss in patients with type 2 diabetes. The weight reduction observed in these trials ranged from approximately 1-2 kg (17,18).

•Real-world evidence: Several real-world studies have corroborated the findings from clinical trials, demonstrating weight loss in individuals using SGLT-2i. These studies have shown weight reductions ranging from 1-5 kg over varying durations of treatment (5,19).

Weight Loss With SGLT-2i in Patients with Obesity

The results of many studies demonstrated reductions in body weight compared to placebo for all SGLT-2i treatments of approximately 1.5–2 kg, and these effects are probably dose-dependent (20). Bays et al. reported that in overweight and obese subjects without diabetes mellitus, canagliflozin significantly

reduced body weight compared with placebo and was generally well tolerated (8). Bays et al., in a recent study, demonstrated that licogliflozin (a dual inhibitor of sodium/glucose co-transporter 1 and 2) produced significant reductions in body weight versus placebo in adults with overweight or obesity. However, the magnitude of weight reduction was modest (21). They suggested that the 50-mg once-daily dose had perhaps the best balance between efficacy and tolerability. He et al. reported similar results with licogliflozin use in obese patients with or without diabetes (22). Hollander et al. studied the coadministrations of canagliflozin and phentermine in phase 2a, a randomized, double-blind, placebo-controlled, multicenter, parallel-group study. Phentermine is a sympathomimetic amine anorectic that plays a role in stimulating the satiety centers in the brain through the upregulation of dopamine, noradrenaline, and serotonin. They highlighted that canagliflozin and phentermine produced meaningful reductions in body weight and were generally well tolerated in individuals who were overweight or obese without type 2 diabetes (23) (**Table 1**). Dapagliflozin/exenatide dual therapy reduced body weight (≥5% body weight loss) and frequency of prediabetes and was well tolerated in obese adults without diabetes (24). Dapagliflozin administration in patients with prediabetes with mild obesity (BMI; 30.3±3.5 kg/m2) decreased body weight, BMI, waist circumference, fasting glucose, and uric acid, with a tendency to increase insulin sensitivity without changes in insulin secretion (25).

There is an ongoing discussion and varying perspectives regarding the use of SGLT-2i for the purpose of weight reduction. Ferrannini et al. found that SGLT-2i used alone results in a disproportionate decrease in body weight due to their glucosuric effects. However, the weight loss observed with SGLT-2i is smaller than expected based solely on their ability to increase urinary glucose excretion. This may be due to the body's adaptive mechanism of increasing energy intake to counterbalance weight loss. According to Ferrannini et al., the human body may have developed an enhanced appetite as a way to stabilize body weight in response to the weight loss effects of SGLT-2i. This concept is supported by other researchers. As a result, there is growing interest in combining SGLT-2i with appetite-suppressing drugs that act on the hypothalamus, such as GLP-1 analogs (26,27). Additionally, a recent meta-analysis including 116 randomized-controlled trials reported that compared with SGLT-2i, SGLT-1/SGLT-2 inhibitors had a significantly larger reduction in weight (28). The summary of a few studies highlighting the outcomes of SGLT-2i use on weight change is given in **Table 1**.

CONCLUSION

The studies included in this review suggest that SGLT-2i are effective as a weight loss therapy in patients with obesity with or without diabetes mellitus. These

Table 1. Several studies are available for revealing favorable outcomes of SGLT-2 inhibitor use for weight reduction.

Study	Study Design	Participants	Outcomes
Licogliflozin, a Novel SGLT-1 and 2 Inhibitor: Body Weight Effects in a Randomized Trial in Adults with Overweight or Obesity (2020) (21)	RCT, 24 weeks, PBO vs licogliflozin (once daily or twice daily)	N=674, adults with overweight or obesity	≥5% weight loss at week 24 revealed significant differences versus placebo, which were most pronounced with highest doses of 50 mg twice daily.
Coadministration of Canagliflozin and Phentermine for Weight Management in Overweight and Obese Individuals Without Diabetes: A Randomized Clinical Trial (2017) (23)	RCT, 26 weeks, phase 2a PBO vs CANA 300 mg	N=335, obeses or overweight without type 2 diabetes	≥%5 weight loss and superior SBP reduction with CANA
Dapagliflozin once daily plus exenatide once weekly in obese adults without diabetes: Sustained reductions in body weight, glycaemia and blood pressure over 1 year (2017) (24)	RCT, 52 weeks, DAPA+Exenatide vs PBO	N=50, obese adults without diabetes	-5.7 kg weight change with treatment, -5.3 kg total body fat, -12 mmHg SBP
Effect of Dapagliflozin on Insulin Secretion and Insulin Sensitivity in Patients with Prediabetes (2018) (25)	RCT, 12 weeks, DAPA vs PBO	N=24, prediabetes with mean BMI 30.3 kg/m^2	BMI, WC, FG, UA reduction with DAPA
Sodium-Glucose Co-Transporter-2 Inhibitors in Non-Diabetic Adults With Overweight or Obesity: A Systematic Review and Meta-Analysis (2021) (29)	Systematic review and meta-analysis of 6 RCTs Various SGLT-2i types	N=872, adults with overweight or obesity without diabetes	-1.42 kg BW, -0.47 BMI with SGLT-2i

SGLT-2; Sodium-glucose co-transporter 2, RCT; randomized controlled trial, PBO; placebo, CANA; canagliflozin, SBP; systolic blood pressure, BMI; body mass index, WC; waist circumference, FG; fasting glucose, UA; uric acid, SGLT-2i; Sodium-glucose co-transporter 2 inhibitor, BW; body weight

medications promote weight loss by facilitating glucose excretion through urine which leads to a loss of about 300 calories per day. However, the body can adapt to this condition by increasing appetite and calorie intake, resulting in less weight loss than initially expected. Since this adaptive response may partially attenuate the weight-reducing effects of SGLT-2i, combining a GLP-1 agonist with SGLT-2i will improve the weight-reduction strategy. Nonetheless, SGLT-2i remains a valuable option for weight management in individuals with obesity, and its benefits extend beyond glycemic control.

DECLARATIONS

Ethics Committee Approval: Not necessary.

Informed Consent Form: Not necessary.

Referee Evaluation Process: Externally peer-reviewed.

Conflict of Interest Statement: Authors declare no conflict of interest.

REFERENCES

1.Apovian CM. Obesity: definition, comorbidities, causes, and burden. *Am J Manag Care*. 2016 Jun;22(7 Suppl):s176-85. PMID: 27356115.

2.McLaren L. Socioeconomic status and obesity. *Epidemiol Rev.* 2007;29:29-48. doi: 10.1093/epirev/mxm001. Epub 2007 May 2. PMID: 17478442.

3.Ling C, Rönn T. Epigenetics in Human Obesity and Type 2 Diabetes. *Cell Metab.* 2019 May 7;29(5):1028-1044. doi: 10.1016/j.cmet.2019.03.009. Epub 2019 Apr 11. PMID: 30982733; PMCID: PMC6509280.

4.Ni L, Yuan C, Chen G, Zhang C, Wu X. SGLT2i: beyond the glucose-lowering effect. *Cardiovasc Diabetol.* 2020 Jun 26;19(1):98. doi: 10.1186/s12933-020-01071-y. PMID: 32590982; PMCID: PMC7320582.

5.Palanca A, van Nes F, Pardo F, Ampudia Blasco FJ, Mathieu C. Real-world Evidence of Efficacy and Safety of SGLT2 Inhibitors as Adjunctive Therapy in Adults With Type 1 Diabetes: A European Two-Center Experience. *Diabetes Care.* 2022 Mar 1;45(3):650-658. doi: 10.2337/dc21-1584. PMID: 35061022.

6.Gronda E, Lopaschuk GD, Arduini A, Santoro A, Benincasa G, Palazzuoli A, Gabrielli D, Napoli C. Mechanisms of action of SGLT2 inhibitors and their beneficial effects on the cardiorenal axis. *Can J Physiol Pharmacol.* 2022 Feb;100(2):93-106. doi: 10.1139/cjpp-2021-0399. PMID: 35112597.

7.Bolinder J, Ljunggren Ö, Johansson L, Wilding J, Langkilde AM, Sjöström CD, Sugg J, Parikh S. Dapagliflozin maintains glycaemic control while reducing weight and body fat mass over 2 years in patients with type 2 diabetes mellitus inadequately controlled on metformin. *Diabetes Obes Metab.* 2014 Feb;16(2):159-69. doi: 10.1111/dom.12189. Epub 2013 Aug 29. PMID: 23906445.

8.Bays HE, Weinstein R, Law G, Canovatchel W. Canagliflozin: effects in overweight and obese subjects without diabetes mellitus. *Obesity (Silver Spring).* 2014 Apr;22(4):1042-9. doi: 10.1002/oby.20663. Epub 2013 Dec 9. PMID: 24227660; PMCID: PMC4285787.

9.He YL, Haynes W, Meyers CD, Amer A, Zhang Y, Mahling P, Mendonza AE, Ma S, Chutkow W, Bachman E. The effects of licogliflozin, a dual SGLT1/2 inhibitor, on body weight in obese patients with or without diabetes. *Diabetes Obes Metab.* 2019 Jun;21(6):1311-1321. doi: 10.1111/dom.13654. Epub 2019 Mar 15. PMID: 30724002.

10. Jensterle M, Rizzo M, Haluzík M, Janež A. Efficacy of GLP-1 RA Approved for Weight Management in Patients With or Without Diabetes: A Narrative Review. *Adv Ther.* 2022 Jun;39(6):2452-2467. doi: 10.1007/s12325-022-02153-x. Epub 2022 May 3. PMID: 35503498; PMCID: PMC9063254.

11.Jepsen MM, Christensen MB. Emerging glucagon-like peptide 1 receptor agonists for the treatment of obesity. *Expert Opin Emerg Drugs.* 2021 Sep;26(3):231-243. doi: 10.1080/14728214.2021.1947240. Epub 2021 Jul 6. PMID: 34176426.

12.Hui F, Zhang Y, Ren T, Li X, Zhao M, Zhao Q. Role of metformin in overweight and obese people without diabetes: a systematic review and network meta-analysis. *Eur J Clin Pharmacol.* 2019 Apr;75(4):437-450. doi: 10.1007/s00228-018-2593-3. Epub 2018 Dec 3. PMID: 30511328.

13.Yerevanian A, Soukas AA. Metformin: Mechanisms in Human Obesity and Weight Loss. *Curr Obes Rep.* 2019 Jun;8(2):156-164. doi: 10.1007/s13679-019-00335-3. PMID: 30874963; PMCID: PMC6520185.

14.Pratama KG, Tandarto K, Hengky A. WEIGHT LOSS EFFECT OF SODIUM-GLUCOSE COTRANSPORTER-2 (SGLT2) INHIBITORS IN PATIENTS WITH OBESITY WITHOUT DIABETES: A SYSTEMATIC REVIEW. *Acta Endocrinol (Buchar).* 2022 Apr-Jun;18(2):216-224. doi: 10.4183/aeb.2022.216. PMID: 36212248; PMCID: PMC9512389.

15.Zinman B, Wanner C, Lachin JM, Fitchett D, Bluhmki E, Hantel S, Mattheus M, Devins T, Johansen OE, Woerle HJ, Broedl UC, Inzucchi SE; EMPA-REG OUTCOME Investigators. Empagliflozin, Cardiovascular Outcomes, and Mortality in Type 2 Diabetes. *N Engl J Med.* 2015 Nov 26;373(22):2117-28. doi: 10.1056/NEJMoa1504720. Epub 2015 Sep 17. PMID: 26378978.

16.Neal B, Perkovic V, Mahaffey KW, de Zeeuw D, Fulcher G, Erondu N, Shaw W, Law G, Desai M, Matthews DR; CANVAS Program Collaborative Group. Canagliflozin and Cardiovascular and Renal Events in Type 2 Diabetes. *N Engl J Med.* 2017 Aug 17;377(7):644-657. doi: 10.1056/NEJMoa1611925. Epub 2017 Jun 12. PMID: 28605608.

17.Furtado RHM, Raz I, Goodrich EL, Murphy SA, Bhatt DL, Leiter LA, McGuire DK, Wilding JPH, Aylward P, Dalby AJ, Dellborg M, Dimulescu D, Nicolau JC, Oude Ophuis AJM, Cahn A, Mosenzon O, Gause-Nilsson I, Langkilde AM, Sabatine MS, Wiviott SD. Efficacy and Safety of Dapagliflozin in Type 2 Diabetes According to Baseline Blood Pressure: Observations From DECLARE-TIMI 58 Trial. *Circulation*. 2022 May 24;145(21):1581-1591. doi: 10.1161/CIRCULATIONAHA.121.058103. Epub 2022 May 5. PMID: 35510542.

18. Sugiyama S, Jinnouchi H, Kurinami N, et al. Dapagliflozin Reduces Fat Mass without Affecting Muscle Mass in Type 2 Diabetes. *J Atheroscler Thromb*. 2018;25(6):467-476. doi:10.5551/jat.40873

19. Busko M. SGLT2 Inhibitors: Real-World Data Show Benefits Outweigh Risks. https://www.medscape.com/viewarticle/990323 March 31, 2023. Accessed date: May 18, 2023.

20.Liu XY, Zhang N, Chen R, Zhao JG, Yu P. Efficacy and safety of sodium-glucose cotransporter 2 inhibitors in type 2 diabetes: a meta-analysis of randomized controlled trials for 1 to 2years. *J Diabetes Complications.* 2015 Nov-Dec;29(8):1295-303. doi: 10.1016/j.jdiacomp.2015.07.011. Epub 2015 Jul 21. PMID: 26365905.

21.Bays HE, Kozlovski P, Shao Q, Proot P, Keefe D. Licogliflozin, a Novel SGLT1 and 2 Inhibitor: Body Weight Effects in a Randomized Trial in Adults with Overweight or Obesity. *Obesity (Silver Spring).* 2020 May;28(5):870-881. doi: 10.1002/oby.22764. Epub 2020 Mar 18. PMID: 32187881; PMCID: PMC7217021.

22.He YL, Haynes W, Meyers CD, Amer A, Zhang Y, Mahling P, Mendonza AE, Ma S, Chutkow W, Bachman E. The effects of licogliflozin, a dual SGLT1/2 inhibitor, on body weight in obese patients with or without diabetes. *Diabetes Obes Metab.* 2019 Jun;21(6):1311-1321. doi: 10.1111/dom.13654. Epub 2019 Mar 15. PMID: 30724002.

23.Hollander P, Bays HE, Rosenstock J, Frustaci ME, Fung A, Vercruysse F, Erondu N. Coadministration of Canagliflozin and Phentermine for Weight Management in Overweight and Obese Individuals Without Diabetes: A Randomized Clinical Trial. *Diabetes Care.* 2017 May;40(5):632-639. doi: 10.2337/dc16-2427. Epub 2017 Mar 13. PMID: 28289041.

24.Lundkvist P, Sjöström CD, Amini S, Pereira MJ, Johnsson E, Eriksson JW. Dapagliflozin once-daily and exenatide once-weekly dual therapy: A 24-week randomized, placebo-controlled, phase II study examining effects on body weight and prediabetes in obese adults without diabetes. *Diabetes Obes Metab.* 2017 Jan;19(1):49-60. doi: 10.1111/dom.12779. Epub 2016 Sep 26. PMID: 27550386; PMCID: PMC5215525.

25.Ramírez-Rodríguez AM, González-Ortiz M, Martínez-Abundis E. Effect of Dapagliflozin on Insulin Secretion and Insulin Sensitivity in Patients with Prediabetes. *Exp Clin Endocrinol Diabetes.* 2020 Aug;128(8):506-511. doi: 10.1055/a-0664-7583. Epub 2018 Aug 27. PMID: 30149417

26.Vallianou NG, Tsilingiris D, Kounatidis D, Lempesis IG, Karampela I, Dalamaga M. Sodiumglucose cotransporter2 inhibitors in obesity and associated cardiometabolic disorders: where do we stand? *Pol Arch Intern Med.* 2022 Oct 21;132(10):16342. doi: 10.20452/pamw.16342. Epub 2022 Sep 12. PMID: 36094176.

27.Ferrannini G, Hach T, Crowe S, Sanghvi A, Hall KD, Ferrannini E. Energy Balance After Sodium-Glucose Cotransporter 2 Inhibition. *Diabetes Care.* 2015 Sep;38(9):1730-5. doi: 10.2337/dc15-0355. Epub 2015 Jul 15. PMID: 26180105; PMCID: PMC4542276.

28.Cheong AJY, Teo YN, Teo YH, Syn NL, Ong HT, Ting AZH, Chia AZQ, Chong EY, Chan MY, Lee CH, Lim AYL, Kong WKF, Wong RCC, Chai P, Sia CH. SGLT inhibitors on weight and body mass: A meta-analysis of 116 randomized-controlled trials. *Obesity (Silver Spring).* 2022 Jan;30(1):117-128. doi: 10.1002/oby.23331. PMID: 34932882.

29.Zheng H, Liu M, Li S, Shi Q, Zhang S, Zhou Y, Su N. Sodium-Glucose Co-Transporter-2 Inhibitors in Non-Diabetic Adults With Overweight or Obesity: A Systematic Review and Meta-Analysis. *Front Endocrinol (Lausanne).* 2021 Aug 16; 12:706914. doi: 10.3389/fendo.2021.706914. PMID: 34484120; PMCID: PMC8415407.