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BRIEF REPORT

SGLT2 Inhibitors and the Clinical Implications of Associated Weight Loss in Type 2 Diabetes: A Narrative Review

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ABSTRACT

Introduction: The obesity epidemic is closely linked to the rising prevalence of type 2 diabetes (T2D). Body weight reduction remains an important challenge in patients with T2D, as it requires changing their overall metabolic control. Of all glucose-lowering therapies, only sodium–glucose cotransporter 2 inhibitors (SGLT2is) and glucagon-like peptide 1 receptor agonists (GLP-1 RAs) consistently result in weight improvement. Moreover, the same two classes have important cardiovascular and renal benefits. We summarize the key available information related to the weight loss effect of SGLT2is in T2D, focusing on the unexploited potential of these drugs.

Methods: Data on weight change with SGLT2is in patients with T2D were extracted from published cardiovascular outcomes trials (CVOTs). A discussion on patient perspectives about weight change is based on key preclinical and clinical trials, meta-analyses, and reviews and is supplemented by the authors' clinical judgment and research experience in the field.

Results: SGLT2is have a unique mode of action resulting in caloric loss through glycosuria. The anticipated weight loss with SGLT2is is not reflected in clinical trial results. There is a discrepancy between the magnitude of improvement in glycemic control and the weight loss, cardiovascular, and renal benefits obtained in large clinical trials.

Conclusion: The relationships between the magnitude of weight loss, improvement in glycemic control, and cardiorenal benefits with SGLT2i are still unclear. Potential mechanisms other than simple glycemic efficacy should be revealed and explained. Better weight control may be achieved if adequately intensive lifestyle changes are implemented and monitored in the T2D population treated with SGLT2is.

Keywords: CVOT; SGLT2 inhibitors; Type 2 diabetes; Weight loss

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Key Summary Points
Why carry out this review?
Obesity is closely linked to type 2 diabetes, and it is often difficult to achieve and maintain the control of these conditions.
SGLT2 inhibitors are among a few therapeutic options with clear benefits on weight management.
Accumulating evidence also demonstrates the important cardiorenal risk reduction in this patient population.
What was learned from this review?
The mechanisms by which SGLT2 inhibition leads to cardiorenal risk reduction are not fully elucidate, but reduction is an important component.
A structured approach to enhance SGLT2 inhibitor effects on weight may be implemented in clinical practice with the potential to enhance healthy behaviors to yield optimal outcomes in patients with type 2 diabetes.

DIGITAL FEATURES

This article is published with digital features, including a summary slide, to facilitate understanding of the article. To view digital features for this article go to https://doi.org/10.6084/m9.figshare.14718531.

INTRODUCTION

Type 2 diabetes (T2D) is a chronic disease with a major impact on patients' lives and health care systems. Its prevalence ranges from 7% to 25% [1] in European Union countries, and it is closely associated with overweight, obesity, and physical inactivity. Current estimates project an increase in T2D incidence of up to 20% in Europe in the next 20 years [1, 2]. In recent years, a new term has emerged, *diabesity*, reflecting the lack of weight control in patients with T2D [3] and the urgent need to find efficient strategies to address both diabetes and obesity.

Lifestyle changes promoting a reduction in caloric intake and an increase in energy expenditure represent the first-line action [4]. Patients with diabetes are educated on how to integrate a balanced, calorie-restricted diet and at least moderate physical activity in their routine. However, the implementation of daily healthy behavior is out of the strict control of the medical team, relying mostly on patients' understanding, motivation, and commitment to reaching realistic goals. Achievement and maintenance of normal weight is one of the most important treatment objectives for patients with T2D. Current therapeutic guidelines for T2D favor the early use of pharmacotherapies with demonstrated cardiovascular (CV) and renal benefits and a positive impact on weight control, irrespective of HbA1c value [4].

The development of sodium–glucose cotransporter 2 (SGLT2) inhibitors (SGLT2is) represents a major turning point in the management of diabetes owing to their unique mechanism of action and proven cardiovascular and renal benefits. One of the first reported additional benefits of SGLT2is was the weight loss effect, a result of caloric excretion and fat mass reduction.

Mechanism of Action and Effect on Energy Balance

Glycosuria is one of the key characteristics of poorly controlled diabetes, along with hyperglycemia and reduced insulin secretion and/or glucose utilization. Kidneys play a key role in maintaining glucose homeostasis, participating in steps along the whole metabolic chain of glucose, including its production (gluconeogenesis), utilization, filtration, reabsorption, and excretion.

SGLT2 is a high-capacity, low-affinity glucose transporter responsible for 90% of glucose reabsorption [5]. SGLT2 transporters are located

in kidneys, mainly in the S1 and S2 segments of the proximal convoluted tubules [6]. The rest of the glucose is further reabsorbed in the S3 segment by SGLT1, a low-capacity, high-affinity transporter. Tubular reabsorption reaches its maximum capacity at approximately 375 mg glucose/min, with a corresponding plasma glucose level of 200 mg/dL. Glycosuria occurs when this threshold is exceeded. If the hyperglycemic status is persistent, enhanced SGLT1/2 expression leads to paradoxically higher rates of glucose reabsorption [7].

The development of SGLT2is represents a major paradigm shift in the treatment of diabetes, turning a "defect" into a "mode of action". Four SGLT2is are currently approved in Europe for T2D treatment in combination with diet, exercise, and lifestyle changes (canagliflozin, dapagliflozin, empagliflozin, and ertugliflozin). They are not specifically approved by regulatory agencies for body weight reduction or treatment of obesity.

SGLT2 Inhibition: Effect on Body Weight

At therapeutic doses, urinary glucose excretion (UGE) is approximately 70–90 g/day, equivalent to 300 kcal/day, with additional diuresis of 400 mL/day [8, 9]. On the basis of the measured number of calories lost per day due to UGE, the expected weight loss would be approximately 10 kg/year [7]. The actual loss in body weight is much less, as shown in clinical trials and in clinical practice [10]. The relationship between SGLT2 inhibition and the caloric effect turned out to be much more complex and not a simple linear function, as initially thought [11]. Clinical trials and observational data show that weight reduction is lower than expected (approximately 2–5 kg), with variations according to baseline weight and concomitant medication. The body weight reduction during treatment with SGLT2is has been considered modest, though it provides large cardiovascular benefits. The mechanisms of weight loss and their influence on cardiorenal effects seem complex and are not fully elucidated.

This short review explores how the weight loss achieved with SGLT2is might influence multiple outcomes in T2D. Our aim is to briefly review the weight-related results reported in the context of cardiovascular outcomes trials (CVOTs) and discuss the possible implications for clinical practice.

METHODS

This is a narrative review based on a literature search in the PubMed database up to February 26, 2021. The search algorithm covered SGLT2 inhibitors or inhibition, canagliflozin, dapagliflozin, empagliflozin, ertugliflozin in connection with weight loss, weight change, metabolic change, adipose tissue, body composition, and CVOTs. Documentation was based on information from full-text publications, including preclinical and clinical trials, meta-analyses, and reviews on this topic. The search strategy was limited to English-language articles. Case reports on weight change with SGLT2is were not included. CVOTs in patients with T2D only were selected. Data extraction was conducted by one reviewer and revised by one coauthor. The selected references were individually searched to identify more information on the topic. The discussion is supplemented by the authors' research experience and clinical judgment.

Compliance with Ethics Guidelines

This article is based on previously conducted studies and does not contain any new studies with human participants or animals performed by any of the authors.

RESULTS

Difference Between Estimated Energy Loss and Actual Weight Reduction

Several years ago, Rajeev et al. [8] explored the discrepancy between the anticipated effect of SGLT2is and actual weight loss reported in clinical trials. They described several adaptive changes, such as compensatory hyperphagia,

increased gluconeogenesis, and a shift toward fatty acid utilization as a metabolic substrate.

Evidence to support compensatory hyperphagia is limited. In rodent models, lack of SGLT2 expression or chronic administration of dapagliflozin or canagliflozin led to weight reduction and increased caloric intake, considered to be compensatory to energy loss [12–14]. Similar predictions come from mathematical models with canagliflozin [15] or empagliflozin [16], showing several-fold increases in calorie intake compared to the adaptation in energy expenditure. However, this theory was not supported by a 12-week randomized controlled trial with dapagliflozin vs. placebo, where weight loss obtained with SGLT2 inhibition was not associated with a significant increase in food intake ($p = 0.659$) [17]. Another clinical trial in patients with T2D [18] showed similar results, with no significant association of dapagliflozin with compensatory carbohydrate intake.

Another possible explanation for the limited body weight decrease is an increase in glucagon effects, with promotion of renal and hepatic gluconeogenesis and a consequent increase in endogenous glucose production. However, the role of SGLT2 inhibition in endocrine regulation remains unclear.

Compensatory metabolic and endocrine processes do not totally counteract the weight loss effect. Clinical trials with SGLT2is have shown a biphasic pattern of weight loss: an initial large effect, probably resulting from enhanced fluid elimination, followed by a slow increase, with mean weights lower than baseline at any assessment [19, 20]. The gradual effect is maintained for up to 4 weeks with dapagliflozin [21] and has been explained by the reduction in visceral and subcutaneous fat mass [21–23].

A Closer Look into Weight Changes Reported in CVOTs

Developed for T2D treatment and currently used as antihyperglycemic drugs, SGLT2is have proven cardiovascular and renal benefits in large CVOTs. Since the primary and key secondary objectives have focused on the reduction of CV and renal events, weight changes were only briefly reported in the primary manuscripts (Table 1) [24–28].

CANVAS Program

A post hoc analysis [29] showed similar cardiorenal results between different baseline body mass index (BMI) groups. The authors acknowledged a substantial variation in weight change over time. The weight decrease with canagliflozin vs. placebo was larger at the 12-month follow-up (− 2.77%; 95% CI − 2.95, − 2.59) than at the 3-month follow-up (− 1.72%; 95% CI − 1.83, − 1.62). The most plausible explanation resides in the time-additive effects of the dual mechanisms of weight loss with SGLT2is. A dose-dependent effect was observed at both time points. Early effects were positively associated with coadministration of insulin or glucagon-like peptide 1 receptor agonists (GLP-1 RA), as well as the absence of a history of heart failure or arterial hypertension (all p for trend < 0.05); however, a possible explanation was not apparent. A contradictory result was the larger weight reduction at 3 months in people with lower initial HbA1c. Nevertheless, the baseline weight did not influence the prevention of CV events by canagliflozin.

CREDENCE Trial

The CREDENCE trial was designed to primarily assess the renal outcomes with canagliflozin 100 mg/day vs. placebo in patients with T2D and reduced kidney function [25]. The average change in weight with canagliflozin vs. placebo (− 0.8 kg; 95% CI 0.69, 0.92) [25] was maintained irrespective of the initial glomerular filtration rate [30].

DECLARE-TIMI 58 Trial

The DECLARE-TIMI 58 trial outcomes (composite risk of CV disease and hospitalization for heart failure and its components, including CV and renal events) were analyzed according to

Table 1 Summary of weight change results with SGLT2is in CVOTs including patients with T2D only

CVOT name and SGLT2i	CVOT study population	Mean follow-up (SD), years	Baseline weight (SD), kg	Weight reduction (SD) with the SGLT2i, kg	Risk reduction for the primary objective
CANVAS [24]: canagliflozin	T2D and either symptomatic ASCVD or multiple CV risk factors *N* = 10,142 Mean age (BL) = 63.3 years Mean HbA1c (BL) = 8.2%	3.6 (2.0)	90.2 (NR)	− 1.6 (2.42)	3P-MACE HR = 0.86; 95% CI 0.75–0.97 *P* < 0.001 (non-inferiority) *P* = 0.02 (superiority) vs. placebo
CREDENCE [25]: canagliflozin	T2D and CKD and albuminuria *N* = 4401 Mean age (BL) = 63 years Mean HbA1c (BL) = 8.3%	2.6 (0.02–4.53)	87.1 (NR)	− 0.8 (1.95)	Composite of ESRD/doubling of serum creatinine vs. baseline/CV or renal death HR = 0.70; 95% CI 0.59–0.82 *P* = 0.00001 vs. placebo
DECLARE-TIMI 58 [26]: dapagliflozin	T2D and either symptomatic atherosclerotic CV disease or multiple CV risk factors *N* = 17,160 Mean age (BL) = 64.0 years Mean HbA1c (BL) = 8.3%	4.2 (3.9–4.4)	91.0 (NR)	− 1.8 (5.0)	3P-MACE HR = 0.93; 95% CI 0.84–1.03 *P* = 0.17 vs. placebo CV death/hHF HR = 0.83; 95% CI 0.73–0.95 *P* = 0.005 vs. placebo
EMPA-REG [27]: empagliflozin	T2D and established ASCVD *N* = 7020 Mean age (BL) = 63.1 years Mean HbA1c (BL) = 8.1%	3 (2.2–3.6)	86.3 (19.0)	− 2.00 (NR)	3P-MACE HR = 0.86; 95% CI 0.74–0.99 *P* = 0.04 (superiority)

Table 1 continued

CVOT name and SGLT2i	CVOT study population	Mean follow-up (SD), years	Baseline weight (SD), kg	Weight reduction (SD) with the SGLT2i, kg	Risk reduction for the primary objective
VERTIS CV [28]: ertugliflozin	Established ASCVD involving the coronary, cerebrovascular, and/or peripheral arterial system *N* = 8246 Mean age (BL) = 64.4 years Mean HbA1c (BL) = 8.2%	3.5	NR Baseline BMI: 31.9 (5.4) kg/m^2	At 1 year: − 2.4 (3.9) kg with 5 mg − 2.8 (4.0) kg with 15 mg	3P-MACE HR = 0.97; 95% CI 0.85–1.11 $P < 0.001$ vs. placebo

3P MACE 3-point major adverse cardiovascular events (cardiovascular death, nonfatal myocardial infarction or nonfatal stroke, *ASCVD* atherosclerotic cardiovascular disease, *BL* baseline, *BMI* body mass index, *CKD* chronic kidney disease, *CI* confidence interval, *CV* cardiovascular, *CVOT* cardiovascular outcome trial, *ESRD* end-stage renal disease, *HbA1c* glycated hemoglobin, *HR* hazard ratio, *NR* not reported, *T2D* type 2 diabetes, *SD* standard deviation, *SGLT2i* sodium–glucose cotransporter 2 inhibitor

baseline BMI categories (normal to very obese) [31]. A similar reduction in body weight (approximately 2% vs. placebo) and similar relative risk for the composite event were observed across the BMI categories.

EMPA-REG Outcomes Trial

A post hoc analysis of EMPA-REG OUTCOMES data [32] evaluating the early benefits showed a significant weight reduction with empagliflozin vs. placebo ($p < 0.0001$) at 12 weeks, 6 months, and 1 year. The clinical and metabolic benefits were apparent in patients with T2D with or without heart failure at baseline and were considered largely independent of HbA1c reduction.

VERTIS CV Trial

The weight change observed with ertugliflozin 5 mg or 15 mg in the VERTIS CV trial [28] was slightly lower than that previously reported. The results from another trial, although not a CVOT, showed that weight loss at 26 weeks was maintained for a longer period of time, up to 104 weeks [33]. No specific results from VERTIS CV on weight change with ertugliflozin by baseline BMI or HbA1c group have been published, but another clinical trial with ertugliflozin in overweight and obese patients concluded that achievement of glycemic control at 26 weeks (HbA1c reduction) was similar irrespective of baseline BMI, and so was the percentage of weight loss (approximately 3–4%) [34].

The impressive cardiorenal outcomes are only partially explained by the SGLT2is' effects on the heart, kidneys, blood vessels, and the whole body [35]. Potential mechanisms include structural (reduction of ventricular mass and wall stress, improvement of fibrosis markers and endothelial function), dynamic (direct inhibition of myocardial Na^+/H^+ pump, reduction of blood pressure, and improvement of the ventricular loading conditions and tubuloglomerular feedback), and energetic changes (improvement of cardiac metabolism).

In this context, the associated weight loss has been investigated as a potential distinctive mediator of CV risk reduction in diabetes. A

recent systematic review and meta-analysis [36] of large CVOTs with different glucose-lowering drugs showed a significant relative reduction in the risk of heart failure of 5.9% (3.9–8.0%) for every difference of 1 kg between treatment groups ($p < 0.0001$). Another meta-analysis with meta-regression [37] concluded that GLP-1 RAs and SGLT2is reduce the risk of cardiovascular and mortality endpoints regardless of the reductions in systolic blood pressure and body weight. In patients with T2D with renal impairment, previous research showed that dapagliflozin 10 mg improved weight and systolic pressure, while the benefit on glycemic control was small [38]. When published, weight change results from the DAPA-CKD trial [39] will probably enable further correlations between weight loss and renal outcomes.

The CV advantages obtained with SGLT2 inhibitors in large CVOTs have been only partially clarified by their mechanism of action and related glycemic control. Different approaches have been taken to explain cardiac and renal improvements, which place this class on a different treatment path than the rest of the oral antihyperglycemic agents [4].

DISCUSSION

Potential Protective Mechanisms of SGLT2 Inhibition Associated with Weight Loss

Intensive lifestyle measures may result in clinically significant weight reduction (at least 5%) that can be maintained in the long term [40], and a minimum 3% reduction in weight is advantageous for metabolic control [41]. In real-life practice, rebound weight gain is common.

The initial decrease in body weight is the result of two major effects of SGLT2 inhibition: caloric loss due to glucose excretion (a process also called calorie restriction mimicry) and loss of body water due to osmotic diuresis. Both mechanisms appear to become effective early after treatment initiation, with glycosuria continuing in the long term without any significant fluid change. We are confident that upcoming studies will clarify whether the weight loss effect is a key component or only an add-on to the impressive cardiorenal outcomes.

The fat loss associated with SGLT2 inhibition is the result of a complex metabolic process described by Ferrannini et al. [16, 42] as a gradual shift to fatty acid utilization. The increase in glucagon concentration in response to reduced blood glucose and insulin levels triggers a cascade of metabolic events leading to lipolysis and lipid oxidation. Increased production of ketone bodies, a more efficient source of energy for the heart that require less oxygen for their metabolism, would allow more efficient cardiac contractility, thereby improving the benefits on heart failure. This explanation is offset by the fact that patients with heart failure present high ketone body levels, even in the absence of SGLT2 inhibition. Moreover, ketoacidosis is a trigger of inflammatory conditions, whereas the use of SGLT2is has been proven to reduce inflammation.

Considering the improvement of cardiac function and the associated body fat reduction, the effect of SGLT2 inhibition on epicardial adipose tissue (EAT) was investigated. A small randomized controlled trial ($N = 40$) showed that 6-month dapagliflozin treatment was associated with a significant reduction in EAT volume compared to baseline, with no changes in the control group [43]. This observation is important since arterial stiffness has been correlated with diabetes, obesity, and hypertension. Despite the limited available information, it is likely that SGLT2 inhibitors act by modulating the risk factors, giving them a synergistic larger effect than initially estimated.

SGLT2 Inhibitors, Obesity, and Inflammation

Obesity is linked to a chronic inflammatory response, with abnormal cytokine and chemokine production. Associated insulin signaling pathways include mitogen-activated protein kinases (MAPKs), IκB-kinase b (IκKb)/nuclear factor κB (NF-κB), and mammalian target of rapamycin (mTOR)/S6 kinase [44]. SGLT2 inhibition leads to activation of lysosomal degradation and inhibition of mTOR, with possible

changes in mitochondrial status followed by a "switch" in inflammatory events. The idea of improving the response to a toxic environment through profound changes in "cellular life history programs" has recently been advanced [45]. This would include the induction of a fasting-like state [46] by SGLT2 inhibition. Such ideas encourage scientists to accept how major improvements are the result of subtle changes.

A Possible Change in Patients' Perspective

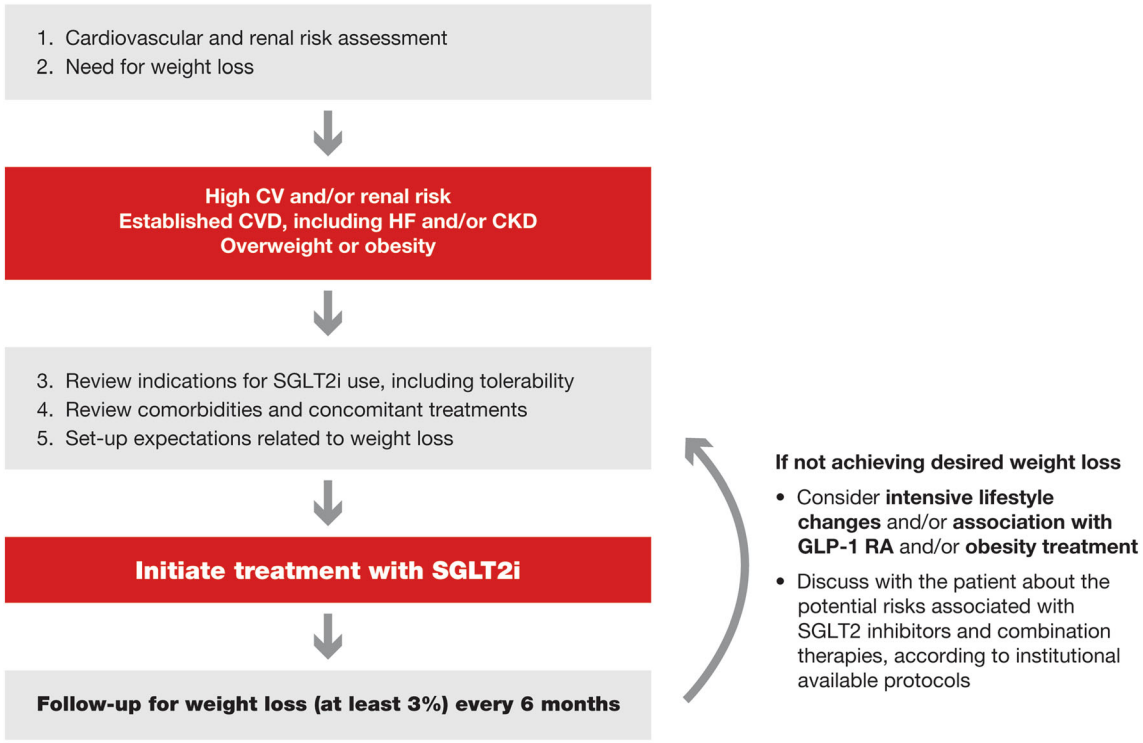
Current guidelines in diabetes are very clear about placing the patient at the center of disease management. Lifestyle changes, including dietary restrictions and an increase in physical activity, form the basis of the treatment and should be adapted to individual needs, and patient preferences should be considered when discussing the overall treatment approach. Metformin remains the first-line pharmacological therapy owing to its effectiveness in both monotherapy and combination therapy, and on the basis of extensive experience [4]. With a neutral overall effect on weight, metformin does not provide cardiorenal protection in patients with diabetes. The paradigm shift from glycemic control to cardiorenal risk control in diabetes places SGLT2is high on the list of pharmacologic agents to be used early in treatment. Additionally, SGLT2is can be used in various therapeutic associations considering their overall efficacy and safety profile and the unique insulin-independent mechanism of action. In clinical practice, the time of intensification with an SGLT2i does not seem to influence the proportion of weight lost [47], but a change of 3–4% is still lower than anticipated on the basis of the calorie excretion mechanism.

With the development of new and more efficacious treatments for diabetes, the choice of antihyperglycemic agent has become important. In patients with high CV risk requiring additional disease control, the association of an SGLT2i with GLP-1 RA seems a rational choice. The DURATION 8 study [48, 49] showed that dapagliflozin plus exenatide once weekly improved glycemic control and resulted in a larger weight loss than either drug alone. Similar results were seen in more recent trials, AWARD-10 [50] and SUSTAIN-9 [51], with other GLP-1 RAs added to a background treatment with an SGLT2i. On the basis of the overall evidence, it seems that sequential or concomitant use of SGLT2is and GLP-1 RA provides the most favorable approach based on their CV protection (heart failure and major adverse cardiovascular events), glycemic control (HbA1c lowering), and metabolic effects (attenuation of compensatory hyperphagia, weight loss, and minimal risk of hypoglycemia).

For patients and medical staff, T2D management requires an ongoing effort to control the disease. We strongly believe that novel agents associated with weight loss—SGLT2is and GLP-1 RAs—should be exploited at a higher rate. Updated guidelines and current treatment recommendations are a solid basis for this opinion. Although many elements of SGLT2is' potential are still not elucidated, it is likely that physicians go through a clear decision-making process when prescribing them in daily clinical practice.

Interviews conducted with patients with T2D under treatment with one SGLT2i provide a new perspective on patient-reported outcomes [52]. Such qualitative research may represent the starting point for developing a different communication framework with patients who are adherent to SGLT2is that will allow them to pursue other positive behaviors to control diabetes. In the overall perception of their health status, patients with T2D ascribe a more important role to observed weight changes [53] than to HbA1c and blood pressure control. From this point of view, the weight loss effect of SGLT2is, although considered modest and below the clinical significance of 5% overall, has the potential to become the anchor for our efforts to shift the perspective of patients toward healthy behaviors and adherence to treatment. The structured clinical approach suggested in Fig. 1 has the potential to address both obesity and T2D, aiming to lower the BMI category and promote the cardiorenal benefits of novel therapies.

This short narrative has focused on weight loss attributed to SGLT2is in CVOTs with exclusive T2D populations. The limitations of a



CKD, chronic kidney disease; CV, cardiovascular; GLP-1 RA, glucagon-like peptide-1 receptor agonists, HF, heart failure; T2D, type 2 diabetes; SGLT2i, sodium-glucose co-transporter 2 inhibitor.

Fig. 1 Suggested practical algorithm to monitor weight loss in patients with T2D treated with an SGLT2i

brief narrative review are inherent. Details on the chemical and molecular pathways influencing the cardiorenal effects are only marginally introduced. An important topic, such as the effect of SGLT2 inhibition on body weight in subjects without diabetes, is left unexplored. We also did not review in detail the relationship between body weight and renal function in diabetes. Results from clinical practice from a combination of an SGLT2i with GLP-1 RA are not included. The accumulating body of evidence highlights the need to explore weight reduction with SGLT2is in more depth in trials with pragmatic designs to provide more valuable insights that will support individualized treatment approaches.

Despite extensive research, the full implications of weight loss associated with SGLT2 inhibition are largely unknown. The cascade of events triggered by glucose excretion seems very complex, interlacing with inflammation, lipolysis, and deeper intracellular changes, so it might take a long time to solve it completely. The effect on abdominal fat is clearly linked to the obesity reduction, and the increased lipolysis and ketone body formation are linked to the improvement in cardiac metabolism. Future studies and assessments could bring us closer to the clinical predictors of better responses to SGLT2is, with a greater metabolic benefit and BMI improvement.

CONCLUSION

The mechanisms by which SGLT2 inhibition leads to cardiorenal risk reduction are not fully elucidated but include improved glycemic control, reduced body weight, lower blood pressure, and osmotic diuresis. CV benefits and weight loss are consistently reported with SGLT2is across different patient population groups, irrespective of baseline BMI, moderate chronic disease, and glycemic control.

Weight reduction remains a crucial goal in the prevention and treatment of diabetes. Along with clinical trials, large real-world studies would allow a better understanding of the appetite patterns and caloric behavior of patients with T2D treated with an SGLT2i to allow this versatile therapeutic class to reach its full potential.

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