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Role of Sodium-Glucose Co-Transporter-2 (SGLT2) Inhibitors in Weight Loss: Understanding the Clinical Evidence

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Abstract **Original Research Article**

Obesity is ubiquitous, affecting millions of people all over the world. Its prevalence is increasing day by day in all age groups, ranging from children to adolescents to adults. It has a significant impact on the overall quality of life. Obesity has a strong relationship with various chronic conditions, including type 2 diabetes mellitus. The risk of developing diabetic mellitus considerably increases in obese individuals. Similarly, obesity in diabetic patients increases their probability of developing serious complications. Moreover, the optimal approach to managing diabetes mellitus (type 2) and obesity should be carried out by means of sustained weight loss and glycemic control. Sodium-glucose cotransporter 2 (SGLT2) inhibitors have been shown to be a revolutionary class of medications with noteworthy weight-loss benefits in addition to their ability to lower blood sugar levels. These remarkable benefits are mentioned in detail in several different clinical trials. Additionally, diverse mechanisms have also been demonstrated comprehensively via which SGLT-2 inhibitors put forth their function of weight loss. FDA-approved SGLT2 inhibitors show a unique mechanism of action by inhibiting the reabsorption of glucose in the renal proximal tubule. By excreting glucose in the urine and by visceral fat lipolysis, these drugs provide a new avenue for weight reduction. SGLT2 inhibitors are now fundamental parts of weight-loss regimens in patients with type 2 diabetes, going beyond their original role as anti-diabetic medications. This article attempts to review the up-to-date literature on the effectiveness of this particular contemporary function of SGLT2 inhibitors.

Keywords: Obesity, Type 2 Diabetes Mellitus, SGLT2 Inhibitors, Weight Loss, Glycemic Control.

INTRODUCTION AND BACKGROUND

Obesity is increasing at an alarming rate all over the world. It has become a major global public health concern owing to this escalation in the prevalence of obesity. According to the World Health Organisation, obesity is the high accumulation of fat that causes the body mass index (BMI) to increase [1]. A normal range of BMI is 18.5 to 24.9; less below is labelled as underweight; ≥25 kg/m2 is overweight; and a BMI ≥ 30 kg/m2 is obesity [1]. There are about 39% of overweight adults and 13% of obese adults above age 18 all over the world. It has been reported by the Global Burden of Disease Study in 2020 that every year about 2.4 million deaths occur due to high BMI [2].

Sedentary lifestyles, urbanisation, and increased consumption of high-calorie processed foods largely contribute to weight gain [3]. Overweight and obesity can lead to various serious diseases, including diabetes, psychological issues, hypertension, stroke, cardiovascular diseases, and even certain types of cancer [4]. In addition to these grave diseases, obesity can lead to a substantial reduction in the average life expectancy and can cause renal, pulmonary, musculoskeletal, mental, and gastrointestinal problems [5]. Obesity also has a major impact on the psychosocial, physical, and behavioural aspects of life. A stigma is also associated with obesity, which may hamper seeking help and healthcare [5]. The prevention of obesity is therefore a critical factor. It can be done by decreasing the intake of foods containing carbohydrates and fats, by consuming whole grains, vegetables, nuts, fruit and legumes and by engaging in regular physical activities [5].

Nevertheless, some individuals, especially those with diabetes mellitus type 2, face challenges in reducing their weight using these methods since it may alter their overall metabolic control. Body mass index

has been found to be strongly linked with insulin resistance and diabetes [6]. Insulin resistance leads to dysregulation of the metabolism of lipids, glucose, and proteins. Additionally, evidence demonstrates that in obese people, all the factors responsible for causing insulin resistance are usually raised [7]. These include proinflammatory markers, glycerol, cytokines, nonesterified fatty acids, and some hormones [7].

Thus, those obese or overweight individuals who are unable to attain weight loss via lifestyle change need anti-obesity drugs like appetite suppressants. However, there are some people who cannot tolerate such treatments and therefore may need additional effective weight-loss modalities.

Recently, a novel glucose-lowering medication, sodium-glucose cotransporter 2 (SGLT2) inhibitors, has been introduced. It generally works to inhibit glucose reabsorption in the renal proximal tubule, and by doing so, it increases glucose excretion via urine [8]. It also leads to weight loss by promoting fat loss, implying that weight loss by SGLT2 inhibitors can be more beneficial in patients with type 2 diabetes mellitus [9]. However, a number of clinical trials have lately reported that SGLT2 inhibitors considerably reduce body weight compared to placebo, even in overweight or obese individuals devoid of diabetes mellitus [9]. For this reason, the aim of the present study is to review the current accredited studies about the overall role of SGLT2 inhibitors in weight reduction.

REVIEW AND METHODOLOGY

The literature review was conducted in October 2023. The data is mainly comprised of study articles published between 2018 and 2023. The chief search engines used to extract data were Cochrane, Google Scholar, and PubMed. A number of keywords were used, such as SGLT2 inhibitors, diabetes mellitus, obesity, weight loss and SGLT2 (Sodium-Glucose Transporter 2) inhibitors, diabetes mellitus type 2 and obesity. Only complete articles published in English were included. The included articles were not more than 6 years old. The inclusion criteria included experimental and observational studies, systematic reviews, meta-analyses and randomised control trials about different SGLT2 inhibitors roles in weight loss.

RESULTS

There were multiple studies that met the inclusion criteria and were included in this literature review.

SGLT2 Inhibitors

SGLT2 inhibitors are FDA-approved drugs for the treatment of type 2 diabetes mellitus and include dapagliflozin, licogliflozin, empagliflozin, canagliflozin, ertugliflozin, bexaglifloxin, etc. [10]. In 1996, SGLT2 inhibitors came into existence in Japan as phlorizin analogues [10]. Later on, they were made available to be used orally, having no harmful effects on the kidney but good gastrointestinal absorption [10]. They improve glycemic control and reduce the risk of adverse cardiovascular events as well as the risk of estimated glomerular filtration rate (eGFR) decline [11]. Their action mechanism is based mainly on the SGLT-2 proteins that are found in the proximal convoluted tubules of the kidney. It means the kidney has a chief function in the regulation of glucose reabsorption as well as the preservation of the body's metabolic balance. Approximately 99% of glucose is reabsorbed by the kidney each day [12]. This glucose reabsorption takes place by means of transporters, namely sodium-glucose co-transporters (SGLTs) and glucose transporters (GLUTs). Preventing SGLT2-mediated reabsorption of glucose is a unique and extremely useful approach to treating hyperglycaemia in type 2 diabetes mellitus patients. SGLT2 inhibitors reduce the renal threshold for glucose by decreasing the filtered glucose reabsorption and promoting the urinary excretion of glucose. This leads to a decline in HbA1c of roughly 0.6–1.0% [13]. The glycemic control occurs regardless of insulin secretion, so there is a very low possibility of hypoglycaemia.

These weight-reducing effects of SGLT-2 inhibitors are especially important for patients with obesity and diabetes mellitus type 2 because a steady decrease in fat mass or weight loss is essential for successful disease management.

SGLT2 inhibitors Role in Weight Loss

In addition to acting as antihyperglycemic drugs, they have been found to cause weight loss in a number of studies. For example, a clinical trial by Bays *et al.*, compared licogliflozin with placebo and found that use of licogliflozin twice daily brought about major weight loss in obese individuals in comparison to placebo [14]. Licogliflozin acts on both SGLT1 and SGLT2, but it has a higher selectivity for SGLT2. Administration of this drug in high doses showed improvement in haemoglobin A1c, waist circumference, and blood pressure [14]. Nevertheless, mild diarrhoea was associated with high doses of licogliflozin, but the frequency declined over time [14]. As a whole, it was well tolerated.

A study was conducted by He *et al.*, on 88 obese patients to evaluate the effects of licogliflozin on weight loss [15]. It was noted that licogliflozin versus placebo in individuals with normal glucose levels produced a significant reduction in weight [15]. Licogliflozin, owing to its twofold inhibition of SGLT1/2, was concluded to be an effective means of managing obesity as well as diabetes mellitus. However, 25 to 43% of patients faced adverse effects such as abdominal distension, flatulence, and abdominal pain [15].

Similarly, the randomised, double-blinded, and prospective trial by Kashyap *et al.,* showed a significant decrease in body weight (−3.7 kg) and BMI (−1.24 kg/m^2) with the use of canagliflozin therapy against placebo [16]. The study was on obese and diabetic patients (n = 16) who underwent bariatric surgery. They also noted that canagliflozin improved body fat composition, accompanied by glycaemic outcomes. Canagliflozin is easily accessible in several countries, like the USA, Japan, and Europe [16].

Ohkuma *et al.,* observed a larger reduction in body weight in patients receiving canagliflozin than placebo [17]. The effect was significant following adjustment for study duration, i.e., after the 1-year follow-up vs. the 3-month follow-up. Kutoh *et al.,* also reported a considerable decrease in the levels of BMI (-4.1%) in diabetic patients who received treatment with canagliflozin for 3 months [18]. They also observed a significant decrease in the levels of triglycerides (-18.6%) [18].

A post hoc analysis by Pellicori *et al.,* demonstrated that empagliflozin significantly reduced weight in diabetic patients at different time intervals compared to placebo (p 0.0001) [19].

A systematic analysis by Pratama *et al.,* consisting of seven studies, reported SGLT2 inhibitors as an effective means of producing weight loss in obese patients [20]. They found it useful even for those individuals who did not have diabetes. Moreover, in a meta-analysis by Cai *et al.,* SGLT-2 inhibitor treatment demonstrated a steady and statistically significant decrease in body weight with the use of dapagliflozin [21]. The analysis based on 55 randomised controlled trials reported a weight reduction from 1.30 to 2.24 kg with the use of different doses of dapagliflozin ($P < 0.001$) [21].

In the study by Wiviott *et al.,* treatment with dapagliflozin vs. placebo showed a 1.8 kg reduction in body weight in about 17,160 patients at an average follow-up of 4 years [22]. The use of dapagliflozin showed reduced rates of hospitalisation for heart-related issues as well as cardiovascular death. Also, dapagliflozin is known to increase high-density lipoprotein (HDL) and reduce triglyceride levels [23]. The most common adverse event associated with dapagliflozin emerges to be genital infections [22, 23]. It can be the consequence of the appearance of minimal glucose concentration in the urine.

A number of recent studies have also reported that dapagliflozin remained successful in reducing weight by 1.98 kg to 2.3 kg [24, 25]. Similarly, a prospective longitudinal observational study comprising 486 diabetic patients showed 3.2kg to 3.9 kg weight reduction after using SGLT-2 inhibitor [26].

A meta-analysis based on 116 randomised-controlled trials was associated with an average decrease in weight of 1.79 kg and a change in BMI of 0.71 kg/m^2 with SGLT-2 inhibitor treatment corresponding to placebo [27]. This study also showed BMI changes (95% CI: -0.94 to -0.47, $p < 0.001$) compared with placebo [27]. For change in average weight, a dose-response association was observed with sotagliflozin, canagliflozin, licogliflozin, and empagliflozin.

A retrospective study by Frieling *et al.,* consisting of 73 patients, studied the difference in weight loss between SGLT-2 inhibitors and GLP-1 receptors in patients with diabetes. 31 patients were treated with SGLT-2 inhibitors, while about 42 patients were administered GLP-1 receptor agonists for 6 months [28]. It was observed that 2.80 kg of weight loss took place in the patients receiving SGLT-2 inhibitors. On the other hand, only 1.15 kg of weight loss occurred in the GLP-1 receptor agonist group [28]. Therefore, it was concluded that SGLT-2 inhibitors could bring about considerable weight loss compared to GLP-1 receptor agonists in diabetic patients, devoid of any renal issues.

The weight-reducing outcomes of SGLT-2 inhibitors are constant even when administered with insulin or other antidiabetic drugs [29]. They can be used as a single therapy or co-administered with other glucose-lowering drugs. Another benefit of SGLT2 inhibitors besides weight loss is the very low incidence of side effects like hypoglycaemia [29].

How Do SGLT2 Inhibitors Cause Weight Loss?

The SGLT2 inhibitor-induced weight loss is the outcome of a complicated metabolic process, i.e., a progressive switch to fatty acid utilisation. A high concentration of glucagon as a result of low insulin levels and blood sugar sets off a series of metabolic processes that cause lipid oxidation and lipolysis [30].

According to a recent meta-analysis of randomised controlled trials, it has been demonstrated that SGLT2 inhibitors lead to a significant decrease in the levels of triglycerides, subcutaneous and visceral adipose tissues, and body weight in diabetic and obese patients. They found a significant reduction in weight with a longer than 6-month follow-up period [31]. They stated that the mechanism of reducing adipose tissue by SGLT2 inhibitors is still not completely comprehensible. Animal studies have shown that SGLT2 inhibitors prompt the depletion signal for glycogen and stimulate the liver-brain-adipose axis [31]. This activation brings about lipolysis.

Several other mechanisms have been proposed. According to Ohkuma *et al.,* SGLT2 inhibitors lead to a reduction in body weight via natriuresis and calorie loss. When glucose is excreted in the urine, it carries calories with it [17]. This caloric loss can result in a diminution in overall caloric intake and contribute to weight loss,

particularly in individuals with poorly controlled diabetes or who have elevated blood glucose levels. Urinary glucose excretion at therapeutic levels ranges between 70 and 90 grams per day, or 300 kilocalories per day [30]. This finding is supported by Yang who reported that SGLT2 inhibitors bring about weight reduction through a steady loss of calories by means of glucosuria along with a series of metabolic response [32].

Lauritsen *et al.*, demonstrated that inhibition of SGLT2 decreased the expression of the protein and GLUT4 gene in fat tissues, presumably by lowering the production of glycerol and shifting substrate use away from lipid storage and glucose oxidation capacity [33]. Another study found that SGLT2 inhibitors augment consumption of fat by stimulating M2 macrophages [34].

A study by Inoue *et al.*, showed that weight loss associated with SGLT2 inhibitors was the consequence of a lessening of subcutaneous and visceral adipose tissue mass [35]. They reported loss of fat from the back and both arms and legs. They confirmed this by carrying out bioelectrical impedance analysis as well as dual-energy X-ray absorptiometry. No change in bone mineral content or muscle mass was observed [35].

DISCUSSION

Obese patients with diabetes mellitus (type 2) are at increased risk of developing serious life-threatening complications. Obesity is an autonomous marker of several cardiovascular causes and resultant complications associated with diabetes [36]. For this reason, diabetes treatment should include the treatment of obesity, since persistent weight in the normal range leads to improvement in glycemic control. Studies have time and again revealed that weight loss is linked to a better life expectancy in individuals with diabetes [37].

Loss of a good amount of weight displays an increased likelihood of diabetes reversal. In fact, if weight gain is managed earlier, it can completely avert the progression from the pre-diabetes phase to the final diabetes phase [37]. To date, several therapies and treatments have been introduced for the purpose of weight management. This review has demonstrated the newest way of achieving weight loss, i.e., via SGLT2 inhibitors. We have therefore reviewed a large number of clinical trials on the role of SGLT-2 inhibitors in producing weight loss in diabetic patients with obesity.

SGLT2 inhibitors have appeared to be very promising therapeutic agents for weight loss as well as for glycemic control. SGLT2 inhibitors exert reversible, effective and selective inhibition of renal proteins [38]. This literature review shows that SGLT2 inhibitor use can result in a major loss of weight, especially in the diabetic obese population. In almost all the studies, reductions in body weight were approximately 1.5kg to 2 kg in comparison to controls in diabetic obese patients. Only one study conducted in recent years has demonstrated the results of SGLT2 inhibitors in obese people without diabetes. For example, a study by Bays *et al.*, found that SGLT2 inhibitors like canagliflozin showed body weight reduction in non-diabetic obese people [14]. Additionally, SGLT-2 inhibitors have appeared to reduce both visceral and subcutaneous adipose tissue by promoting lipolysis.

Currently, more attention is paid to managing type 2 diabetes mellitus by considering continual improvements in long-term effects, quality of life and protection of body organs. SGLT-2 inhibitors have been shown to impart cardio-renal benefits [39, 40]. These studies have found that these drugs are effective in lessening the risk of mortality and hospitalisation associated with renal diseases and cardiovascular events. Collectively, these studies emphasise the potential of sodium-glucose cotransporter 2 (SGLT2) inhibitors in people with diabetes mellitus to provide benefits beyond a reduction in blood glucose levels or glucose regulation. Their additional cardio-renal benefits, besides weight reduction advantages, draw attention to their potential to revolutionise diabetes and obesity medicine. SGLT-2 inhibitors can attract a broad range of patients due to their ability to lower glucose, reduce cardiovascular risk, aid in weight loss, and minimise the chance of hypoglycaemia.

CONCLUSION

The highlight of our review is the beneficial outcomes of SGLT-2 inhibitors in causing weight loss. Weight loss is crucial for overweight or obese patients with type 2 diabetes mellitus. SGLT2 inhibitors mark a paradigm shift in the management of diabetes. However, our review has not thoroughly studied the adverse effects associated with these drugs. Similarly, not sufficient evidence is available to support the weight-reducing role of SGLT-2 inhibitors in obese people devoid of diabetes. Additional trials are needed to further evaluate the side effects as well as the role of SGLT-2 inhibitors in the non-diabetic population in detail. Nevertheless, these drugs definitely demonstrate the potential of tailored therapy to improve patient outcomes along with their quality of life.

Also, healthcare practitioners need to be well-informed about the novel research and adjust their treatment methods in light of the constantly changing role of SGLT2 inhibitors. We also encourage meticulous research in this area to facilitate overweight and obese patients who are unable to lose weight. Additionally, studies focusing on genotypic and phenotypic aspects that can assist in the determination of therapy responders to SGLT2 inhibitor-based weight-loss regimens are required.

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