

Use of SGLT-2 Inhibitors in Patients with Type 2 Diabetes Mellitus and Abdominal Obesity: An Asian Perspective and Expert Recommendations

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The prevalence of obesity in Asia is of epidemic proportions, with an estimated 1 billion overweight/obese individuals in the region. The majority of patients with type 2 diabetes mellitus (T2DM) are overweight/obese, which increases the risk of cardiorenal outcomes in these patients; hence, sustained reductions in body weight and visceral adiposity are important management goals. However, most of the glucose-lowering therapies such as insulin, sulfonylureas, glinides, and thiazolidinediones induce weight gain, which makes the management of overweight/obese T2DM patients challenging. Sodium-glucose cotransporter-2 (SGLT-2) inhibitors are the only oral glucose-lowering agents that have been shown to reduce body weight and visceral adiposity. In addition, SGLT-2 inhibitors therapy reduces ectopic fat deposition and improves adipose tissue function and weight-related quality of life. In this article, we aim to consolidate the existing literature on the effects of SGLT-2 inhibitors in Asian patients with T2DM and to produce clinical recommendations on their use in overweight or obese patients with T2DM. Recommendations from international and regional guidelines, as well as published data from clinical trials in Asian populations and cardiovascular outcomes trials are reviewed. Based on the available data, SGLT-2 inhibitors represent an evidence-based therapeutic option for the management of overweight/obese patients with T2DM.

Keywords: Diabetes mellitus, type 2; Obesity; Sodium-glucose transporter 2 inhibitors

INTRODUCTION

Obesity is a serious global health concern and is a major contributing factor to the development of type 2 diabetes mellitus (T2DM). The pathophysiology of obesity and T2DM is closely

linked with insulin resistance, which plays a key role in the dysregulation of glucose, lipid, and protein metabolism [1]. The chronic positive net energy balance increases adiposity and circulating levels of free fatty acids (FFAs), which accelerate the development of T2DM through impaired hepatic and

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peripheral glucose metabolism, reduced insulin clearance, impaired pancreatic β -cell function, ectopic fat deposition, and activation of pro-inflammatory pathways [2,3].

The measures of abdominal adiposity, such as waist circumference (WC), correlate with insulin resistance and markers of cardiovascular disease (CVD) better than body mass index (BMI) does [4,5]. Asian populations have higher abdominal obesity for the same BMI compared with their Caucasian counterparts, partly explaining the higher insulin resistance and excessive risk of T2DM and CVD among Asian populations [6,7]. Sniderman et al. [8] proposed that the superficial subcutaneous fat compartment is less developed, with a reduced storage capacity, in South Asians compared with Caucasians, which results in the preferential distribution of fat in visceral or deep subcutaneous depots. The underlying reason for this less developed superficial subcutaneous compartment has been suggested to be the heat stress or the chronic energy deficiency from malnutrition in the evolutionary past, resulting in a preference for the highly vascular visceral adipose tissue with high lipolytic activity [8,9]. The harmful effects of higher abdominal obesity in Asians are well recognized, and the World Health Organization (WHO)'s expert committee has recommended a lower BMI level as an actionable cutoff for the risk of T2DM and CVD in Asians (23 kg/m² vs. 25 kg/m² in Caucasians) [10]. For WC, the WHO provided gender-specific cutoff points for the risk of metabolic complications: 94 cm (men) and 80 cm (women) for increased risk, and 102 cm (men) and 88 cm (women) for the substantially increased risk [11]. Population and geography-specific WC cutoffs are provided by the International Diabetes Federation and these are lower for Asian men compared with their Caucasian counterparts: 90 cm (men) and 80 cm (women) for South Asian, Chinese, and Japanese populations versus 94 cm (men) and 80 cm (women) for Caucasians [12]. In Korea, the appropriate WC cutoff for the risk of metabolic syndrome was determined to be 90 cm in men and 85 cm in women [13].

It has been well recognized that weight reduction is a key strategy in the management of obese patients with T2DM. However, most of the glucose-lowering therapies, including insulin, sulfonylureas (SUs), glinides, and thiazolidinediones (TZDs), induce weight gain. The recently introduced glucagon-like peptide-1 receptor agonists (GLP-1 RAs) and sodium-glucose cotransporter-2 (SGLT-2) inhibitors have been shown to reduce body weight and have become the preferred agents for the management of overweight/obese patients with

T2DM [14,15]. Previously, we reviewed the effects of SGLT-2 inhibitors on various cardiovascular (CV) risk factors, and developed expert recommendations on the clinical use of SGLT-2 inhibitors in Asian T2DM patients with CVD or multiple risk factors [16]. In the present article, we aim to review and consolidate the existing literature on the effects of SGLT-2 inhibitors on body weight and adiposity in Asian patients with T2DM. We then produced a series of clinical recommendations on the use of SGLT-2 inhibitors in overweight/obese patients with T2DM.

EPIDEMIOLOGY AND ASSOCIATED COMPLICATIONS OF OVERWEIGHT/OBESITY AND T2DM IN ASIA

The worldwide prevalence of overweight adults aged >18 years is estimated to be about 1.9 billion (39% of adults worldwide), and that of obesity is approximately 650 million (13% of adults worldwide) [17,18]. Data from the Global Burden of Disease Study show that high BMI accounts for 4 million deaths annually, of which more than two-thirds are due to CVD [19]. In addition, high BMI contributes to 120 million disability-adjusted life-years. Of note, about 34% of high BMI-related deaths and 32% of disability-adjusted life-years occur in individuals with BMI 25 to 30 kg/m².

In the Asia Pacific region, an estimated 1 billion people (40.9%) are overweight/obese (2013 data; using BMI cutoff of 25 kg/m² for overweight and 30 kg/m² for obesity) [20]. The Global Burden of Disease Study reported region-wise prevalence estimates for overweight and obese adults. Within Asia Pacific, the prevalence of overweight and obesity is as follows: Australasia 68.6% (men) and 56.7% (women), East Asia 28.0% (men) and 27.1% (women), Southeast Asia 22.1% (men) and 28.3% (women), South Asia 20.2% (men) and 22.5% (women), and high-income Asian countries (Brunei, Japan, Singapore, and South Korea) 31.7% (men) and 20.6% (women) [19]. Also, the region accounts for about 56.7% of the global diabetes prevalence, with 158.8 million (9.5%) and 82 million (8.5%) adults with diabetes in the Western Pacific and Southeast Asia regions, respectively [21]. Over 85% of all T2DM patients are either overweight or obese, rendering a vast majority of T2DM patients at high risk of CV morbidity and mortality [22]. In the Joint Asia Diabetes Evaluation (JADE) program involving 3,687 patients from nine Asian countries, 30.1% (range, 20.8% to 38.7%) of patients with T2DM had a BMI of ≥ 27.5 kg/m²

and 53.5% (range, 19.4% to 76.4%) had abdominal obesity (WC \geq 80 cm in women or \geq 90 cm in men) [23]. Data from the Korea National Health and Nutrition Examination Survey, a nationally representative survey of the Korean population, showed that 50.4% of Korean patients with T2DM were obese (BMI \geq 25 kg/m²) and 47.8% have abdominal obesity (WC \geq 85 cm in women or \geq 90 cm in men) [24].

Obesity increases the risk of hypertension, dyslipidemia, and coronary heart diseases in patients with T2DM. In addition, obesity and T2DM are chronic inflammatory states that further increase the risk of CV and cerebrovascular complications [25-27]. A pooled data analysis of 33 cohort studies ($n=310,283$; mean follow-up 6.9 years) by the Asia Pacific Cohort Studies Collaboration (APCSC) showed that each 2-units' decrease in BMI is associated with a 12% lower risk of ischemic stroke and 11% lower risk of ischemic heart disease [28]. Another pooled data analysis by APCSC involving six cohort studies in adults aged \geq 20 years ($n=45,988$; mean follow-up 6.1 years) revealed that each standard deviation increase in BMI, WC, and the waist-to-hip ratio increases the risk of ischemic heart disease by 17% to 36% [29]. Also, metabolic syndrome is independently associated with ischemic heart disease and ischemic stroke [30].

A U-shaped relationship has been reported between BMI and mortality due to heart failure (HF), with a $>60\%$ higher risk of HF mortality in both underweight and obese individuals compared with healthy-weight individuals [31]. A pooled analysis of the Framingham Heart, Framingham Offspring, Chicago Heart Association Detection Project in Industry, and Atherosclerosis Risk In Communities (ARIC) studies evaluated the risk of incident HF in individuals with or without hypertension, obesity, or diabetes. Men and women without hypertension, obesity, or diabetes at the age of 45 years have 73% and 85% lower risk of incident HF compared with those with all three risk factors, respectively. In addition, individuals without any of the three risk factors at the age of 45 years live 3 to 15 years longer, free of HF, than those with one, two, or all three risk factors [32].

Furthermore, obesity is independently associated with the development and progression of chronic kidney disease (CKD) [33]. Results from the Renal and Vascular End-Stage Disease (PREVEND) study showed that obesity and central fat distribution are associated with a 1.7-fold higher risk of microalbuminuria and 2.7-fold higher risk of decreased glomerular filtration rate [34]. Similarly, a multinational, observational

study of 20,828 outpatients with hypertension from 26 countries in Europe, North and Latin America, the Middle East, and Asia, showed that abnormal WC is associated with microalbuminuria, independent of BMI [35]. A retrospective analysis of National Diabetes Audit data (United Kingdom) showed that patients with T2DM and severe kidney disease (estimated glomerular filtration rate [eGFR] <30 mL/min/1.73 m²) are up to 1.75 times more likely to be obese compared with those with normal kidney function [36]. Furthermore, the risk of CKD (eGFR <60 mL/min/1.73 m²) is increased by 55% in the presence of metabolic syndrome [37].

The chronic elevation of circulatory FFAs and reduced FFA oxidation in obese individuals lead to ectopic fat deposition in non-adipose tissues, such as liver, skeletal muscle, heart, and pancreatic β -cells. Non-alcoholic fatty liver disease (NAFLD) is frequently reported in obese T2DM patients, which may increase the risk of non-alcoholic steatohepatitis, cirrhosis, and hepatocellular cancer [38].

There is a positive association between the presence of diabetes and high BMI (>25 kg/m²) and the incidence of cancer. Pearson-Stuttard et al. [39] analyzed the incidence of malignancies attributable to diabetes and high BMI as a combined risk factor, across 175 countries. Overall, 5.7% of all incident cancers are attributable to the combined effects of diabetes and high BMI as independent risk factors [39]. Of these 804,100 cancer cases, 23.8% occurred in East and Southeast Asia. Among the specific cancer types, 24.5% of liver cancer and 38.4% of endometrial cancer cases are attributable to these risk factors [39].

Furthermore, obstructive sleep apnea is prevalent in patients with abdominal obesity and may adversely affect glucose control in patients with T2DM [40].

CURRENT GUIDELINES FOR THE MANAGEMENT OF OVERWEIGHT/OBESE PATIENTS WITH T2DM

The clinical practice guidelines from Asian countries for the management of T2DM recommend a weight loss goal of 5% to 10% to improve glycemic control, blood pressure, lipid profile and quality of life (QoL) in overweight/obese patients with T2DM [41-45]. Similarly, guidelines from Western countries recommend a weight loss goal of 5% to 15% in these patients [14,46,47].

For the management of hyperglycemia in overweight/obese

patients with T2DM, the guidelines recommend the use of glucose-lowering drugs (GLDs) that promote weight loss or that are weight-neutral [15,48]. Insulin secretagogues, such as SUs, and glinides have been shown to increase body weight in T2DM patients [49,50]. TZDs are associated with weight gain in the range of 3.6 kg (at 3 years) to 4.8 kg (at 5 years) in large randomized controlled trials [51,52]. Several meta-analyses investigating the effect of oral GLDs on body weight showed that the addition of SUs, TZDs, and glinides to metformin is associated with significant weight gain in patients with T2DM (range, 1 to 5 kg) [53,54]. Conversely, metformin, α -glucosidase inhibitors, and dipeptidyl peptidase-4 (DPP-4) inhibitors have a neutral effect on body weight [54-56]. Currently, GLDs that promote weight loss include SGLT-2 inhibitors and GLP-1 RAs. The 2018 guidelines from the American Diabetes Association and the European Association for the Study of Diabetes provided a treatment algorithm for patients with a compelling need to minimize weight gain or promote weight loss, and recommended either GLP-1 RAs or SGLT-2 inhibitors as the preferred choice of therapy after metformin [57].

Methods

An expert panel comprising 12 endocrinology experts from China, Hong Kong, India, Indonesia, Malaysia, the Philippines, Singapore, South Korea, Taiwan, Thailand, and Vietnam met four times (Bangkok, November 2017; Shanghai, March 2018; Orlando, June 2018; Kuala Lumpur, November 2018) to review the clinical evidence and develop clinical recommendations on the use of SGLT-2 inhibitors in overweight/obese Asian patients with T2DM. A literature search was conducted in the MEDLINE database using the search string: (“canagliflozin” OR “dapagliflozin” OR “empagliflozin” OR “ipragliflozin” OR “luseogliflozin” OR “tofogliflozin”) AND “type 2 diabetes.” The panel critically analyzed the studies of SGLT-2 inhibitors conducted in Asia as well as recommendations from international and regional guidelines. Following discussions, the group reached consensus on a series of recommendations supported by scientific evidence and experts’ clinical opinion.

ROLE OF SGLT-2 INHIBITORS IN MANAGING OVERWEIGHT/OBESE PATIENTS WITH T2DM: AN ASIAN PERSPECTIVE

SGLT-2 inhibitors selectively and reversibly inhibit SGLT-2

transporters in the proximal convoluted tubule, preventing the renal reabsorption of glucose, thereby increasing urinary glucose excretion. The glucose-lowering effects of SGLT-2 inhibitors are independent of insulin function; hence, they are effective at all stages of T2DM [58]. The glycemic efficacy and safety of SGLT-2 inhibitors as monotherapy or in combination with other GLDs are well established. Results from three CV outcomes trials (EMPA-REG OUTCOME, CANVAS, DECLARE-TIMI 58) showed beneficial effects of SGLT-2 inhibitors in reducing the risk of CV outcomes in patients with T2DM [59-61].

In the DECLARE-TIMI 58 trial, dapagliflozin treatment reduced the body weight by -1.8 kg compared with placebo at the median follow-up of 4.2 years [60]. Similar results are reported with empagliflozin and canagliflozin in the EMPA-REG OUTCOME and CANVAS trials respectively [59,61]. In all three cardiovascular outcome trials (CVOTs) the beneficial CV effects of SGLT-2 inhibitors were consistent across BMI subgroups (<30 or ≥ 30 kg/m²). Furthermore, in a meta-analysis of 55 randomized controlled trials, SGLT-2 inhibitor treatment was associated with a consistent and significant reduction in body weight with a dose-dependent response observed for dapagliflozin [62]. A recent, single-center real-world study from India including 486 patients with T2DM reported a mean weight loss of 3.2 and 3.9 kg with SGLT-2 inhibitor therapy at 6 and 12 months, respectively [63].

These effects of SGLT-2 inhibitors on body weight are of particular significance for overweight/obese patients with T2DM, in whom consistent weight loss and reduction in fat mass are critical for effective management (Fig. 1). In the following sections, we summarize the effects of SGLT-2 inhibitors on body weight, fat mass, and adipose tissue function in Asian T2DM patients.

Effects on body weight in patients with T2DM

In Western populations, SGLT-2 inhibitor treatment induces a weight loss as monotherapy (weighted mean difference vs. placebo: -1.74 kg; 95% confidence interval [CI], -2.03 to -1.45) and as combination therapy (weighted mean difference vs. other GLDs: -1.80 kg; 95% CI, -3.50 to -0.11 kg) [64]. Similar results are observed in Asian patients with T2DM. Treatment with SGLT-2 inhibitors resulted in a significant reduction in body weight, ranging from -0.5 to -3.9 kg (study duration range, 8 to 104 weeks). The effect of SGLT-2 inhibitors on body weight in Asian patients with T2DM is summarized in Table 1 [65-106].

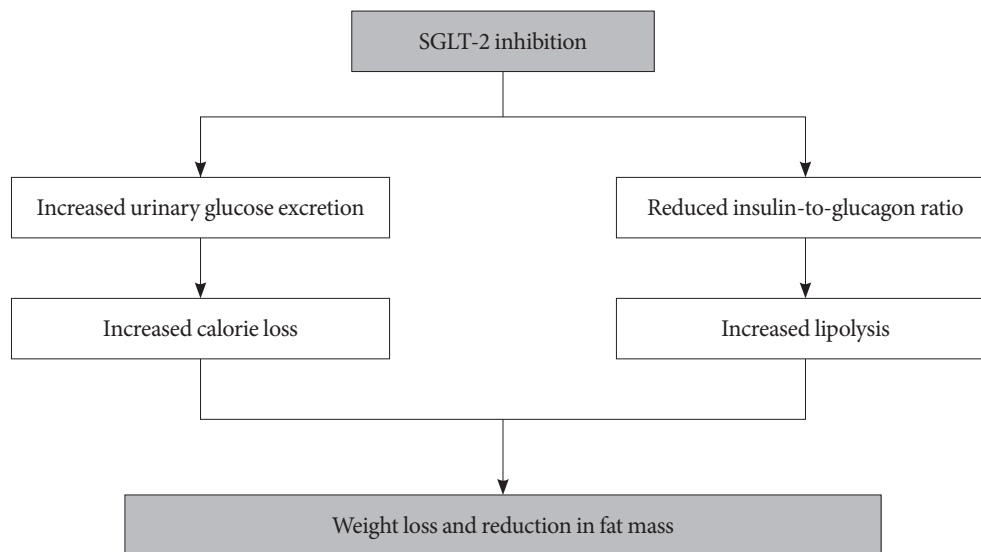


Fig. 1. Proposed mechanisms of effects of sodium-glucose cotransporter-2 (SGLT-2) inhibitors on body weight and fat mass.

As monotherapy in treatment-naïve Asian and Japanese patients with T2DM, consistent reduction in body weight is observed with dapagliflozin (range, -1.24 to -2.25 kg), canagliflozin (range, -1.98 to -3.19 kg), and empagliflozin treatments (range, -2.5 to -3.1 kg) (study duration up to 24 weeks) (Table 1). Similar effects are observed with ipragliflozin, luseogliflozin, and tofogliflozin, with body weight reductions ranging from -1.1 to -2.97 kg (study duration of 8 to 52 weeks) (Table 1) [65-67].

The reduction in body weight is also reported when SGLT-2 inhibitors are used in combination with other oral GLDs (range, -1.56 to -3.9 kg; study duration up to 52 weeks) (Table 1). Two studies reported on the effects of canagliflozin and luseogliflozin as an add-on to GLP-1 RAs in Japanese patients with T2DM. Addition of canagliflozin 100 mg to GLP-1 RAs resulted in a body weight reduction of -3.29 kg (4.46%) at 52 weeks [68]. Luseogliflozin as an add-on to liraglutide was associated with significant weight loss (-2.71 kg), with 33.9% of patients achieving a $\geq 5\%$ reduction at 52 weeks [69]. Furthermore, the 28-week DURATION-8 trial demonstrated comparable effects of an SGLT-2 inhibitor (dapagliflozin) and GLP-1 RA (exenatide) on body weight (-2.22 kg vs. -1.56 kg, respectively), whereas an additive effect was observed with combination therapy (-3.55 kg). As GLP-1 RAs also exert weight-lowering effects, these results indicate additive effects of SGLT-2 inhibitors and GLP-1 RAs on weight reduction.

The weight-lowering effects of SGLT-2 inhibitors are consis-

tent even when used as an add-on to insulin therapy. In studies with follow-up of up to 52 weeks, weight reduction with SGLT-2 inhibitor treatment ranged from -0.5 to -3.4 kg [70].

Effect on abdominal adiposity

In Western populations, SGLT-2 inhibitor treatment reduces WC by about -1.20 cm (weighted mean difference vs. placebo; 95% CI, -2.00 to -0.43) [107]. Similar results are observed in Asian patients with T2DM. Across the studies in patients with T2DM, treatment with SGLT-2 inhibitors reduced WC as monotherapy (range, -1.59 to -2.82 cm), or in combination with other oral GLDs (range, -1.39 to -3.82 cm) or in combination with insulin (range, -0.7 to -1.4 cm) [65,70,71-78,108]. Table 1 summarizes the effects of SGLT-2 inhibitors on WC in Asian T2DM patients.

In addition, Ohta et al. [109] evaluated the effects of ipragliflozin on intrahepatic lipid content and subcutaneous and visceral fat volume in Japanese T2DM patients. Treatment with ipragliflozin for 24 weeks was associated with significant reductions in subcutaneous and visceral fat volume, intrahepatic lipid content and fat mass, and appendicular skeletal mass indices. In another 12-month study in obese Japanese T2DM patients ($n=20$), treatment with ipragliflozin significantly reduced both visceral and subcutaneous fat volume at 3 months; the reduction in subcutaneous fat volume remained significant at 12 months follow-up [110]. The PRIME-V study compared the effects of ipragliflozin and metformin, as an add-on to

Table 1. Effect of SGLT-2 inhibitors on body weight and waist circumference in Asian patients with T2DM

Study	Design and population	Intervention	Effect on body weight	Effect on waist circumference
Monotherapy				
Inagaki et al. (2013) [79]	Phase II, 12-wk randomized study; Japanese T2DM (<i>n</i> =383)	Canagliflozin (50, 100, 200, or 300 mg); placebo	-1.98 kg (50 mg); -2.51 kg (100 mg); -2.39 kg (200 mg); -3.19 kg (300 mg); -0.78 kg (placebo)	-1.59 cm (50 mg), -1.81 cm (100 mg), -1.83 cm (200 mg), -2.21 cm (300 mg); -0.59 cm (placebo)
Inagaki et al. (2014) [73]	Phase III, 24-wk double-blind randomized study; Japanese T2DM (<i>n</i> =272)	Canagliflozin (100, 200 mg); placebo	-3.76% (100 mg), -4.02% (200 mg); -0.76% (placebo)	-2.21 cm (100 mg); -2.82 cm (200 mg); -1.03 cm (placebo)
Kaku et al. (2013) [80]	Phase II, 12-wk randomized study; Japanese T2DM (<i>n</i> =279)	Dapagliflozin (1, 2.5, 5, or 10 mg/day); placebo	-1.25 kg (1 mg); -1.24 kg (2.5 mg); -2.06 kg (5 mg); -1.91 kg (10 mg); -0.05 (placebo)	-
Ji et al. (2014) [74]	Phase III, 24-wk double-blind randomized study; drug-naïve Asian T2DM (<i>n</i> =393)	Dapagliflozin (5 or 10 mg); placebo	-1.64 kg (5 mg); -2.25 kg (10 mg); -0.27 kg (placebo)	-2.77 cm (5 mg); -2.20 cm (10 mg); -0.72 cm (placebo)
Kaku et al. (2014) [81]	Phase III, 24-wk double-blind randomized study; Japanese T2DM (<i>n</i> =261)	Dapagliflozin (5 or 10 mg); placebo	-2.13 kg (5 mg); -2.22 kg (10 mg); -0.84 kg (placebo)	-
Kadowaki et al. (2014) [82]	Phase II, 12-wk randomized study; Japanese T2DM (<i>n</i> =547)	Empagliflozin (5, 10, 25, or 50 mg); placebo	-2.5 kg (5 mg); -2.6 kg (10 mg); -2.9 kg (25 mg); -3.1 kg (50 mg); -0.9 kg (placebo)	-2.4 cm (5 mg); -2.3 cm (10 mg); -2.6 cm (25 mg); -2.6 cm (50 mg); -1.3 cm (placebo)
Kadowaki et al. (2015) [75]	40-wk extension study; Japanese T2DM (<i>n</i> =532)	Empagliflozin (10, 25 mg)	-3.1 kg (10 mg); -3.1 kg (25 mg)	-2.8 cm (10 mg); -2.8 cm (25 mg)
Kashiwagi et al. (2014) [66]	Phase II, 12-wk randomized study; Japanese T2DM (<i>n</i> =361)	Ipragliflozin (12.5, 25, 50, or 100 mg/day); placebo	-1.46 kg (12.5 mg); -1.69 kg (25 mg); -1.81 kg (50 mg); -2.1 kg (100 mg); -0.39 kg (placebo)	-
Kashiwagi et al. (2015) [83]	Phase III, 16-wk double-blind randomized study; Japanese T2DM (<i>n</i> =131)	Ipragliflozin (50 mg); placebo	-2.31 kg (50 mg); -1.03 kg (placebo)	-1.61 cm (50 mg); -0.41 cm (placebo)
Seino et al. (2015) [67]	52-wk open-label study; Japanese T2DM (<i>n</i> =299)	Luseogliflozin (2.5 mg, option to uptitrate to 5 mg)	12 wk: -1.77 kg (2.5/5 mg) 24 wk: -1.91 kg (2.5/5 mg) 36 wk: -2.35 kg (2.5/5 mg) 52 wk: -2.68 kg (2.5/5 mg)	-
Hirose et al. (2016) [84]	8-wk open-label study (<i>n</i> =17)	Tofogliflozin (20 mg)	-1.1 kg (20 mg)	-
Kaku et al. (2014) [65]	Phase II/III, 24-wk double-blind randomized study; Japanese T2DM (<i>n</i> =235)	Tofogliflozin (10, 20, or 40 mg); placebo	-2.23 kg (10 mg); -2.85 kg (20 mg); -2.97 kg (40 mg); -0.36 kg (placebo)	-2.42 cm (10 mg); -2.47 cm (20 mg); -2.27 cm (40 mg); 0.02 cm (placebo)

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Table 1. Continued

Study	Design and population	Intervention	Effect on body weight	Effect on waist circumference
Add-on to oral antidiabetic agents				
Ji et al. (2015) [85]	Phase III, 18-wk double-blind randomized study; Asian T2DM (<i>n</i> =678)	Canagliflozin (100, 300 mg)+Met or SU+Met; placebo	-1.9 kg (100 mg); -2.1 kg (300 mg); -0.5 kg (placebo)	-
Inagaki et al. (2015) [72]	52-wk open-label randomized study; Japanese T2DM (<i>n</i> =1,299)	Canagliflozin (100, 200 mg); other GLDs	-4.42% (100 mg); -4.70% (200 mg); -2.94% (100 mg+SU); -3.51% (200 mg+SU); -3.97% (100 mg+glinide); -4.37% (200 mg+glinide); -4.03% (100 mg+α-GI); -4.98% (200 mg+α-GI); -4.42% (100 mg+BG); -5.54% (200 mg+BG); -3.37% (100 mg+TZD); -3.43% (200 mg+TZD); -4.00% (100 mg+DPP-4i); -4.37% (200 mg+DPP-4i)	-2.76 cm (100 mg); -3.34 cm (200 mg); -1.96 cm (100 mg+SU); -1.72 cm (200 mg+SU); -2.93 cm (100 mg+glinide); -3.24 cm (200 mg+glinide); -2.27 cm (100 mg+α-GI); -2.57 (200 mg+α-GI); -3.40 cm (100 mg+BG); -3.82 cm (200 mg+BG); -3.12 cm (100 mg+TZD); -2.64 cm (200 mg+TZD); -3.34 cm (100 mg+DPP-4i); -2.37 cm (200 mg+DPP-4i)
Kadowaki et al. (2017) [86]	Phase III, 24-wk double-blind randomized study; Japanese T2DM (<i>n</i> =138)	Canagliflozin (100 mg); teneligliptin; placebo	-2.29 kg (100 mg+teneligliptin); -0.78 kg (placebo+teneligliptin)	-
Kadowaki et al. (2018) [87]	52-wk open-label study; Japanese T2DM (<i>n</i> =153)	Canagliflozin (100 mg); teneligliptin	-2.86 kg (100 mg+teneligliptin)	-
Harashima et al. (2018) [68]	Phase IV, 52-wk open-label; Japanese T2DM (<i>n</i> =71)	Canagliflozin (100 mg); liraglutide	-3.29 kg (100 mg+liraglutide)	-3.39 cm (100 mg+liraglutide)
Kaku et al. (2014) [81]	Phase III, 52-wk open-label study; Japanese T2DM (<i>n</i> =728)	Dapagliflozin (5 mg, option to uptitrate to 10 mg); other GLDs	-2.6 kg (monotherapy); -2.1 kg (combination therapy)	-2.1 cm (monotherapy); -2.0 cm (combination therapy)
Yang et al. (2016) [78]	Phase III, 24-wk randomized double-blind study; Asian T2DM (<i>n</i> =444)	Dapagliflozin (5, 10 mg); Met; placebo	-1.8 kg (5 mg+Met); -2.6 kg (10 mg+Met); -0.7 kg (placebo+Met)	-1.96 cm (5 mg+Met); -2.15 cm (10 mg+Met); -0.39 cm (placebo+Met)
Araki et al. (2015) [88]	Phase III, 52-wk randomized study; Japanese T2DM (<i>n</i> =1,160)	Empagliflozin (10, 25 mg); other GLDs	SU: -2.3 kg (10 mg+SU); -2.8 kg (25 mg+SU) BG: -3.9 kg (10 mg+BG); -3.4 kg (25 mg+BG) TZD: -2.6 kg (10 mg+TZD); -2.8 kg (25 mg+TZD) α-GI: -3.8 kg (10 mg+α-GI); -3.4 kg (25 mg+α-GI) DPP-4i: -2.9 kg (10 mg+DPP-4i); -2.8 kg (25 mg+DPP-4i) Glinide: -2.6 kg (10 mg+glinide); -3.1 kg (25 mg+glinide)	-

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Table 1. Continued

Study	Design and population	Intervention	Effect on body weight	Effect on waist circumference
Kashiwagi et al. (2015) [89]	Phase III, 24-wk randomized study; Japanese T2DM (<i>n</i> =168)	Ipragliflozin (50 mg); Met; placebo	-2.33 kg (50 mg+Met); -0.63 kg (placebo+Met)	-2.39 cm (50 mg+Met); -0.48 cm (placebo+Met)
Lu et al. (2016) [76]	Phase III, 24-wk randomized double-blind study; Asian T2DM (<i>n</i> =171)	Ipragliflozin (50 mg); Met; placebo	-2.93 kg (50 mg+Met); -1.70 kg (placebo+Met)	-1.72 cm (50 mg+Met); -0.85 cm (placebo+Met)
Kashiwagi et al. (2015) [90]	Phase III, 24-wk randomized double-blind study; Japanese T2DM (<i>n</i> =152)	Ipragliflozin (50 mg); pioglitazone; placebo	-2.29 kg (50 mg+pioglitazone); 0.51 kg (placebo+pioglitazone)	-1.82 cm (50 mg+pioglitazone); 0.14 cm (placebo+pioglitazone)
Kashiwagi et al. (2015) [91]	Phase III, 24-wk randomized double-blind study; Japanese T2DM (<i>n</i> =243)	Ipragliflozin (50, 100 mg); SU; placebo	-2.33 kg (50 mg+SU); -0.88 kg (placebo+SU)	-1.61 cm (50 mg+SU); -0.87 cm (placebo+SU)
Seino et al. (2018) [69]	52-wk, open-label study; Japanese T2DM (<i>n</i> =76)	Luseogliflozin (2.5 mg, option to uptitrate to 5 mg); liraglutide	12 wk: -1.65 kg (2.5/5 mg+GLP-RA) 12 wk: -2.52 kg (2.5/5 mg+GLP-RA) 36 wk: -2.86 kg (2.5/5 mg+GLP-RA) 52 wk: -2.71 kg (2.5/5 mg+GLP-RA)	12 wk: -1.39 cm (2.5/5 mg+GLP-RA) 12 wk: -2.63 cm (2.5/5 mg+GLP-RA) 36 wk: -3.09 cm (2.5/5 mg+GLP-RA) 52 wk: -2.86 cm (2.5/5 mg+GLP-RA)
Ikeda et al. (2015) [92]	Phase II, 12-wk randomized, double-blind study (<i>n</i> =398)	Tofogliflozin (2.5, 5, 10, 20, or 40 mg); Met; placebo	-1.56 kg (2.5 mg+Met); -1.85 kg (5 mg+Met); -2.24 kg (10 mg+Met); -2.55 kg (20 mg+Met); -2.82 kg (40 mg+Met); -0.74 kg (placebo+Met)	-
Add-on to insulin				
Inagaki et al. (2016) [93]	Phase IV, 16-wk double-blind randomized study; Japanese T2DM (<i>n</i> =146)	Canagliflozin (100 mg); insulin; placebo	-1.49 kg (100 mg+insulin); 0.15 kg (placebo+insulin)	-
Inagaki et al. (2018) [94]	Phase IV, 52-wk (16-wk double-blind randomized placebo-controlled study+36-wk open-label extension); Japanese T2DM (<i>n</i> =146)	Canagliflozin (100 mg); insulin; placebo	-0.99 kg (placebo+insulin → 100 mg+insulin); -1.52 kg (100 mg+insulin → 100 mg+insulin)	-
Araki et al. (2016) [70]	Phase IV, 16-wk double-blind randomized placebo-controlled study; Japanese T2DM (<i>n</i> =182)	Dapagliflozin (5 mg); insulin; placebo	-0.55 kg (5 mg+insulin); 0.66 kg (placebo+insulin)	Placebo-corrected mean reduction: -1.00 cm
Araki et al. (2017) [71]	36-wk open-label extension of Araki et al. 2016 [70] (<i>n</i> =175)	Dapagliflozin (5 mg); insulin	-1.5 kg (5 mg+insulin → 5 mg+insulin); -1.37 kg (placebo+insulin → 100 mg+insulin)	-1.4 cm (5 mg+insulin → 5 mg+insulin); -0.9 cm (placebo+insulin → 100 mg+insulin)
Yang et al. (2018) [95]	Phase III, 24-wk randomized double-blind study; Asian T2DM (<i>n</i> =272)	Dapagliflozin (10 mg); insulin; placebo	-1.00 kg (10 mg+insulin); 0.37 kg (placebo+insulin)	-0.70 cm (10 mg+insulin); 0.00 cm (placebo+insulin)

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Table 1. Continued

Study	Design and population	Intervention	Effect on body weight	Effect on waist circumference
Ishihara et al. (2016) [96]	Phase IV, 16-wk double-blind randomized placebo-controlled study; Japanese T2DM (<i>n</i> =262)	Ipragliflozin (50 mg); insulin; placebo	-1.09 kg (10 mg+insulin); -0.05 kg (placebo+insulin)	-1.36 cm (10 mg+insulin); -0.84 cm (placebo+insulin)
Seino et al. (2018) [77]	Phase IV, 52-wk (16-wk double-blind randomized placebo-controlled study+36-wk open-label extension); Japanese T2DM (<i>n</i> =233)	Luseogliflozin (2.5 mg); insulin; placebo	-1.32 kg (2.5 mg+insulin); -0.05 kg (placebo+insulin)	-1.16 cm (2.5 mg+insulin); 0.04 cm (placebo+insulin)
Terauchi et al. (2017) [97]	Phase IV, 16-wk double-blind randomized placebo-controlled study; Japanese T2DM (<i>n</i> =211)	Tofogliflozin (20 mg); insulin; placebo	-1.34 kg (20 mg+insulin); 0.03 kg (placebo+insulin)	-
Terauchi et al. (2018) [98]	36-wk open-label extension of Terauchi et al. (2017) [97] (<i>n</i> =210)	Tofogliflozin (20 mg); insulin	-1.52 kg (20 mg+insulin → 20 mg+insulin); -2.13 kg (placebo+insulin → 20 mg+insulin)	-
Suzuki et al. (2016) [99]	24-wk randomized active-controlled study; Japanese T2DM (<i>n</i> =53)	Tofogliflozin (20 mg); insulin; insulin glargine	0.6 kg (insulin); -2.9 kg (20 mg+insulin); -3.4 kg (20 mg+insulin glargine)	-
Pooled analyses				
John et al. (2016) [100]	Pooled data from four 26-wk placebo-controlled studies (<i>n</i> =2,313) and a 104-wk active-controlled study (<i>n</i> =1,450) in T2DM patients in hot climate countries	Canagliflozin (100, 300 mg); placebo; glim+Met; canagliflozin (100, 300 mg)+Met	Placebo-controlled trials Hot climate subset: -1.9 kg (100 mg); -2.4 (300 mg); -0.3 kg (placebo) Other climate subset: -2.8 kg (100 mg); -3.4 kg (300 mg); -0.7 kg (placebo) Active-controlled trials Hot climate subset: -2.6 kg (100 mg+Met); -2.8 (300 mg+Met); +1.3 (glim+Met) Other climate subset: -3.9 kg (100 mg+Met); -3.9 (300 mg+Met); 0.6 (glim+Met)	-
Yang et al. (2017) [101]	Pooled data from eight Phase IIb/III double-blind placebo-controlled trials of up to 24 wk (<i>n</i> =1,453)	Dapagliflozin (5, 10 mg); placebo	-1.9 kg (5 mg); -2.4 kg (10 mg); -0.6 kg (placebo)	-

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Table 1. Continued

Study	Design and population	Intervention	Effect on body weight	Effect on waist circumference
Yoon et al. (2016) [102]	Pooled data from four Phase III trials up to 24 wk (<i>n</i> =1,326)	Empagliflozin (10, 25 mg); placebo, other GLDs	Pooled data: -1.6 kg (10 mg); -1.8 kg (10 mg) Monotherapy: -1.7 kg (10 mg); -2.1 kg (25 mg) Met: -1.4 kg (10 mg+Met); -1.5 kg (10 mg+Met) Met+SU: -1.5 kg (10 mg+Met+SU); -1.9 kg (10 mg+Met+SU) Pioglitazone: -2.0 kg (10 mg+pioglitazone); -1.7 kg (10 mg+pioglitazone)	-
Prasanna Kumar et al. (2016) [103]	Pooled subgroup analysis of patients enrolled from India (<i>n</i> =124) in four randomized Phase III trials	Canagliflozin (100, 300 mg); placebo; other GLDs	Overall population: -2.6 (100 mg); -3.3 (300 mg) Indian subgroup: -1.7 (100 mg); -2.2 (300 mg)	-
Seino et al. (2015) [104]	Pooled analysis of two 52-wk studies; Japanese T2DM (<i>n</i> =708)	Luseogliflozin (2.5 mg); other GLDs	SU: -2.23 kg (2.5 mg+SU) BG: -2.86 kg (2.5 mg+BG) DPP-4i: -1.96 kg (2.5 mg+DPP-4i) TZD: -2.32 kg (2.5 mg+TZD) Glinide: -2.88 kg (2.5 mg+glinide) α -GI: -2.80 kg (2.5 mg+ α -GI) SU+placebo (24 wk): 0.16 kg (placebo+SU)	-
Post-marketing study				
Utsunomiya et al. (2017) [105]	1-yr prospective, observational, post-marketing study (<i>n</i> =1,424)	Tofogliflozin	-1.18 kg (4 wk); -1.81 kg (12 wk); -2.01 kg (24 wk); -1.72 kg (36 wk); -2.55 (52 wk)	-
Nakamura et al. (2018) [106]	24-mo post-marketing surveillance study (<i>n</i> =8,757)	Ipragliflozin	-1.32 kg (1 mo); -2.16 kg (3 mo); -2.45 kg (6 mo); -2.81 kg (12 mo); -3.11 (24 mo)	-

SGLT-2, sodium glucose cotransporter-2; T2DM, type 2 diabetes mellitus; GLD, glucose-lowering drug; SU, sulfonylurea; α -GI, alpha glucosidase inhibitor; BG, biguanide; TZD, thiazolidinedione; DPP-4i, dipeptidyl peptidase-4 inhibitor; Met, metformin; GLP-RA, glucagon-like peptide-1 receptor agonist; glim, glimepiride.

DPP-4 inhibitor, on visceral fat reduction in Japanese patients with T2DM. Treatment with ipragliflozin in combination with DPP-4 inhibitor was associated with significant reductions in visceral fat area ($P=0.04$), subcutaneous fat area ($P=0.004$), total fat area ($P=0.004$), and WC ($P=0.001$), compared with metformin+DPP-4 inhibitor [111].

Furthermore, a 16-week study in Japanese patients with T2DM showed that the decrease in total fat mass accounts for 71% of total body weight reduction induced by SGLT-2 inhibitor treatment, with the remainder due to loss in water volume (22%) [112]. Another study revealed that SGLT-2 inhibitor-in-

duced weight loss is not associated with reduction in the muscle mass [113]. In this study, 6-month treatment with dapagliflozin resulted in a significant reduction in body weight and total fat mass, with no significant effect on skeletal muscle mass and psoas muscle index.

Effect on adipose tissue function

Few studies have assessed the effects of SGLT-2 inhibitors on the adipose tissue in obese Asian patients with T2DM. In a 12-week study of dapagliflozin in obese patients with T2DM, there was a significant increase in the plasma adiponectin and

decrease in high-sensitivity C-reactive protein levels but no significant changes in plasminogen activator inhibitor-1 levels [114].

Effect on ectopic fat

Obesity results in ectopic fat deposition which leads to impaired insulin sensitivity, non-alcoholic steatohepatitis, impaired insulin secretion, and diastolic dysfunction [115,116]. The prospective, open-label, randomized E-LIFT study (effect of empagliflozin on liver fat content in patients with T2DM), examined the effect of empagliflozin (10 mg/day as add-on to the standard therapy) on liver fat content (using magnetic resonance imaging-derived proton density fat fraction [MRI-PDFF]) in patients with T2DM and NAFLD. At 20 weeks, treatment with empagliflozin significantly reduced liver fat content (mean MRI-PDFF difference: -4.0% ; $P < 0.0001$) and serum alanine aminotransferase levels (-10.9 IU/L; $P = 0.005$), compared with the control group [117]. Another open-label randomized study compared the effects of ipragliflozin and pioglitazone on liver fat content (change in liver-to-spleen [L/S] ratio on computed tomography scan) in patients with T2DM and NAFLD [118]. At 24 weeks, treatment with either ipragliflozin or pioglitazone improved liver fat content, with no significant difference between the two groups (L/S ratio increased by 0.22 in ipragliflozin vs. 0.21 in pioglitazone; $P = 0.90$). In addition, both treatments reduced the levels of serum aspartate transaminase and alanine transaminase [118].

Furthermore, in two 12-week pilot studies, luseogliflozin and ipragliflozin reduced the epicardial fat volume in overweight/obese patients with T2DM [119,120].

Effect on weight loss-related QoL and treatment satisfaction

Overweight and obesity negatively affect the patient QoL. A placebo-controlled study in patients with T2DM ($n = 180$) evaluated the effect of dapagliflozin on weight change- and health-related quality of life (HRQoL), using the Study to Help Improve Early evaluation and management of risk factors Leading to Diabetes Weight Questionnaire-9 (SHIELD-WQ-9) survey [121]. Treatment with dapagliflozin was associated with improvement in most of the HRQoL domains at week 24, 50, and 102, and these changes correlated with the weight loss. Similarly, in a study assessing the treatment satisfaction in overweight patients with T2DM ($n = 221$) using the Oral Hypoglycemic Agent-Questionnaire (OHA-Q) version 2, treat-

ment with dapagliflozin was associated with a significant improvement in patient-reported treatment satisfaction [122]. Changes in the OHA-Q total score correlated with changes in body weight and glycosylated hemoglobin. Similar results were observed in a pooled analysis of four randomized controlled trials of canagliflozin [123]. A higher proportion of patients receiving canagliflozin reported interest in continuing treatment upon study completion.

RELATIONSHIP BETWEEN SGLT-2 INHIBITOR-INDUCED WEIGHT LOSS AND IMPROVEMENT OF HYPERGLYCEMIA AND CARDIOVASCULAR OUTCOMES

Weight loss might contribute to the CV benefits observed with SGLT-2 inhibitors in multiple trials. The randomized Look AHEAD trial studied the impact of weight loss on the primary prevention of CV outcomes in overweight/obese patients with T2DM [124]. The trial compared the efficacy of intensive lifestyle intervention with diabetes support and education in 5,145 adults with T2DM and a mean BMI of 36.0 kg/m². After a median follow-up of 9.6 years, lifestyle intervention resulted in a significant weight loss (-8.7% at 1 year, and -6.0% at the end of study) but did not show a beneficial effect on mortality and CV outcomes [124]. However, a recent analysis from the study revealed a significant association between magnitude of weight loss and long-term risk of CV outcomes. Participants from both intensive lifestyle intervention and diabetes support and education groups who achieved a weight loss of $> 10\%$ had a significantly lower risk of CV outcomes (composite of CV death, myocardial infarction, stroke, or angina hospitalization; hazard ratio, 0.79; 95% CI, 0.64 to 0.98) [125]. In addition, weight loss in the intensive lifestyle intervention group was associated with improved glycemic control, QoL, physical functioning and mobility, and reduced risk of CKD, sleep apnea, urinary incontinence, and depression [126-132]. In other studies, weight loss interventions such as anti-obesity drugs (orlistat, rimonabant, and sibutramine) and bariatric surgery have been shown to improve CV risk factors (T2DM, hypertension, and hyperlipidemia) in people with obesity [133-135].

The mechanism of SGLT-2 inhibitor-induced weight reduction is likely due to calorie loss and diuresis induced by urinary glucose excretion. A study to quantify the effect of SGLT-2 inhibitor-induced calorie loss on body weight showed a difference in the observed and expected weight loss based on uri-

nary energy loss [136]. Over 90 weeks, the mean urinary energy loss with empagliflozin treatment was 206 kcal/day, which was expected to result in a weight loss of -11.3 kg (assuming no compensatory changes in energy intake), in contrast with the actual weight loss of -3.2 kg (29% of the predicted weight loss). This difference in the calorie-to-weight loss was higher in leaner patients (lower BMI) and those with higher eGFR [136]. Considering that the resting and postprandial energy expenditures were unaltered after chronic SGLT-2 inhibitor treatment [137], the difference in the calorie-to-weight loss was attributable to an adaptive increase in calorie intake after 10 weeks of treatment. In addition, the calorie deficit induced by glycosuria leads to a shift in substrate utilization from glucose to lipids, resulting in increased lipolysis and FFA oxidation. Of note, more than two-thirds of SGLT-2 inhibitor-induced weight loss is attributable to a reduction in fat mass [58,138,139]. Further-

more, recent studies have shown that SGLT-2 is expressed in the pancreatic alpha cells, and its inhibition triggers secretion of glucagon directly. Altered (reduced) insulin-to-glucagon ratio simulates “starvation” state leading to increased lipolysis and mobilization of FFAs [140,141]. In addition, studies on diet-induced obese rodent models suggested that SGLT-2 inhibition increases fat utilization (oxidation) and browning of white adipose tissue, reduces hepatic fat content, and attenuates obesity-induced inflammation and insulin resistance [142-144].

The role of weight loss induced by SGLT-2 inhibitors should be considered in combination with their other effects, which include: (1) diuretic and natriuretic effects and reduction in cardiac preload; (2) shift in cardiac energy substrate from fat and glucose oxidation to more efficient ketone bodies; (3) reduced epicardial fat volume leading to a decrease in cardiac fibrosis and enhanced contractility; (4) increase in hematocrit;

Table 2. Clinical recommendations on the use of SGLT-2 inhibitors for the management of Asian patients with T2DM and abdominal obesity

Clinical recommendations
<p>Overweight/obesity burden and associated complications in Asian patients with T2DM</p> <ul style="list-style-type: none"> • Overweight/obesity is a major driver of the increasing prevalence of T2DM in Asia, and most of the patients with T2DM are overweight/obese. • Asian populations have higher abdominal adiposity for any given BMI compared with their Caucasian counterparts. • Visceral or abdominal adiposity is strongly associated with risk of adverse CV outcomes and has been shown to be superior to BMI in predicting CVD risk. • Overweight/obesity in patients with T2DM independently increases the risk of hypertension, dyslipidemia, and CHD; it is also associated with other complications such as ectopic fat deposition (e.g., NAFLD).
<p>Weight loss as an essential management goal in overweight/obese patients with T2DM</p> <ul style="list-style-type: none"> • Weight loss is an important management goal in patients with T2DM, who are overweight/obese. • Lifestyle modification (diet, physical activity, and behavioral therapy) designed to achieve and maintain weight loss should be prescribed for patients with T2DM who are overweight/obese. • Limited glucose-lowering pharmacological therapies are available that promote weight loss in T2DM. • In overweight/obese patients with T2DM, use of glucose-lowering medications that promote weight loss or are weight neutral is recommended. <ul style="list-style-type: none"> ◦ Use of medications that are associated with weight gain should be minimized in overweight/obese patients with T2DM.
<p>Role of SGLT-2 inhibitors in the management of Asian patients with T2DM and abdominal obesity</p> <ul style="list-style-type: none"> • SGLT-2 inhibitor is recommended to promote weight loss and reduction in visceral adiposity in Asian patients with T2DM and abdominal obesity. • SGLT-2 inhibitors promote weight loss in Asian patients with T2DM as monotherapy or in combination with other GLDs. <ul style="list-style-type: none"> ◦ More than two-thirds of SGLT-2 inhibitor-induced weight loss is attributable to a reduction in body fat mass. • SGLT-2 inhibitor treatment reduces WC (a measure of abdominal or visceral adiposity) and ectopic fat deposition in non-adipose tissues, and improves adipose tissue function, HRQoL, and patient-reported treatment satisfaction.

SGLT-2, sodium glucose cotransporter-2; T2DM, type 2 diabetes mellitus; BMI, body mass index; CV, cardiovascular; CVD, cardiovascular disease; CHD, coronary heart disease; NAFLD, non-alcoholic fatty liver disease; GLD, glucose-lowering drug; WC, waist circumference; HRQoL, health-related quality of life.

and (5) renoprotective effects [58,139,145,146]. In addition, SGLT-2 inhibitors have been shown to enhance utilization of FFAs and improve adipose tissue function. These effects may lead to a reduction in inflammation, improvements in insulin resistance, glycemic control, and blood pressure control.

CONCLUSIONS

Management of overweight/obese patients with T2DM poses a challenge to clinicians because of there being fewer therapeutic options available for both glycemic control and weight reduction. Some of the older, established GLDs induce weight gain as a side effect. SGLT-2 inhibitors are novel oral GLDs that promote weight loss, decrease adiposity, and improve CV outcomes. As most of the T2DM patients are overweight/obese and at high risk of CVD, SGLT-2 inhibitors offer an effective therapeutic option for the management of these patients, particularly in the Asian region, which has a high burden of abdominal adiposity and CVD. Based on the current evidence on SGLT-2 inhibitors in the Asian population, results from the large CVOTs, and clinical experience, a series of clinical recommendations have been developed (Table 2).

CONFLICTS OF INTEREST

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