Review Article

SGLT2 Inhibitors: Paradigm Shift from Diabetes Care to Metabolic Care—An Indian Perspective

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Abstract

The prevalence and burden of diabetes are on the rise in India, making it 'the diabetes capital of the world'. Comorbidities such as obesity, cardiovascular (CV) complications, chronic kidney disease (CKD), non-alcoholic fatty liver disease (NAFLD), and neurodegenerative diseases are common in patients with diabetes. Recent breakthroughs in diabetes medications and continuous glucose monitoring have resulted in a paradigm shift in diabetes care. Hence, a review in the Indian context is warranted. This review focuses on the existing evidence (gathered by a systematic literature search utilising online databases such as PubMed) on the metabolic, cardio-renoprotective, and hepatoprotective effects of sodium-glucose co-transporter 2 (SGLT2) inhibition, particularly in the Indian setting. The study revealed that the SGLT2 inhibitors (SGLT2i), with their numerous pleiotropic benefits, have received considerable attention recently as a novel class of antihyperglycaemic agents (AHAs) for the management of diabetes. SGLT2i play a crucial role in the transition from glycaemic control to metabolic care, particularly in the context of obesity, CV disease and renal disease. In addition to improving glycaemic control, SGLT2i have been shown to promote weight loss, reduce blood pressure and improve lipid profiles, which are key components of metabolic health. Moreover, SGLT2i have demonstrated renal protective effects, including a reduction in albuminuria and a slower decline in the estimated glomerular filtration rate (eGFR), suggesting a potential role in the management of renal dysfunction.

Keywords: Diabetes, metabolic care, obesity, organ protection, SGLT inhibitors

Introduction

Type 2 diabetes mellitus (T2DM), the silent epidemic of the twenty-first century,[1,2] is a serious global health concern associated with the majority of disease burden and is considered one of the leading causes of death and reduced life expectancy, worldwide. Currently, 463 million people are suffering from diabetes, worldwide (~90% of them have T2DM), and this figure would reach ~700 million by 2045.[3-5] India has the second-highest prevalence of adults with diabetes, making it 'the diabetes capital of the world'. With every fifth diabetic in the world being of Indian origin, the number is expected to reach 134 million by 2045. In addition, around 57% of these people are estimated to be still undiagnosed.[1] Among the most common causes of death in India, diabetes-related deaths surprisingly have risen by 54.2% from 11th position in 2009 to 8th position in 2019.[2] In a recent cross-sectional population-based survey conducted by the Indian Council of Medical Research-India Diabetes (ICMR-INDIAB), the overall weighted prevalence of diabetes was reported as 11.4% (95% confidence interval (CI) 10.2–12.5; 10,151 of 1,07,119 individuals) and prediabetes was 15.3% (13.9–16.6; 15,496 of 1,07,119 individuals). The occurrence of diabetes in India was notably higher than previously reported by other studies; an estimated 101 million people had diabetes, and the number of individuals with prediabetes was 136 million. It was also noted that although the diabetes epidemic is stabilising in

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the more developed urban regions of the country, it continues to rise in most other rural states.[6] Obesity, cardiovascular (CV) complications, renal disease, depression, respiratory illness, osteoporosis, and endocrine abnormalities are among the conditions that are often seen in patients with diabetes.[7]

Implications of T2DM on overall metabolic health outcomes

As per the ICMR-INDIAB study, only 7.7% of Indians with diabetes achieved a collective target of good glycaemic control (glycated haemoglobin [HbA1c] <7%), blood pressure control (<140/90 mm Hg), and low-density lipoprotein cholesterol (LDL-C) control (<100 mg/dL).[8] The A_1chieve study reported that nearly 23.6% and 21.1% of patients with T2DM have associated CV and renal complications, respectively, in India.[9] Obesity is a growing concern; being overweight or obese is a major modifiable risk factor in T2DM, accounting for 90% of patients with diabetes.[10] Moreover, obesity increases long-term CV and renal complications in patients with diabetes.[11] A cross-sectional observational study from India reported that 39.5% and 60.5% of patients with newly diagnosed diabetes were at 'high risk' and 'very high risk' for CV complications, respectively.[12] The median annual direct and indirect costs associated with diabetes care were estimated to be ₹ 25,391 and ₹ 4,970, respectively, in India;[13,14] patients with ≥2 comorbidities pay an additional 48% cost towards disease management.[15]

The word 'metabesity' was coined recently to describe a group of metabolic illnesses that share similar metabolic and inflammatory causes. These diseases include diabetes, obesity, metabolic syndrome, CV disease, neurodegenerative diseases, and premature ageing. This demonstrates the necessity of integrative methods to address metabolic health in patients with T2DM as most metabolic disorders are intertwined with T2DM.[16] Therefore, it is the need of the hour to focus the antidiabetic treatment approaches not only on glycaemic control but also towards the prevention of diabetes-related comorbidities or complications, including obesity, metabolic disorders, CV diseases (myocardial infarction [MI], heart failure [HF], stroke, atherosclerotic CV disease [ASCVD], etc.), diabetic kidney disease (DKD), and fatty liver disease.

Targeting sodium-glucose co-transporter (SGLT) receptors for glycaemic control and beyond

The SGLT family of receptors in humans contains six different isoforms, of which SGLT1 and SGLT2 have been most extensively studied[17] [Table 1]. SGLT1 receptors are primarily expressed in the small intestine, heart and skeletal muscle; however, these receptors are also located in the brain, liver, lungs, kidney, prostate, colon, pancreas, stomach, trachea, cervix, and testis.[18-20] In the kidney, SGLT2 receptors are predominantly expressed in the apical brush border of the early proximal tubule (S1 or S2 segments) and SGLT1 is expressed in the apical brush border of the later parts of the proximal tubule (S2 or S3 segment). Each is responsible for 90% and 10% reabsorption of filtered glucose, respectively[4,21] [Figure 1]. A healthy human kidney filters ~1 mol (180 g) of glucose through glomeruli per day. Almost all of this filtered glucose (>99%) is reabsorbed by SGLT2 and SGLT1 along the tubular system.[21] The SGLT1 receptors, present on the brush border membrane of the small intestine, are primarily responsible for dietary glucose absorption [Figure 2]. Additionally, intestinal SGLT1 regulates the release of hormones associated with glucose homeostasis, such as glucose-dependent insulinotropic peptide (GIP), glucagon-like peptide (GLP)-1 and peptide YY (PYY).[22] As the inhibition of SGLT2 and SGLT1 is not insulin-dependent and is not affected by deteriorating β-cell function or insulin resistance, these inhibitors are expected to be effective at any stage of T2DM, as long as glomerular filtration is adequate.[23] As evident from CV outcome trials (CVOTs) and DKD trials to date, SGLT2 inhibitors (SGLT2i) have shown a favourable tolerability profile, low potential for hypoglycaemia and beneficial CV effects and renal risk reduction; thus, they can be used as first-line therapy in the management of T2DM.[24,25] When SGLT2i are used in hyperglycaemic conditions, ~40%–50% of unabsorbed glucose is available for reabsorption at the later part of proximal tubules; this indirectly increases the transport maximum of the SGLT1 receptor capacity in the distal tubules.[26] SGLT2i including canagliflozin (CANA), empagliflozin (EMPA), dapagliflozin (DAPA) and ertugliflozin (ERTU) are approved by the United States Food and Drug Administration (USFDA) and the European Medicines Agency (EMA);[27] of these, CANA (100 mg and 300 mg), DAPA (5 mg and 10 mg), and EMPA (10 mg and 25 mg) are the most widely used worldwide. These were approved in India in November 2014, February 2015 and May 2015, respectively.[28,29] The SGLT2i remogliflozin was approved in India in April 2019.[30]

Paradigm shift in diabetes management with SGLT inhibitors

Recent breakthroughs in diabetes medications have resulted in a paradigm shift in diabetes care [Figure 2]. SGLT2i, with their numerous pleiotropic benefits, have received a lot of attention recently as a novel class of antihyperglycaemic agents (AHAs) for T2DM management. With the discovery of novel therapies such as SGLTis and GLP-1 receptor agonists (RAs), T2DM management has undergone a paradigm shift like never before—'From AHAs with potential cardio-toxic effects to AHAs with proven cardio-renoprotection and beyond'.[31]

American Diabetes Association (ADA) 2023 recommends SGLT2i or GLP-1 RA as the first-line therapy (alone or in combination with other AHA) for patients with diabetes who have or are at risk of atherosclerosis, HF or chronic kidney disease (CKD).[32] Similarly, the European Society of Cardiology (ESC) 2019 and American Heart Association (AHA) 2022 recommended providing SGLT2i as first-line therapy in patients with diabetes to lower the risk of HF and ASCVD and to reduce the progression of DKD.[33,34] Additionally, Kidney Disease Improving Global Outcomes (KDIGO) 2020 recommends the use of SGLT2i with metformin in patients with diabetes and CKD.[35]

Table 1: Comparison between SGLT1 and SGLT2 receptors

	SGLT1 receptor[23,89]	SGLT2 receptor[23,89]
Description	Low-capacity, high-affinity glucose co-transport protein	High-capacity, low-affinity glucose co-transport protein
Location of action in the proximal tubule	Distal S2 and S3 segments	S1 and S2 segments
Renal glucose absorption capacity	5%–10% (~10 g per day)	90%–95% (160–180 g per day)
Additional action in the small intestine	Primary glucose co-transporter	None
Distribution	Intestine, trachea, kidney, heart, brain, testes, prostate	Kidney
Apparent affinity for glucose ($K_{0.5}$ mM)	0.4	2
Substrates	Glucose, galactose	Glucose

Apparent affinity values ($K_{0.5}$) are approximate as determined by inhibition of the transport of α-methyl-D-glucoside in various cell types, and tissue distribution of transporters is mostly based on mRNA expression. mRNA, messenger RNA; SGLT, sodium-glucose co-transporter

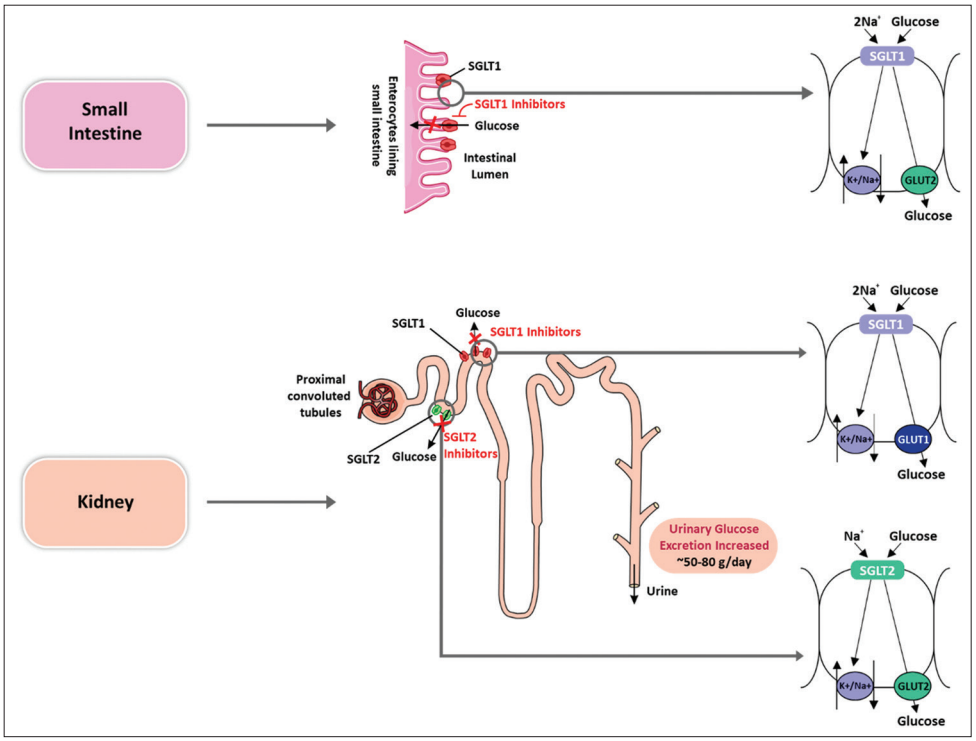

Figure 1: Glucose transport through the intestine and renal tubules by SGLT. GLUT, glucose transporter; K, potassium; Na, sodium; SGLT, sodium-glucose co-transporter

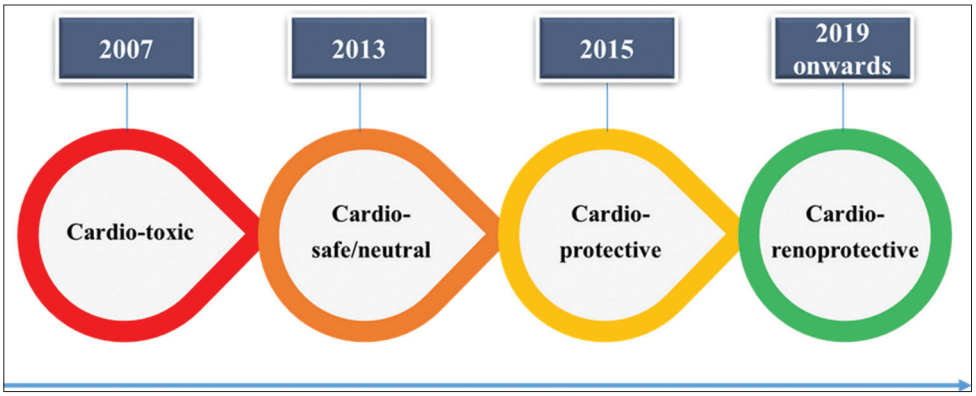

Figure 2: Paradigm shift in diabetes management with regard to the availability of novel antihyperglycaemic agents ('from cardio-toxic to cardio-renoprotective')[90]

Three CVOTs, the Canagliflozin Cardiovascular Assessment Study (CANVAS) Program[36] (CANA), EMPA-REG OUTCOME[37,38] (EMPA) and the Dapagliflozin Effect on CardiovascuLAR Events (DECLARE-TIMI 58)[39] (DAPA),

Table 2: Summary of SGLT2i pivotal studies with cardiovascular and renal endpoints in patients with T2DM

Study name	Treatment	Key CV and renal outcomes	Key outcomes
EMPA-REG OUTCOME[37,38]	EMPA (10 or 25 mg)	MACE: CV death + MI + Stroke	MACE: HR 95% CI; 0.86 (0.74–0.99)
		HHF	HHF: HR 95% CI; 0.65 (0.50–0.85)
		Renal composite: progression of macroalbuminuria + doubling of SCr + RRT initiation + renal death	Renal composite: HR 95% CI; 0.61 (0.53–0.70)
CANVAS and CANVAS-R[36]	CANA (100 or 300 mg)	MACE: CV death + MI + Stroke	MACE: HR 95% CI; 0.86 (0.75–0.97)
		HHF	HHF: HR 95% CI; 0.67 (0.52–0.87)
		Progression of albuminuria	Progression of albuminuria: HR 95% CI; 0.73 (0.67–0.79)
		Renal composite: 40% eGFR reduction + RRT initiation + renal death	Renal composite: HR 95% CI; 0.60 (0.47–0.77)
CREDENCE[41]	CANA (100 mg)	MACE: CV death + MI + Stroke	MACE: HR 95% CI; 0.80 (0.67–0.95)
		HHF	HHF: HR 95% CI; 0.61 (0.47–0.80)
		Renal composite: ESRD + doubling of SCr + renal death	Renal composite: HR 95% CI; 0.70 (0.59–0.82)
DECLARE-TIMI 58[39]	DAPA (10 mg)	MACE: CV death + MI + Stroke	MACE: HR 95% CI; 0.93 (0.84 to 1.03)
		CV death + HHF	CV death or HHF: HR 95% CI; 0.83 (0.73–0.95)
		Renal composite: 40% eGFR reduction + renal death	Renal composite: HR 95% CI; 0.76 (0.67–0.87)

CANA, canagliflozin; CV, cardiovascular; DAPA, dapagliflozin; eGFR, estimated glomerular filtration rate; EMPA, empagliflozin; ESRD, end-stage renal disease; HHF, heart failure for hospitalisation; HR, hazard ratio, MACE, major adverse cardiovascular event; MI, myocardial infarction; RRT, renal replacement therapy; SCr, serum creatinine

reported a reduction in composite endpoints (nonfatal MI, nonfatal stroke and CV death) of three-point major adverse CV events (3P MACE), CV mortality, risk of hospitalisation for HF in patients with diabetes and established CV disease (secondary prevention cohort).[40] Additionally, through the Canagliflozin and Renal Events in Diabetes With Established Nephropathy Clinical Evaluation (CREDENCE) trial, CANA demonstrated a significant risk reduction in composite renal outcomes in patients with T2DM suffering from DKD [Table 2].[41] More recently, other SGLT2i are also proven to be renoprotective agents in patients with T2DM suffering from CKD in the DAPA-CKD and EMPA-KIDNEY trials.[41,42]

Materials and Methods

On 26 May 2023, a comprehensive literature search was undertaken using keywords related to diabetes mellitus, India, sodium-glucose-linked transporter, SGLT2i and many concomitant disorders such as HF, CV mortality, non-alcoholic fatty liver disease (NAFLD), acute kidney injury, and MACE in the PubMed database. To gather the most current evidence, the search time was limited to the last 10 years. Of the 696 papers identified, 80 were deemed appropriate for inclusion in this review. The reference lists of the relevant papers were also reviewed to find relevant research that may have been overlooked during the search procedure. This review article included all review articles and original research that discussed the effectiveness of SGLT2 inhibition in patients with diabetes and related comorbidities.

Paradigm shift from diabetes care to metabolic care with SGLT2i

Glycaemic control

As postprandial hyperglycaemia increases the risk of complications related to diabetes and CV, treatment strategies are aimed especially at reducing blood glucose elevations after a meal.[22] SGLT2i consistently show a significant reductions in HbA1c levels, with an average decrease of approximately 0.5% to 1.0%.[43] They are effective in reducing fasting plasma glucose (FPG) levels and have a positive impact on postprandial plasma glucose (PPG) control. CANA 300 was associated with more reductions in PPG excursion and insulin excursion compared with placebo.[44,45] Stein P *et al.* demonstrated that the reductions in the incremental PPG were mostly attributed to the delayed and blunted oral glucose absorption in the small intestine rather than the increased urinary glucose excretion (UGE) for CANA 300.[44] UGE of CANA 300 is ~119 g/day (loss of 476 kcal/day), which is ~30% higher compared with other SGLT2i, such as DAPA 10 mg (~70 g/day or 280 kcal/day), EMPA 10 mg (~64 g/day), EMPA 25 mg (~78 g/day) and remogliflozin 100 mg (~72 g/day or 288 kcal/day).[46-51] These properties of CANA 300 might be attributed to better glycaemic and body weight control, among the class in patients with diabetes. Twenty-four weeks of treatment with CANA in Japanese patients with T2DM significantly reduced HbA1c from 7.94 ± 0.69 to 7.18 ± 0.64 ($P < 0.001$) and FPG from 154.1 ± 33.8 to 130.2 ± 29.6 ($P < 0.001$); glucose infusion rate (GIR) increased from 3.25 ± 1.53 to 4.11 ± 1.30 mg/kg/min ($P < 0.05$).[52] Another real-world study in Japan showed continuous improvement in glycaemic control in patients treated with CANA 100 that was maintained for up to 3 years (mean change of –0.68%).[53] In an Indian prospective, interventional, nonrandomised study of patients with inadequately controlled T2DM having HbA1c >8.5% and body mass index (BMI) >25 kg/m^2 who were receiving SGLT2i on the background of triple-drug therapy, a significant reduction in the HbA1c values was observed within the groups at the end of 24 weeks. The mean HbA1c reductions were 3.08% for CANA, 2.87% for EMPA, 2.74% for DAPA and 2.79% for the remogliflozin groups.[54] In another Indian study that assessed the efficacy of SGLT2i

as an add-on therapy, significant reductions were observed in the levels of HbA1c (–1.63 ± 0.99%), fasting blood glucose (FBG) (–63.65 ± 19.93 mg/dL) and post-prandial blood glucose (PPBG) (–79.28 ± 23.57 mg/dL) ($P = 0.001$).[55] Another real-world Indian study in a triple-drug regimen observed a mean reduction of 1.02 ± 0.24% in the HbA1c levels and a mean weight reduction of 2.64 ± 1.27 kg when SGLT2i (DAPA and CANA 100) were added to the regimen.[56] In another study conducted with Indian patients who were not adequately responding to triple-drug therapy, the efficacy of CANA 100 was observed as a reduction in the HbA1c levels by 1.9% and a reduction in body weight by 3.01 kg over a 12-week period compared with baseline.[57]

Body weight reduction

Several meta-analyses have investigated the magnitude of weight loss associated with SGLT2i and have revealed that, on average, patients can expect to lose around 2–3 kg of weight after 6 months of treatment.[58] Considering the effect of increased UGE demonstrated by CANA, a reduction in body weight of up to ≥5% was observed across phase three studies with either 100 mg or 300 mg doses.[58,59] Real-world clinical outcomes from Spain showed that switching to CANA 300 from other SGLT2i therapies improved several cardiometabolic parameters in patients with T2DM along with significant reductions in body weight by 2.1 kg.[60] CANA 100 was found to contribute to a significant reduction in both body fat mass (1.31 kg) and lean mass (1.15 kg), resulting in an overall reduction in body weight. Computed tomography (CT) scans revealed reductions in both the abdominal visceral fat area (8.7%) and the abdominal subcutaneous fat area (7.7%). The lecithin/sphingomyelin (L/S) ratio, an index of fatty liver, improved significantly from 0.90 ± 0.24 to 1.02 ± 0.20 ($P < 0.001$), following the administration of CANA 100 in Japanese patients.[52] Another real-world study including 1,232 patients with T2DM reported a body weight reduction of 3.0 kg with CANA 300 at 6 months, along with improvements in glycaemic parameters.[61] Similarly, CANA 300 also reduced body weights (4.3 kg ± 2.2 kg) at 24 weeks of time point in overweight and obese patients with T2DM.[62] In addition, the highest caloric loss associated with CANA 300 could also result in additional weight loss in patients with diabetes.[46-50] In line with the global data, CANA 300 also reported greater body weight reductions in patients with diabetes from India.[55,63,64] Further large studies are warranted to elucidate the true clinical benefits of SGLT2i in weight loss.

CV protection

Several meta-analyses and clinical studies reported improved CV outcomes with SGLT2i versus placebo.[65-67] Meta-analysis including 10 randomised controlled trials (RCTs) concluded that among SGLT2i (CANA, EMPA, DAPA and sotagliflozin (SOTA)), the overall hazard ratio (HR) for CV mortality across all trials was 0.85 (0.78–0.92), indicating a reduced risk of CV mortality in patients receiving SGLT2i. When examining specific SGLT2i, the HRs for CV mortality were 0.81 (0.63–1.03) for EMPA, 0.88 (0.78–1.00) for DAPA and 0.84 (0.72–0.98) for CANA; only CANA showed a statistically significant reduction in both all-cause mortality and CV mortality in patients with T2DM.[68] The EMPA-REG OUTCOME trial evaluated EMPA, and the DECLARE-TIMI 58 trial investigated DAPA; both reported significant reductions in the 3P MACE composite endpoints, including nonfatal MI, nonfatal stroke and CV death. Additionally, both trials showed a decreased risk of CV mortality and a reduced risk of hospitalisation for HF in patients with diabetes and established CV disease. In the CANVAS program, CANA treatment resulted in a significantly lower risk of CV events versus placebo in patients with diabetes and an elevated risk of CV disease.[69] Furthermore, a meta-regression analysis found that the advantages of HF are indirectly connected to the receptor selectivity of SGLT2i. In terms of HF outcomes, non-selective SGLT2i may be preferable to the highly selective SGLT2i.[70] CANA showed a significant reduction in the 3P MACE in the CANVAS program with all three components, comprising CV death, nonfatal MI and nonfatal stroke, contributing to the final composite endpoint of 3P MACE unlike other SGLT2i.[71] Based on these differential benefits, CANA has become the only SGLT2i to be approved for 3P MACE risk reduction in adult patients with T2DM by the Drug Controller General of India (DCGI).[72,73]

Renoprotective effects

At present, CANA has strong and direct evidence for providing renal benefits in patients with DKD. CREDENCE is the first published SGLT2i study, examining the effects of CANA on renal outcomes in patients with DKD.[41,74] Based on the findings from this study, CANA is the first T2DM medication that has been approved for reducing the risks associated with end-stage kidney disease (ESKD), deterioration of kidney function, CV death and hospitalisation due to HF. The DAPA-CKD and EMPA-Kidney trials have highlighted the clinical benefits of SGLT2i, DAPA and EMPA in improving outcomes for individuals with CKD. The KDIGO 2020 guidelines recommend SGLT2i as first-line therapy alongside metformin for managing patients with T2DM and CKD. The evidence from the DAPA-CKD trial is particularly notable as it demonstrates a significant reduction in the risk of CKD progression and associated CV complications, similar to the findings of the CREDENCE study.[75-77]

CANA 100 was found to reduce the risk of ESKD and doubling of serum creatinine levels in patients from East and South-East Asian countries (HR 0.54, 95% confidence interval (CI): 0.35 to 0.84, ($P = 0.2035$).[78] A network meta-analysis of SGLT2i showed favourable renal protective effect and safety; CANA 100 mg (mean differences = −193.25, 95% CI: −279.16 to − 107.34, $P < 0.05$) reduced urine albumin-creatinine ratio levels compared with other controls.[79]

Hepatoprotective effects

Non-alcoholic fatty liver disease (NAFLD), a hepatic manifestation of metabolic syndrome, affects nearly 70% of patients with T2DM.[80] SGLT2i are associated with

improvements in various hepatic outcomes in patients with diabetes and NAFLD.[81] The use of SGLT2i DAPA, EMPA or CANA in patients with T2DM and NAFLD is linked to improvements in liver steatosis and fibrosis markers, as well as reductions in circulating pro-inflammatory and redox status.[82] Studies reported beneficial outcomes with dual SGLTis, including CANA in the reductions in liver enzymes in patients with liver diseases.[83,84] Evidence suggests that SGLT2i improve NAFLD in patients with T2DM by markedly reducing hepatic enzymes.[85-87] In the Effect of Empagliflozin on Liver Fat Content in Patients With Type 2 Diabetes (E-LIFT) study, 50 patients with T2DM and NAFLD were randomly assigned to standard treatment + EMPA 10 mg daily or standard treatment without EMPA for 20 weeks. EMPA showed a reduction in liver fat measured by the mean Magnetic Resonance Imaging-Proton Density Fat Fraction (MRI-PDFF) difference as − 4.0%, $P < 0.0001$.[85] A retrospective 5-year follow-up study, with SGLT2i, indicated a favourable histological impact on NAFLD in patients with T2DM.[88] Furthermore, large studies are required to demonstrate the true clinical benefits of SGLT2i in hepatoprotective effects.

Conclusion

The transition from diabetes care to metabolic care represents a paradigm shift in the management of metabolic disorders. By taking a comprehensive approach that targets the underlying pathophysiology and addressing the multiple metabolic abnormalities associated with these disorders, metabolic care has the potential to improve outcomes and reduce the risk of complications. By addressing not only diabetes but also other comorbidities such as obesity, CVD, NAFLD, DKD and hypertension, metabolic care aims to improve patient outcomes and reduce the risk of CVD. Furthermore, the implementation of personalised and evidence-based interventions, including lifestyle modifications and pharmacotherapy, can help achieve optimal metabolic control and prevent the development of complications. This shift requires a more patient-centred approach that focuses on individualised care, emphasises lifestyle modifications and utilises a multidisciplinary team-based approach. By embracing this transition, healthcare providers can better address the complex and interconnected nature of metabolic disorders and provide more effective and personalised care to their patients. Patients with T2DM requiring additional benefits for the management of multiple comorbidities along with glycaemic control may find SGLTi a promising therapy, especially considering the diabetes burden, obesity and associated CV and other comorbidities in the Indian population.

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Conflicts of interest

There are no conflicts of interest.

Author contributions

All authors contributed to the conceptualization, design, methodology, data collection, data analysis and interpretation, manuscript drafting, critical revision of the article, provided final approval for the version to be published, and agreed to be accountable for all aspects of the work.

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