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Expert opinion on the clinical approach of using sodium glucose cotransporter-2 inhibitors for managing diabetic patients with cardiovascular and renal complications in Indian settings

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Objective: To evaluate the prescription practice of sodium-glucose co-transporter-2 (SGLT2) inhibitors with a special focus on dapagliflozin to treat cardiac and renal disorders in obese Indian diabetic patients. **Methods:** A cross-sectional, questionnaire-based study was conducted to collect the perspectives of physicians with expertise in treating diabetic obese patients with cardiac and renal disorders in endocrinology across India between June 2022 and December 2022. Descriptive statistics were used to summarize the characteristics of the study by employing frequencies and percentages. **Results:** Among the 1,446 survey participants, 80% of them indicated that young diabetic patients with obesity, and obese patients with cardio-renal complications may require SGLT2 inhibitors. Furthermore, patients aged between 41-50 and 51-60 years also required SGLT2 inhibitors for diabetes management according to 57% and 27% of the respondents. The majority of the respondents (91.29% and 90.53%) recommended dapagliflozin as the best SGLT2 inhibitor for treating patients with chronic kidney disease and heart failure. Additionally, about 59% and 66% of the experts indicated that patients would experience an average weight loss of 2-3 kilograms and an average blood pressure reduction of 3-6 mm Hg after 12 weeks of treatment with dapagliflozin, respectively. **Conclusion:** Experts recommend the use of SGLT2 inhibitors for the treatment of young diabetic patients with obesity and obese subjects with cardiorenal complications. Dapagliflozin monotherapy was preferred for patients with chronic kidney disease and heart failure. Furthermore, experts highly recommend the combinations of dapagliflozin + metformin and DPP4 inhibitors + metformin + dapagliflozin for effective diabetes management.

Keywords: Chronic kidney disease, Diabetes, Dapagliflozin, Heart failure, Obesity

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Introduction

Type 2 diabetes was estimated to affect more than 415 million adults globally, but by 2040, more than 640 million adults were expected to have the disease [1]. Diabetic patients have an elevated risk of developing cardiovascular disease and chronic renal disease [2,3]. Hence, reducing the risk of unfavourable cardiovascular and renal outcomes has become a cornerstone of type 2 diabetes care plans [4]. Asian-Indian phenotype and the presence of other modifiable/non-modifiable risk factors have a significant negative impact on the epidemiology of type 2 diabetes in India. Around, 69% of type 2 diabetes patients in India did not achieve the desired glycated haemoglobin (HbA1c) level due to various reasons, including noncompliance with lifestyle recommendations [5]. Indians were more prone to diabetes and early cardiovascular disease due to the Asian-Indian phenotype, which was characterized by a higher degree of central obesity, hyperinsulinemia, insulin resistance, atherogenic dyslipidemia, and hyperinsulinemia [6,7].

The selection of different antidiabetic drug combinations should be tailored to the patient's needs in the context of prioritizing patient-centric, holistic cardio-metabolic risk management. Combining therapy with sodium-glucose co-transporter-2 (SGLT2) inhibitors and dipeptidyl peptidase 4 (DPP4) inhibitors confers several benefits. These include reduction in metabolic and vascular risk, improvement in glycemia and adiposity, safety, and the ease of long-term compliance [8].

There were literature studies comparing dapagliflozin monotherapy with sulphonyl urea's (SUs), as well as its combination with metformin, pioglitazone, SUs, sitagliptin (with or without metformin), metformin + SU, or insulin (with or without other oral antidiabetic therapy). When compared to the control group, treatment with dapagliflozin, either alone or in combination with metformin, sitagliptin, glimepiride, pioglitazone, or insulin, significantly reduced the mean change from baseline in HbA1c at week 24. The reduction was noted across subgroups, including gender, race, age at onset of disease, and baseline body mass index [9].

The United States Food and Drug Administration (US-FDA) has approved dapagliflozin as the first Member of a new class of SGLT2 inhibitors. It was used in combination with diet and exercise to improve glycemic control in adults with type 2 diabetes mellitus and to lower the risk of hospitalization due to heart failure in adults with diabetes and a history of cardiovascular disease or multiple cardiovascular risk factors. It has most recently been licensed to lower the risk of cardiovascular death in individuals with heart failure and a decreased ejection fraction (New York Heart Association Classes II–IV) [10].

There was a dearth of data available on the preference for dapagliflozin in the actual clinical practice among clinicians. So, this study was intended to examine the prescription pattern of SGLT2 inhibitors in Indian settings with a special focus on dapagliflozin for the management of cardio-renal complications in obese diabetic patients.

Methodology

We carried out a cross-sectional, questionnaire-based survey among physicians in treating diabetic obese patients with cardiac and renal problems in major Indian cities from June 2022 to December 2022.

Questionnaire

The questionnaire booklet titled ZUCAPRIDE (Expert opinion on Dapagliflozin and its combinations) study was sent to the physicians who were interested in participating. The ZUCAPRIDE study questionnaire included questions on current practices, preferences, clinical observations, and experiences related to the use of SGLT2 inhibitors in routine settings, particularly dapagliflozin for the management of diabetic obese patients with cardiac and renal problems. The study was conducted after receiving approval from Bangalore Ethics, an Independent Ethics Committee which is recognized by the Indian Regulatory Authority, Drug Controller General of India.

Participants

An invitation was sent to leading doctors in managing cardio-renal complications among diabetic patients in March 2022 for participation in this Indian survey. About 1446 doctors from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data.

Physicians were asked to complete the questionnaire without discussing it with peers. A written informed consent was obtained from each physician prior initiation of the study.

Statistical Analysis

Descriptive statistics were used to summarize the characteristics of the study by employing frequencies and percentages. Graphical representation of data was done by using Microsoft Excel and Word, which was also used to obtain various types of graphs like bar diagrams and column diagrams.

Results

The present survey included 1446 participants, and the majority of them (80.01%) indicated the need for SGLT2 inhibitors to manage diabetes in young patients with obesity, as well as those with obesity and cardiac or renal complications. (Figure 1) Approximately 57% and 27% of the respondents, indicated that SGLT2 inhibitors are also preferred for managing diabetes in patients aged between 41-50 and 51-60 years of age, respectively. Only nearly 13% of them opted for SGLT2 inhibitors in the age group of less than 40 years.

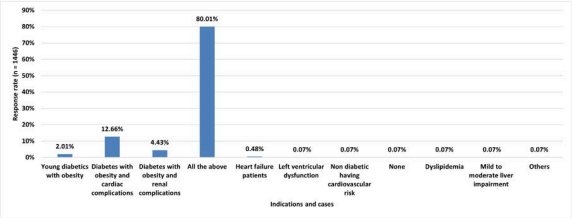

Figure 1: Response to the indications and cases that require SGLT2 inhibitors for managing diabetes.

About 97% of the participants preferred dapagliflozin over empagliflozin, canagliflozin, remogliflozin, and others in clinical practice. (Table 1) Dapagliflozin was the preferred choice among SGLT2 inhibitors for the majority of the respondents (91.29% and 90.53%) when treating patients with heart failure and chronic kidney disease whereas it was only 6% for Empagliflozin and only approximately 2% for Canagliflozin. Approximately 50% of the respondents favoured the combination of DPP4 inhibitors + metformin as oral antidiabetic drugs along with dapagliflozin for treating these patients.

However, SUs + metformin and DPP4 inhibitors along with dapagliflozin are also preferred choices among 26% and 21% of the participants and the SUs + metformin + pioglitazone combination in only 3% approximately.

Table 1: Distribution of response on the preference of SGLT2 inhibitors in clinical practice

Preference of SGLT2 inhibitors in clinical practice	Response rate (n = 1446)
Dapagliflozin	1403 (97.03%)
Empagliflozin	31 (2.14%)
Canagliflozin	7 (0.48%)
Remogliflozin	4 (0.28%)
Others	1 (0.07%)

Approximately 59% of the participants reported an average weight loss of 2-3 kgs among patients following dapagliflozin for 12 weeks. However, 26% and 13% of the experts indicated that patients would reduce 3-4 kgs and <2 kgs of weight after 12 weeks of dapagliflozin treatment. (Table 2a) Moreover, 66% of the experts noted an average blood pressure (BP) reduction of 3-6 mm Hg with dapagliflozin therapy for 12 weeks. Moreover, 18% and 14% of the experts indicated that >6 mm Hg and <3 mm Hg of BP reduction would be observed after 12 weeks of dapagliflozin treatment. (Table 2b)

Table 2a: Distribution of response on the average weight reduction observed with 12 weeks of dapagliflozin therapy

Average weight reduction observed with dapagliflozin after 12 weeks	Response rate (n = 1446)
<2 kgs	194 (13.42%)
2-3 kgs	851 (58.85%)
3-4 kgs	369 (25.52%)
>5 kgs	31 (2.14%)
Others	1 (0.07%)

Table 2b: Distribution of response on the average BP reduction observed with 12 weeks of dapagliflozin therapy

Average BP reduction observed with dapagliflozin after 12 weeks	Response rate (n = 1446)
<3 mmHg	204 (14.11%)
3-6 mmHg	956 (66.11%)
>6 mmHg	257 (17.77%)
Not observed	28 (1.94%)
Others	1 (0.07%)

The majority of the experts (97.44%) preferred dapagliflozin in combination with metformin for the effective treatment of diabetic patients. (Table 3) Approximately 40% of the experts indicated that they would observe a 0.75% to 1% mean HbA1c change after dapagliflozin + metformin combination therapy among patients in their clinical settings.

However, more than 1% of mean HbA1c change was reported to be observed following this combination therapy by 32% of the respondents. However, 25% of the experts reported 0.5% to 0.75% mean HbA1c change after taking the same combination therapy and only 3.39% of them highlighted less than 0.5% reduction in HbA1c. In addition, 53% of the experts noted that they would observe a mean weight loss of 2-3 kgs in patients treated with the same combination therapy. However, 33% of the experts reported a mean weight reduction of 3-4 kgs in patients after undergoing the combination therapy and nearly 9% of them noted less than 2 kgs of weight reduction.

Table 3: Distribution of response to the preferred SGLT2 inhibitors and metformin combination

Preferred combination of SGLT2 inhibitors + metformin	Response rate (n = 1446)
Dapagliflozin + metformin	1409 (97.44%)
Empagliflozin + metformin	23 (1.59%)
Canagliflozin + metformin	9 (0.62%)
Remogliflozin + metformin	4 (0.28%)
Others	1 (0.07%)

Low risk of hypoglycemia, weight loss, cardioprotection, and renal protection are the advantages reported for using SGLT2 inhibitors + metformin combination over the SUs + metformin combination by 91% of the respondents. (Figure 2)

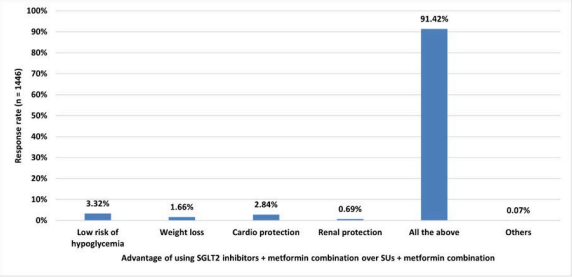

Figure 2: Distribution of response on the advantage of using SGLT2 inhibitors + metformin combination over SUs + metformin

Approximately 53% of the experts stated that a 6-month follow-up might be required to observe an improvement in ejection fraction in heart failure patients. Around 35% of the experts indicated that 3 months of follow-up in these patients would be sufficient to notice improvements in ejection fraction and nearly 8% of them marked 9 months follow-up was needed.

Discussion

The current survey findings recommended SGLT2 inhibitors as an ideal therapeutic choice for managing diabetes in young patients with obesity and those with both obesity and cardiac or renal complications. Experts also preferred SGLT2 inhibitors for diabetes management in patients aged 41-50 years and 51-60 years. SGLT2 inhibitors were previously reported to reduce the incidence of severe adverse cardiovascular events and hospitalization due to heart failure, and lower serum creatinine, albuminuria, and renal disease-related mortality in patients with renal complications [11-15]. The current study also preferred SGLT2 inhibitors for managing patients with diabetes, heart failure, and chronic kidney disease.

A majority of the participants preferred dapagliflozin over empagliflozin, canagliflozin, remogliflozin, and the other SGLT2 inhibitors in Indian clinical practice for treating heart failure and chronic kidney disease patients. Phase-2 and phase-3 randomized controlled trials (RCTs) findings have demonstrated that SGLT2 inhibitors (dapagliflozin and empagliflozin) were effective in lowering HbA1c (by 2-4 mmol/L), body weight (by 1-2 kg), and the overall amount of insulin needed when compared to placebo [16,17]. By these findings, the current survey respondents noted that the use of dapagliflozin for 12 weeks contributed to an average weight loss of 2-3 kgs and an average BP reduction of 3-6 mm Hg. Apart from monotherapy, the effectiveness of dapagliflozin as an adjuvant therapy has also been explored by several studies.

Some experts also preferred combination therapies such as dapagliflozin + metformin and observed 0.75 to 1% mean HbA1c as well as weight reduction of 2-3 kgs among patients treated with this therapy. Henry et al. indicated that patients receiving combination therapy of dapagliflozin (5 mg and 10 mg) and metformin extended-release (XR) demonstrated significant reductions in mean fasting

Plasma glucose values and HbA1c at the end of 24 weeks when compared to patients receiving dapagliflozin monotherapy [18]. Bailey et al. reported that the therapy with dapagliflozin as an add-on to metformin reduced HbA1c by an additional 4-6 mmol/mol (0.4-0.55%) compared to metformin alone. Additionally, individuals receiving dapagliflozin in addition to metformin reported greater weight loss (-2.2 to -3.0 kg) and reductions in fasting plasma glucose (-17.8 to -23.4 mg/dl) than those taking metformin alone (which was 5.9 mg/dl and 0.9 kg) [19]. In agreement with these findings, the majority of the current respondents noted that the use of SGLT2 inhibitors + metformin was beneficial in lowering the risk of hypoglycemia, promoting weight loss, and providing cardiorenal protection, according to the majority of the respondents.

Studies involving SGLT2 inhibitors and DPP4 inhibitor agents indicated that these medications have favourable effects on time-in-range. According to systematic reviews and meta-analyses by Lee et al., diabetic patients receiving these medications experience lower glycemic variability [20,21]. Anoop et al. denoted that due to increased DPP4 enzyme activity in Asian Indian individuals with type 2 diabetes, DPP4 inhibitors have been proven to have better efficacy in such patients [22]. A significant proportion of current survey participants preferred the combination of DPP4 inhibitors + metformin along with dapagliflozin for treating diabetic patients with cardiorenal complications. Gan et al. noted that in individuals of Asian ancestry, SGLT2 inhibitors and, to a lesser extent, DPP4 inhibitors are associated with increased glucose-lowering efficacy [23]. A subgroup analysis found that in Asian patients with type 2 diabetes mellitus and existing cardiovascular disease, empagliflozin consistently reduced the risk of cardiovascular events, death, and renal outcomes [24,25].

The current survey findings may assist clinicians in decision-making in routine practice and improving patient outcomes, especially when considering the increasing challenges posed by cardiorenal complications in diabetic patients. The study highlights the significance of medication adherence and customized treatment options for managing obese diabetic patients with cardiovascular and renal complications.

It was important to acknowledge certain limitations of the study. Relying on the expert judgment in the study introduced the potential for bias, as different perspectives and preferences may have influenced the survey findings. It was essential to consider these limitations when interpreting the results and to conduct further research to validate the findings.

Conclusion

Experts recommend the use of SGLT2 inhibitors for the treatment of young diabetic patients with obesity and obese subjects with cardiorenal complications. Dapagliflozin monotherapy was preferred for treating patients with heart failure and chronic kidney disease. Experts also advocated the combinations of dapagliflozin + metformin and DPP4 inhibitors + metformin + dapagliflozin for diabetes management.

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