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Expert opinion on fixed-dose combinations of sitagliptin + dapagliflozin and the triple drug combination of dapagliflozin + sitagliptin + metformin in the management of type 2 diabetes mellitus in Indian settings

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Abstract
Aim: To gather clinicians' perspectives regarding the prescription practice of the fixed-dose combinations (FDC) of sitagliptin + dapagliflozin and the triple drug combination of dapagliflozin + sitagliptin + metformin for managing type 2 diabetes mellitus (T2DM) in Indian settings.
Methodology: The cross-sectional survey, gathered the opinions of clinicians across India using a multiple-response questionnaire comprising 22 questions. The survey focused on garnering insights, clinical observations, and experiences related to the utilization of FDCs for the management of T2DM. Descriptive statistics were employed for data analysis, depicting categorical variables as percentages. Graphical representations were created using Microsoft Excel 2013.
Results: The respondents predominantly recommended sitagliptin and dapagliflozin FDC therapy for T2DM patients with comorbidities such as hypertension and vascular diseases, leading to non-glycemic benefits like reduced body weight, blood pressure, and increased vasodilation. Around 82% of the clinicians favored this FDC therapy due to its superior cardiovascular and renal safety profile. Notably, 41% of clinicians suggested benefits for patients with an initial HbA1c level of 8%. The majority indicated preference for patients with atherosclerotic cardiovascular disease (31%) and chronic kidney disease up to stage 3 (28%). Clinicians reported reduced glycemic variability (65%), lower risk of urinary tract infections (74%), and a significant body weight reduction (44%) with the therapy. According to 63% of the clinicians, sitagliptin, dapagliflozin, and metformin FDC therapy decreases endogenous glucose production. The majority (44%) of the clinicians reported 2-3 kg body weight reduction with this therapy in T2DM individuals, and attainment of rapid and sustained glycemic goals (47%).
Conclusion: Majority of the clinicians endorsed sitagliptin and dapagliflozin FDC for managing T2DM, citing non-glycemic benefits, superior cardiovascular safety, and positive outcomes in patients with specific comorbidities. Survey respondents also recommend the sitagliptin, dapagliflozin, and metformin FDC, highlighting its effectiveness in reducing endogenous glucose production, inducing significant body weight reduction, and facilitating the attainment of rapid, sustained glycemic goals.

Keywords: Type 2 diabetes mellitus, fixed-dose combinations, Sitagliptin, Dapagliflozin, Metformin

Introduction
Diabetes stands as a leading contributor to premature fatalities globally, with an immense burden on healthcare systems. According to estimates from the International Diabetes Federation (IDF), the condition afflicted 537 million globally in 2021, resulting in total health-related expenditures of around $966 billion and it is estimated to surpass $1054 billion by 2045. Alarmingly, the prevalence is projected to reach 643 million by 2030 and a staggering 783 million by 2045. Notably, 75% of those affected reside in low and middle-income nations [1, 2]. India is emerging as global hub of diabetes, with an estimated 77 million individuals affected [3, 4].
Dapagliflozin, metformin, and sitagliptin, as anti-diabetic agents, exert their effects through distinct mechanisms. Dapagliflozin is a highly potent, reversible, and selective inhibitor of sodium-glucose cotransporter-2 (SGLT2). It increases the amount of glucose excreted in the urine and improves both fasting (FPG) and post-prandial plasma glucose levels in patients with T2D [5]. Metformin, a well-established biguanide, regulates blood glucose by inhibiting

liver sugar production and absorption [6, 7]. Sitagliptin, a DPP-IV inhibitor, enhances incretin hormone utilization, promoting insulin secretion, suppressing glucagon release, delaying gastric emptying, and potentially modulating β-cell proliferation [8].

The use of fixed-dose combinations (FDCs) in managing type 2 diabetes mellitus (T2DM) is gaining widespread popularity due to several benefits. These advantages encompass a reduction in pill intake, decreased risk of adverse effects, cost-effectiveness, and improved patient compliance, resulting in enhanced efficacy [9, 10].

The present survey was aimed to gather expert opinion regarding the prescription patterns of FDCs namely sitagliptin + dapagliflozin and the triple drug combination of dapagliflozin + sitagliptin + metformin for treating T2DM in Indian healthcare settings.

Methods

A cross sectional, multiple-response questionnaire based survey conducted among physicians specialized in managing T2DM in the major Indian cities from June 2023 to December 2023.

Questionnaire

The questionnaire booklet titled PROTECT (Sitagliptin and other OAD combinations in Management of T2DM: Expert Perspective Study) was sent to the doctors who were interested to participate. The PROTECT study questionnaire comprised 22 queries related to clinicians' perspectives, clinical observations, and experiences in managing T2DM using FDCs. The study was performed after obtaining approval from Bangalore Ethics, an Independent Ethics Committee which was recognized by the Indian Regulatory Authority, Drug Controller General of India.

Participants

An invitation was sent to professionals across India based on their expertise and experience in treating T2DM in the month of March 2023 for participation in this Indian survey. About 413 clinicians from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. Clinicians had the discretion to skip questions they did not wish to answer. Written informed consent was obtained from all participants, who were required to independently complete the questionnaire without consulting peers. Unanswered questions were treated as non-attempts.

Results

Out of 413 survey respondents, approximately 33% reported an incidence of uncontrolled T2DM) ranging from 11-20%. Regarding coronary artery disease (CAD) among individuals with T2DM, 61% of clinicians reported an incidence between 11-20%. Among the respondents, 28%, 20%, 16%, and 12% acknowledged that early and aggressive attainment of glycemic goals in T2DM management leads to improved clinical outcomes, end-organ protection, reduced mortality rates, delayed disease progression, and preservation of beta cell function, respectively. Moreover, 23% concurred with all the aforementioned benefits. In terms of the incidence of proteinuria and glomerulosclerosis in T2DM patients, the majority (48%) of clinicians reported a range of 11-20%.

According to 30% of the respondents, both genders are equally prone to developing 'diabetic renal disease.' More than half (54%) of the respondents suggested proteinuria as the ideal marker for the progression of micro albuminuria in individuals with T2DM. In contrast, 46% of the respondents stated that an altered glomerular filtration rate serves as a better marker. Majority (57%) of the respondents reported that 11% to 20% of individuals with T2DM had chronic kidney disease (CKD). Approximately 59% of the clinicians T2DM patients presenting to routine practice has increased risk for cardiovascular disease as the probable co-morbid condition noted.

Majority (61%) of the respondents reported that hypoglycemia increases the risk of diabetic CKD progression. According to half of the respondents, micro albuminuria screening along with FBG, HbA1c, and lipid levels should be conducted in newly diagnosed T2DM individuals every 3 months. Majority of the respondents preferred early initiation of SGLT2 therapy in individuals with high CV risk and BMI.

Around 32% of the clinicians reported that the FDC of DPP-4 inhibitor and SGLT2 inhibitor improve insulin sensitivity, while 29% of the clinicians reported it to preserve beta cell protection. Around 84% of the clinicians reported dapagliflozin and sitagliptin combination as the commonly used SGLT2i+ DPP4i combination in T2DM individuals with estimated glomerular filtration rate (eGFR) <45ml/min. According to 41% of the surveyed clinicians, the use of sitagliptin and dapagliflozin FDC therapy for T2DM management results in reduced gastric emptying. More than half (71%) of clinicians reported reduction in body weight as the major non-glycemic benefits noted in T2DM patients with concomitant hypertension and vascular diseases receiving sitagliptin and dapagliflozin (Table 1).

Table 1: Distribution of response to non-glycemic benefits of sitagliptin and dapagliflozin FDC therapy in T2DM with concomitant hypertension and vascular diseases

Benefits	Response rate (n = 413)
Reduces body weight	295 (71.43%)
Increases vasodilation	54 (13.08%)
Reduces BP	59 (14.29%)
All of the above	5 (1.21%)

A large majority (82%) of clinicians recommended that patients receiving sitagliptin and dapagliflozin FDC therapy would have a better cardiovascular and renal safety profile (Fig. 1). Among the surveyed clinicians, 41% indicated that diabetic patients initially diagnosed with an HbA1c level of 8% would benefit from sitagliptin and dapagliflozin FDC therapy (Table 2).

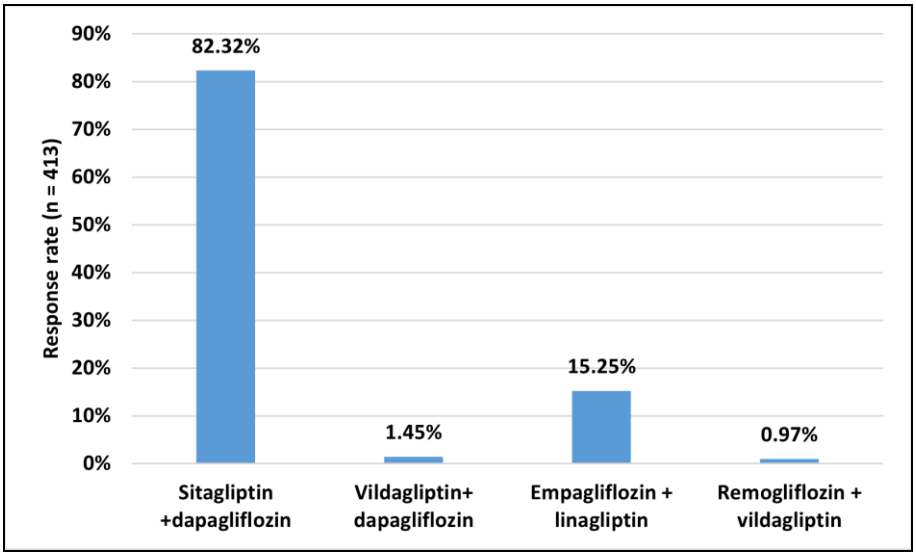

Fig 1: Distribution of response to SGLT2 inhibitor and DPP4i FDC therapy offering better cardiovascular safety & renal safety profile

Table 2: Distribution of response to category of diabetes individuals who benefit from sitagliptin and dapagliflozin FDC therapy

Patient category	Response rate (n = 413)
Patients with atherosclerotic cardiovascular disease	129 (31.23%)
Patients with CKD (up to stage 3)	115 (27.85%)
Patients with HbA1c 8% at diagnosis	169 (40.92%)

Sixty-five percent of respondents reported that sitagliptin and dapagliflozin FDC therapy reduces glycemic variability in individuals with T2DM. The majority of clinicians (74%) reported a lower risk of urinary tract infection (UTI) with sitagliptin and dapagliflozin FDC therapy. According to 63% of the clinicians, sitagliptin, dapagliflozin, and metformin FDC therapy decreases endogenous glucose production (Fig. 2). Majority (44%) of the clinicians reported 2-3 kg body weight reduction with sitagliptin, dapagliflozin and metformin FDC therapy in T2DM individuals (Table 3). Additionally, 47% indicated the attainment of rapid and sustained glycemic goals with sitagliptin, dapagliflozin, and metformin FDC therapy (Fig. 3).

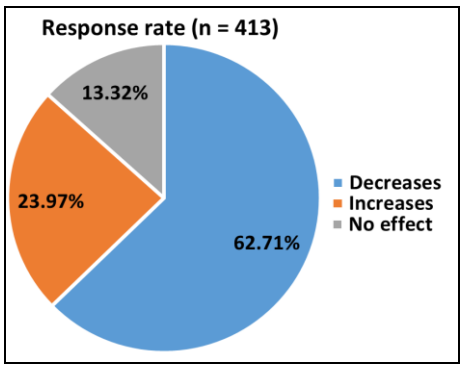

Fig 2: Distribution of response to role of sitagliptin, dapagliflozin and metformin FDC therapy in endogenous glucose production

Table 3: Distribution of response to body weight reduction with sitagliptin, dapagliflozin and metformin FDC therapy in patients with T2DM

Body weight	Response rate (n = 413)
1 kg to 2 kg	75 (18.16%)
2 kg to 3 kg	182 (44.07%)
3 kg to 4 kg	117 (28.33%)
4 kg to 5 kg	39 (9.44%)

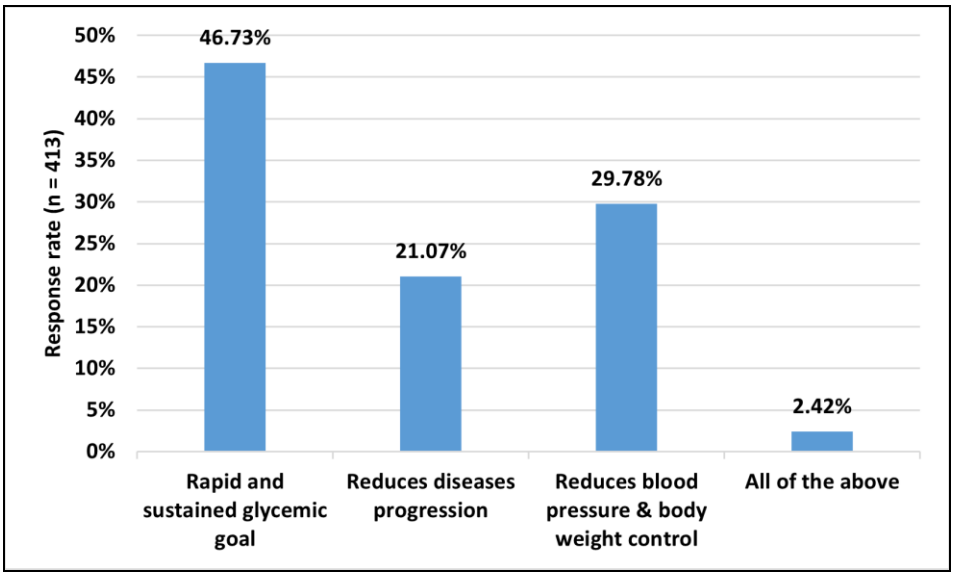

Fig 3: Distribution of response to benefits of sitagliptin, dapagliflozin and metformin FDC therapy

Discussion

This present survey indicates a preference for sitagliptin + dapagliflozin combination, in the management of T2DM. Additionally, the study underscores the efficacy and prescription trends of dapagliflozin + sitagliptin + metformin FDC therapy for T2DM.

Most of the current survey clinicians recommended the FDC therapy with sitagliptin and dapagliflozin for patients initially diagnosed with an HbA1c level of 8%. A real-world retrospective study revealed that the dapagliflozin and sitagliptin FDC significantly contributed to a decrease in HbA1c levels from 8.9 to 7.2 in individuals with T2DM in the Indian population, thereby affirming the safety and efficacy of this combination [11]. According to Bhattacharyya *et al*., a real-world study conducted in India, a once-daily FDC of dapagliflozin and sitagliptin significantly improves glycemic parameters, such as average daily glucose, time in target, and time above the target, in Indian patients with T2DM at the end of 15 days [10].

Majority of the current survey clinicians highlighted an increased risk for CVD in T2DM patients presenting to routine practice. T2DM is intricately linked to CVD, the foremost cause of morbidity and mortality in diabetic patients. Common CV risk factors, such as obesity, hypertension, and dyslipidemia, increase the risk of cardiac events. Independent biological mechanisms associated with DM further elevate the risk, with diabetic individuals facing two to four times higher chances of CVD compared to non-diabetic counterparts. Notably, CVDs are the primary cause of death in patients with T2DM, particularly in low- and middle-income countries [12, 13].

Patients with T2DM are twice as likely to develop CKD in comparison to those who do not have T2DM. The prevalence of CKD in diabetic patients varies between 27.1% and 83.6% depending on the presence of risk factors. If a patient with T2DM develops diabetic kidney disease, their risk of mortality increases threefold [14]. In line with these findings, the present survey has noted that hypoglycemia escalates the risk of diabetic CKD progression, and both the genders are equally susceptible to diabetic renal disease.

The clinicians reported that sitagliptin and dapagliflozin FDC therapy has a superior cardiovascular profile, offering benefits such as reduced body weight, lowered blood pressure, and increased vasodilation. Additionally, the majority of clinicians recommended the use of sitagliptin and dapagliflozin FDC therapy for an improved renal profile, citing benefits such as a lower risk of urinary tract infection (UTI) and an eGFR <45 ml / min. A cross-sectional questionnaire-based survey of 873 diabetologists conducted by Mehta *et al*. found that 66% of the clinicians preferred dapagliflozin + sitagliptin as a FDC for T2DM patients with cardiovascular or renal risk [15]. Ravikumar *et al*. suggested that dapagliflozin and sitagliptin are crucial components in managing cardiometabolic risks associated with T2DM. These medications have been proven to be safe and effective in achieving rapid and sustained glycemic control. Furthermore, they have also been shown to improve both insulin resistance and beta cell function [16]. Bhattacharjee *et al*. found that the combination of dapagliflozin and sitagliptin is effective and safe in reducing BMI among Indian patients with T2DM [11].

Most clinicians reported rapid and sustained glycemic goals and decreased endogenous glucose production with sitagliptin, dapagliflozin, and metformin FDC therapy. They further reported benefits such as a 2-3 kg body weight reduction. A phase 3 randomized, open-label, active-controlled study by Sahay *et al* compared the efficacy and safety of a triple drug FDC of dapagliflozin + sitagliptin + metformin extended release (ER) with sitagliptin + metformin sustained release (SR) and dapagliflozin + metformin ER in patients with poorly controlled T2DM receiving metformin. The study reported a significant reduction in HbA1c and fasting blood glucose from baseline with dapagliflozin + sitagliptin + metformin ER compared to sitagliptin + metformin SR and dapagliflozin + metformin ER. Furthermore, dapagliflozin + sitagliptin + metformin ER showed a significant reduction in postprandial blood glucose compared to dapagliflozin + metformin ER and a significant reduction in fasting blood glucose with dapagliflozin + sitagliptin + metformin ER compared to sitagliptin + metformin SR. The proportion of patients achieving HbA1c <7.0% (53 mmol/mol) at week 16 was significantly higher with dapagliflozin + sitagliptin + metformin ER (38.5%) versus sitagliptin + metformin SR (12.8%) and dapagliflozin + metformin ER (21.3%) [17].

In a survey study, 76% of clinicians strongly recommended the FDC for a triple combination of dapagliflozin + sitagliptin + metformin for T2DM patients with CV or renal risk. Jabbour *et al*. observed that a 24-week treatment with dapagliflozin 10 mg in combination with sitagliptin or sitagliptin plus metformin, once daily, was well-tolerated. This was followed by a 24-week extension period where a significant reduction in glycemic parameters and body weight was observed. These benefits were sustained through the entire 48 weeks of treatment [18].

The present study provides valuable insights into the clinicians' perspectives on the use of FDC for the management of T2DM in India. The major strength of the survey is collecting expert opinions through a meticulously created and validated questionnaire. The survey findings can be helpful in making informed decisions to achieve optimal treatment outcomes in T2DM patients. However, it is crucial to note that study has certain limitations. As the conclusions were based on expert opinions, there was a possibility of bias influencing the findings. Therefore, further research with larger sample sizes and randomized controlled procedures is necessary to validate the survey results.

Conclusion

The survey highlights clinicians' preference for FDC therapy involving sitagliptin and dapagliflozin in managing patients initially diagnosed with an HbA1c level of 8%. Reported benefits include a superior cardiovascular profile with reduced body weight, decreased blood pressure, and increased vasodilation. Additionally, favorable renal outcomes are noted, such as a diminished risk of urinary tract infection (UTI) and improved estimated glomerular filtration rate (eGFR) for patients with levels less than 45 ml/min. Clinicians also recommend sitagliptin, dapagliflozin, and metformin FDC therapy for achieving rapid and sustained glycemic goals, along with a reduction in body weight.

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Conflict of interest
The author declares no conflict of interest

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