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Original Research Article

Synergizing sodium-dependent glucose transporter inhibitors with dipeptidyl-peptidase 4 inhibitor and metformin: a novel approach to diabetes management in India

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ABSTRACT

Background: The rising prevalence of diabetes in India necessitates effective and targeted management strategies. This article explores the efficacy of synergistic action of key antidiabetic agents, including metformin, sodium-dependent glucose transporter-2 (SGLT-2) inhibitors, and dipeptidyl-peptidase-4 (DPP-4) inhibitors, in a fixed dose combination.
Methods: The current survey obtained the opinion of the health care professionals (HCPs) on the benefits and significance of the triple fixed dose combinations (FDCs) of dapagliflozin, sitagliptin, and metformin in type 2 diabetes mellitus (T2DM) management.
Results: The poll indicates that ~97% of the healthcare practitioners agreeing on the importance of achieving better time in range with the FDC and the potential benefits of early initiation of the FDC for improved glycemic control and cardio-renal outcomes. Majority of HCPs (77%) express confidence in the safety profile of the combination in T2DM. Almost all (99%) of the HCPs agree on the need for collating real-world data from HCPs to understand the effectiveness of FDC in India and for devising evidence based strategies.
Conclusions: The triple FDC of dapagliflozin, sitagliptin, and metformin stands out as a promising approach for diabetes management. The study also underscores the importance of conducting extensive, large scale real-world studies to gather more data, contributing to evidence based strategies for diabetes management in the Indian population.

Keywords: Diabetes management, FDC, HCPs, Safety profile, Glycemic control, Cardio-renal outcomes, Indian population

INTRODUCTION

Type 2 diabetes mellitus (T2DM) is a rapidly escalating health concern in India, with an anticipated 69.9 million cases expected by 2025.[1] Insights from the ICMR-INDIAB study conducted between 18th October 2008, and 17th December 2020, involving 113,043 participants (79,506 rural and 33,537 urban) reveal alarming statistics. The overall weighted prevalence of diabetes is 11.4%, prediabetes is 15.3%, hypertension is 35.5%, generalized

obesity is 28.6%, abdominal obesity is 39.5%, and dyslipidemia is 81.2%. Urban areas exhibit higher prevalence rates for all metabolic non-communicable diseases except prediabetes. Additionally, in states with lower human development indices, the diabetes-to-prediabetes ratio is less than one.[2]

The pathogenesis of T2DM among Indian population has been observed to be different compared to other ethnic races.[3] Indian individuals with T2DM exhibit higher insulin resistance, altered β-cell function, and distinct body mass index (BMI) profiles compared to Europeans. Notably, there is a tendency for early-onset T2DM and increased severity of insulin-deficit cases at diagnosis among South-Asians. These unique phenotypic characteristics may impact the efficacy of antidiabetic medications in this population, necessitating personalized and targeted management strategies. Genetic, environmental, and lifestyle factors contribute to the heterogeneity in T2DM presentation among Indians.[3]

Poor glycaemic control has been associated with increasing risk of complications including neuropathy and nephropathy.[4,5] Every 1% increase in glycated haemoglobin (HbA1c) levels above the threshold of 7% has been associated with a 38% increase in macrovascular complications such as cardiovascular disease.[6] The persistent, escalating burden of diabetes in India and the diminishing efficacy of individual drugs over time necessitates a multi-drug therapy approach for managing diabetes.[7]

Therefore, early combination therapy is adopted to ensure lasting legacy effect in treatment. This approach aims to improve the patient's glycemic profile without worsening the side-effect profile over the long term.[7] A compelling avenue in diabetes management lies in the exploration of fixed dose combinations (FDCs). In India, FDCs are popular due to the reduced pill burden, decrease in risk of side effects, cost-effectiveness, and improved patient compliance.[8] The FDC of dapagliflozin (dapa), sitagliptin (sita) and metformin (met) targets distinct facets of glucose regulation, synergistically providing a comprehensive strategy to tackle the complexities of diabetes.[8]

Due to limited evidence available on its efficacy and safety, there is a need to understand the clinical value of this FDC in the Indian context. Hence, the current survey was conducted among Indian health care professionals (HCPs) on the efficacy and clinical benefits of this FDC for managing diabetes in the Indian population.

METHODS

Study design and population

A prospective survey was conducted using four independent polls among practising physicians, endocrinologists and diabetologists in different practice settings across India (North, East, South and West). The HCPs were from primary, secondary and tertiary care settings. The four polls (Table 1) conducted were designed to obtain a quick response (<30 seconds) on their opinion towards the FDC of sodium-dependent glucose transporter inhibitors (SGLT2i) with dipeptidyl-peptidase 4 inhibitor (DPP-4i) and Metformin to facilitate responses relevant to real-world evidence based on their medical practice. By random sampling method, different HCPs were approached, and the four polls were conducted by representatives (Table 1). The responses included a designated Likert scale on a five-point scale. No personal information of the participating HCPs was collected.

Statistical methodology

The survey was conducted using a Google form, and the responses were collated in an Excel sheet. Responses to the questions ranged from strongly agree to strongly disagree. The responses were recorded, and the proportion of responses was calculated and expressed as N (%).

RESULTS

The survey yielded insightful perspectives on the triple FDC of dapa + sita + met in the management of T2DM in the Indian population. Notably, in poll 1 (N=98), a significant majority (63.3%) who strongly agree and 33.7% who agree, emphasize the importance of optimizing time in range (TIR) with this combination for improved glycemic control. Furthermore, poll 2 (N=106) highlighted the potential benefits of collating real-world data from HCPs regarding the geographical availability of the FDC, with 63.2% strongly agreeing and 35.8% agreeing on its utility in showcasing when and where to use dapa + sita + met. Moving to poll 3 (N=119), a robust consensus emerged, with 66.4% strongly agreeing and 30.3% agreeing that early initiation of the triple combination offers superior HbA1c control and cardio-renal benefits (Figure 1). Lastly, in poll 4 (N=107), respondents expressed confidence in the safety profile of dapa + sita + met, with 28% strongly agreeing and 55.1% agreeing that common side effects typically associated with SGLT2 inhibitors appear to be minimal with this combination based on their routine clinical practice (Figure 1).

Table 1: Poll questions.

Question no.	Poll questions
Q1	Do you think better time in range (TIR) will be a significant benefit for patients on triple FDC of dapa + sita + met?
Q2	The FDC of dapa + sita + met is available only in India. Is it a good idea to collate real- world data from all of us and show the rest of the country when and where to use it?

Continued.

Question no.	Poll questions
Q3	In your opinion, early initiation of FDC of dapa + sita + met provides better HbA1c control, cardio-renal benefits?
Q4	Is it observed that common side-effects which are otherwise seen with SGLT2 is are minimal with the combination of dapa + sita + met? What is your opinion based on your routine clinical practice

FDC – Fixed dose combinations; dapa – dapagliflozin, sita – sitagliptin, met – metformin; HbA1c – haemoglobin A1c; SGLT2i – sodium glucose co-transporter 2

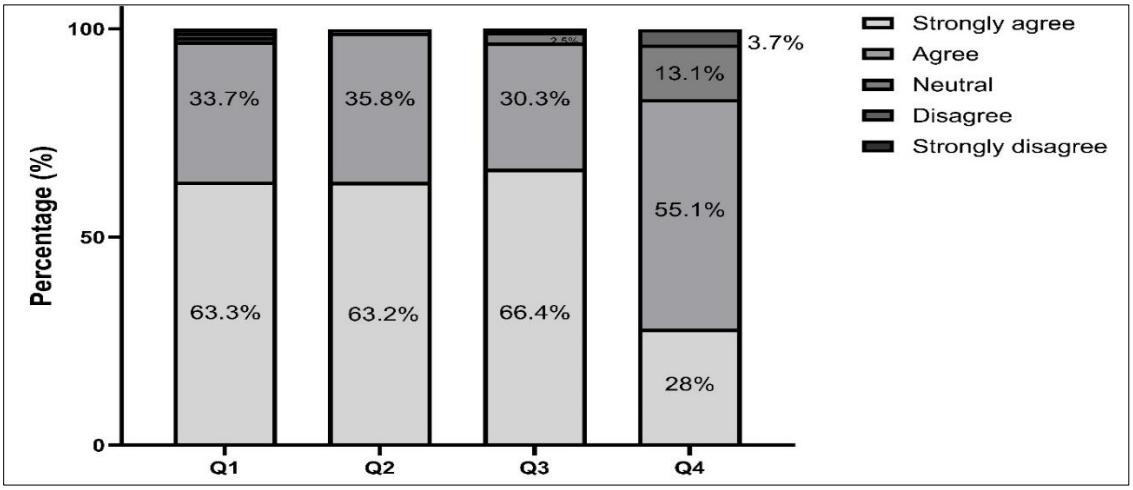

Figure 1: Responses to poll questions on triple FDC of dapa+sita+met by HCPs participating in the survey.
The length of the stacked bar represents the proportion of responses received. Q1 to Q4 represents the poll questions posed to the HCPs in this survey.

DISCUSSION

Combination of antiglycemic agents provide unique benefits by targeting multiple pathophysiologies of T2DM and improving patient compliance to medication. The study aimed to understand the perspectives of healthcare practitioners in India on the efficacy and clinical benefits of the FDC of dapa + sita + met for managing diabetes in the Indian population. The multifaceted concept of the "ominous octet" encapsulates eight interconnected physiological factors including insulin resistance, increased glucose production by the liver, impaired insulin secretion, inappropriate glucagon secretion, adipose tissue dysfunction, alterations in incretin hormones, neurotransmitter dysfunction, and increased kidney glucose reabsorption highlights the complexity of T2DM pathophysiology and serves as a foundation for developing comprehensive therapeutic strategies.[9] Chadha et al, discuss the unique cardio-metabolic risks in Asian Indian individuals with T2DM and propose a patient-centric approach for managing these risks. They advocate for combinations of antidiabetic agents, specifically focusing on the efficacy of DPP4i and SGLT2i.[10] The article outlines the diverse clinical benefits of this combination, including improved glycemia and adiposity, reduced metabolic and vascular risks, safety considerations, and enhanced compliance.[10] The authors emphasize the relevance of these findings to the Asian Indian T2DM population, providing a detailed review and practical guidance for the optimal clinical use of the SGLT2i + DPP4i combination in this context.[10]

In poll 1, almost by all HCPs (63.3% strongly agree, and 33.7% agree) consider achieving optimal TIR as a significant benefit offered by triple FDC. A study involving 6,225 adult participants from Shanghai, China categorized individuals based on TIR levels (>85%, 71–85%, 51–70%, <50%), analyzed their risks of all-cause and cardiovascular disease (CVD) mortality over a 6.9-year follow-up. The findings revealed significant associations between lower TIR and heightened risks of all-cause and CVD mortality. This supports TIR as a valid surrogate marker for predicting long term adverse clinical outcomes in patients with T2DM.[11]

The DIVERSITY-CVR study in Japanese patients with early-stage type 2 diabetes treated with dapagliflozin and sitagliptin indicated that sitagliptin was associated with improved TIR and achieving HbA1c <7.0% in patients with a lower BMI, whereas dapagliflozin showed superiority in achieving TIR >70% in the higher BMI group.[12] Thus, an FDC combination of SGLT2i, DPP4i and metformin may be useful in increasing TIR among individuals who lack optimal glycaemic control with a single or dual combination.

A study conducted for 48-weeks with dapagliflozin as an add-on therapy in inadequately controlled T2DM patients on sitagliptin with or without metformin demonstrated significant reductions in HbA1c levels, along with weight loss and sustained glycemic control. Adverse events were balanced between groups, although signs of genital infection were more frequent with dapagliflozin.[13]

A randomized, double-blind, placebo-controlled phase 3 trial observed that compared dapagliflozin to placebo in patients with poor glycemic control, showed a significant improvement in mean improvement in amplitude glycemic excursion (MAGE), reduced 24-hour mean blood glucose and lower mean plasma glucose concentrations.[14] Moreover, plasma 8-iso PGF2α, a marker of oxidative stress, notably decreased in the dapagliflozin group, suggesting a potential cardiovascular benefit. This study provides valuable insights into the favorable effects of dapagliflozin on glycemic variability and oxidative stress reduction in patients with newly diagnosed T2DM.[14] A prospective open-label pilot study reported that Sitagliptin, whether administered alone or in combination, led to a decrease in average 24-hour blood glucose levels, 24-hour glycemic fluctuation range, MAGE and hyperglycaemic time.[15]

Poll 2 delves into the geographical availability of the FDC. 63.2% strongly agree and 35.8% agree that aggregating real-world data from HCPs can be beneficial in illustrating the appropriate utilization of the dapa + sita + met combination. While FDC combinations might not be available in other parts of the world, it does not diminish their rationality. The use of FDC medications has gained popularity in India due to several factors, including enhanced patient compliance and the unique challenges posed by the socioeconomic status of the population. The distinct healthcare landscape in India, characterized by diverse patient needs and resource constraints, has fostered the adoption of FDCs as a practical and effective approach to treatment.[13] Hence, collating data from real-world studies in India may assist in guiding and optimizing its usage.

Poll 3 delves into opinions about early initiation of FDC and its potential benefits. The results show a robust agreement, with 66.4% strongly agreeing and 30.3% agreeing that early initiation of the triple combination provides better HbA1c control and cardio-renal benefits. A study compared the efficacy and safety of a triple FDC of dapa + sita + met with two dual combinations in patients with poorly controlled type 2 diabetes on metformin monotherapy. Results indicate that the triple FDC demonstrated superior glycemic control, with significantly greater reductions in HbA1c compared to dual combinations. It also showed advantages in postprandial and fasting blood glucose levels, and a higher proportion of patients achieved target HbA1c levels. The triple FDC was well-tolerated, suggesting its potential as an effective and safe therapeutic option for this patient population.[16,17] The VERIFY study (clinicaltrials.gov: NCT01528254) spanning 5 years revealed that early combination therapy, particularly with vildagliptin–metformin, in type 2 diabetes significantly delayed time to loss of glycemic control, doubled the duration of extended glycemic control, and postponed secondary treatment failure compared to metformin alone. These findings suggest that early combination therapy offers a promising shift in disease management for improved glycemic outcomes.[18]

Poll 4 focuses on the observation of side effects. Respondents express confidence in the combination's safety profile, with 28% strongly agreeing and 55.1% agreeing that common side effects typically associated with SGLT2 inhibitors appear to be minimal with the combination of dapa+sita+met, based on their routine clinical practice. Studies undertaken with the triple dose combination of dapa+sita+met observed better or similar side-effect profiles with their respective comparator groups, with one study observing no side effects.[19-21]

Limitations

The current study was conducted as a qualitative survey among the physicians and therefore lacks quants. This lends scope for future large scale clinical studies on the topic.

CONCLUSION

The participating HCPs agree that the FDC's benefit of achieving optimal TIR is of great significance in T2DM management, and that early initiation may be useful in curbing hyperglycaemia and risk of complications. From their clinical practice, they also observe that the common side effects associated with dapagliflozin appear to be minimal with FDC use. The respondents highlight the need for aggregating real-world data from HCPs on the FDC and that it can be beneficial in determining the appropriate utilization of the FDC combination in the Indian T2DM setting. The survey calls for real-world studies on the safety and efficacy of FDC of dapa+sita+met in diabetes management among the Indian population.

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