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Expert perspectives on the use of a triple combination of voglibose, glimepiride and metformin for the management of diabetes in Indian settings

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Abstract
Objective: The current survey-based study aims to gather expert opinion regarding the use of a triple combination of voglibose, glimepiride, and metformin for the management of type 2 diabetes mellitus (T2DM) in Indian settings.
Methodology: The cross-sectional survey utilized a 24-item, multiple-response questionnaire to gather expert opinions from specialists with expertise in managing diabetes. The survey encompassed questions about current prescription practices, clinical observations, preferences, and experiences related to using voglibose + glimepiride + metformin in routine settings for diabetes management.
Results: Majority of clinicians (92.49%) indicated that the combination therapy of voglibose, glimepiride, and metformin effectively addressed all aspects of the glycemic hexad, including fasting blood glucose (FBG), postprandial blood glucose (PPBG), glycated hemoglobin (HbA1c) levels, nocturnal hypoglycemia, glycemic variability, and hypoglycemia. About 76% of clinicians preferred the voglibose triple-drug fixed-dose combination (FDC) over bolus insulin for managing post-meal hyperglycemia. According to 57% of clinicians, approximately 11 to 20% of diabetic patients were prescribed voglibose + glimepiride + metformin triple-drug FDC therapy for postprandial glucose and HbA1c (PGA1c) management. With voglibose + glimepiride + metformin FDC therapy, nearly 45% of clinicians reported observing a weight reduction of around 2 to 3 kg in patients. Approximately 61% of clinicians recommended voglibose + glimepiride + metformin triple-drug FDC therapy for diabetic patients with high PGA1c levels.
Conclusion: The survey findings underscored the effectiveness of voglibose, glimepiride, and metformin combination therapy in managing all aspects of the glycemic hexad. The experts favored the voglibose triple-drug FDC over bolus insulin for managing post-meal hyperglycemia. They also recommended voglibose + glimepiride + metformin triple-drug FDC therapy for diabetic patients with high PGA1c levels, indicating its potential as a preferred treatment option.

Keywords: Diabetes, Type 2 diabetes mellitus, Voglibose, Metformin, Glimepiride, Glycemic level

Introduction
Diabetes has emerged as a global health crisis, with a staggering 537 million adults aged 20 to 79 years living with the condition, reaching epidemic proportions by affecting approximately one in every ten individuals [1]. The number of individuals suffering from diabetes is projected to rise to 643 million by 2030 and further increase to 783 million by 2045. In 2021 alone, 6.7 million deaths were attributed to diabetes, indicating that one person died every five seconds due to this pervasive ailment [2].
Type 2 diabetes mellitus (T2DM) affects an estimated 462 million people globally, with low and middle-income countries experiencing the most alarming growth rates. India, in particular, stands out as a hotspot for diabetes, ranking second globally in terms of the diabetic population [2]. Despite efforts to combat this issue, a significant number of people with T2DM in India are unable to achieve recommended glycemic control targets. More than half of patients cannot reach the target glycated hemoglobin (HbA1c) level of ≤7%, highlighting the need for better diabetes management strategies. It is essential to maintain HbA1c levels <7% for successful diabetes management, which serves as a cornerstone of treatment recommendations. Pre-diabetes, an early stage of diabetes characterized by HbA1c levels ranging from 5.7% to 6.4%, serves as a critical indicator for early intervention and prevention efforts [3].

Postprandial glucose + HbA1c (PGA1c) emphasizes the significance of managing both postprandial blood glucose (PPBG) levels and HbA1c in treating individuals with T2DM. Controlling PPBG alongside HbA1c is crucial for achieving optimal disease management [4]. Fixed-dose combinations (FDC) simplify treatment, addressing multiple pathophysiological defects, overcoming clinical inertia, achieving glycemic targets promptly, and delaying complications, thereby reducing concerns about regimen complexity and patient burden [4, 5].

Many existing medications for managing T2DM carry the risk of adverse effects such as hypoglycemia and weight gain. This underscores the need for new treatments that offer better benefits with fewer drawbacks. In this context, the triple-drug combination of metformin + glimepiride + voglibose emerges as a promising solution, effectively controlling both fasting blood glucose (FBG) and PPBG levels, thereby influencing HbA1c values in Indian patients with T2DM. This approach aligns with guidelines advocating for triple oral antidiabetic drug combinations before insulin initiation, emphasizing its significance in T2DM management [4]. Metformin improves insulin sensitivity and reduces hepatic glucose production, glimepiride enhances insulin secretion, and voglibose slows down carbohydrate digestion, improving glycemic control [6, 4]. For patients with T2DM who consume a high carbohydrate diet, a combination of metformin, glimepiride, and voglibose has been suggested as an effective treatment option. This combination can help inhibit the absorption of starch by impeding the final step of carbohydrate digestion at the brush border of the intestinal epithelium [7]. The present survey is intended to gather clinicians' perspectives regarding the prescription practice of a triple combination of metformin + glimepiride + voglibose in T2DM treatment in Indian settings.

Methodology

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

Questionnaire

The questionnaire booklet titled STEP (Prospective Study of Triple Drug Combination of Voglibose + Glimepiride+ Metformin FDC therapy for its Effectiveness in Real World Population) study was sent to the doctors who were interested to participate. The STEP study comprised 24 questions about current feedback, clinical observations, and clinical experience of specialists in managing T2DM using a triple combination of voglibose, glimepiride, and metformin in routine settings. 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 426 clinicians from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. They were instructed to complete the survey alone and not consult their colleagues. Written informed consent was obtained from all the participants prior to the study.

Statistical analysis

The data were analyzed using descriptive statistics. Categorical variables were presented as percentages to provide a clear insight into their distribution. The frequency of occurrence and the corresponding percentage were used to represent the distribution of each variable. To visualize the distribution of the categorical variables, graphs, and pie charts were created using Microsoft Excel 2013 (version 16.0.13901.20400).

Results

Among the 426 clinicians surveyed, 51% responded that overweight T2DM individuals with CV risk factors constitute the subgroup most often experiencing uncontrolled glycemic levels and diabetic complications. According to 48% of the clinicians, about 20 to 30% of diabetic individuals are aware of a high carbohydrate diet. Approximately 43% of the clinicians stated that the incidence of glycemic variability and nocturnal hypoglycemia among individuals with high PGA1c (both PPBG and HbA1c) levels ranges from 11% to 20%. As reported by 62% of the clinicians, the preferred combination in managing high PGA1c (both PPBG and HbA1c) levels is alpha-glucosidase enzyme inhibitors with sulfonylureas (SU) + metformin (FDC therapy). More than half (60.33%) of the clinicians indicated that PGA1c plays a role in increasing the risk of cardiovascular disease and all-cause mortality.

According to 68% of the clinicians, increased lipid levels are associated with PGA1c levels. Approximately 64% of the clinicians reported that voglibose therapy offers benefits such as less glycemic variability, effective reduction in post-prandial glucose levels, lower risk of hypoglycemic episodes, and compatibility with other OADs for managing PGA1c control. Around 69% of the clinicians recommend voglibose + SU + metformin FDC therapy for elderly patients with high PGA1c levels.

As reported by 48% and 45% of the clinicians respectively, the importance of postprandial self-monitoring of blood glucose in metabolic health includes improving glycemic and lipid control levels, as well as reducing cardiovascular risks and glycemic variability risk in patients. Majority (92.49%) of the clinicians reported that voglibose, glimepiride, and metformin FDC are effective in controlling all the parameters of glycemic hexad namely FBG, PBG, HbA1c, nocturnal hypoglycemia, glycemic variability and hypoglycemia (Fig. 1).

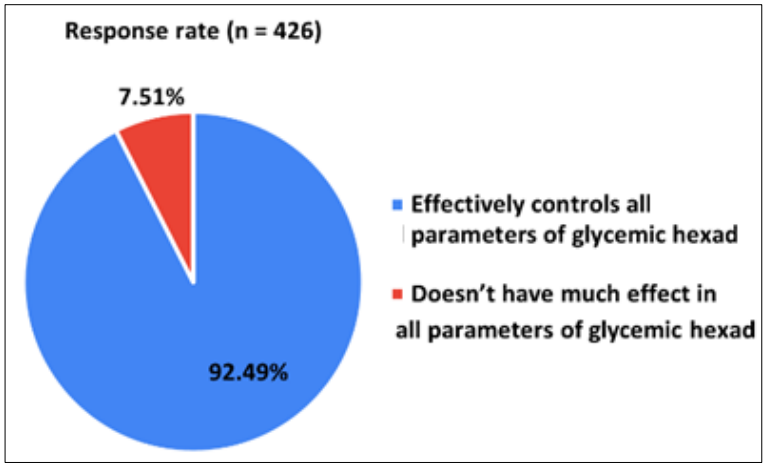

Fig 1: Distribution of response on the effectiveness of voglibose, glimepiride, and metformin FDC in addressing parameters of glycemic hexad

Around 39% of the clinicians responded that they recommend about 20 minutes of walking time for patients to reduce PPBG levels after each meal. About 57% of the clinicians reported that physical group meetings are the preferred patient education method for reducing high carbohydrate intake to manage PGA1c. Both continuous glucose monitoring systems and self-monitoring of blood glucose levels are the preferred methodologies to measure glycemic variability in individuals with T2DM, according to 71% of the clinicians. Approximately 71% of the clinicians responded that the major reasons for post-meal hyperglycemia include decreased insulin secretion, decreased insulin sensitivity, and the inability to adequately suppress hepatic glucose production.

Around 53% of the clinicians agreed that voglibose helps in reducing visceral adipose tissue area (VAT) and subcutaneous adipose tissue ratio (SAT). About 44% of the clinicians responded that 10 to 15% of uncontrolled PGA1c individuals adhere to the recommended therapy. Around 76% of the clinicians reported that the voglibose triple-drug FDC is preferred over bolus insulin in controlling post-meal hyperglycemia (Table 1). Approximately 39% of the clinicians reported that 10 to 15% of individuals with T2DM are unable to follow a consistent carbohydrate diet in day-to-day life. As reported by 57% of the clinicians, around 11 to 20% of diabetic individuals are on voglibose + glimepiride + metformin triple-drug FDC therapy for PGA1c management (Fig. 2).

Table 1: Distribution of response on the comparison of voglibose triple drug FDC vs. bolus insulin for post-meal hyperglycemia control

Opinion	Response rate (n = 426)
Voglibose triple drug FDC can be preferred	76.29%
Voglibose triple drug FDC is mildly effective	20.66%
Voglibose triple drug FDC is not effective	3.05%

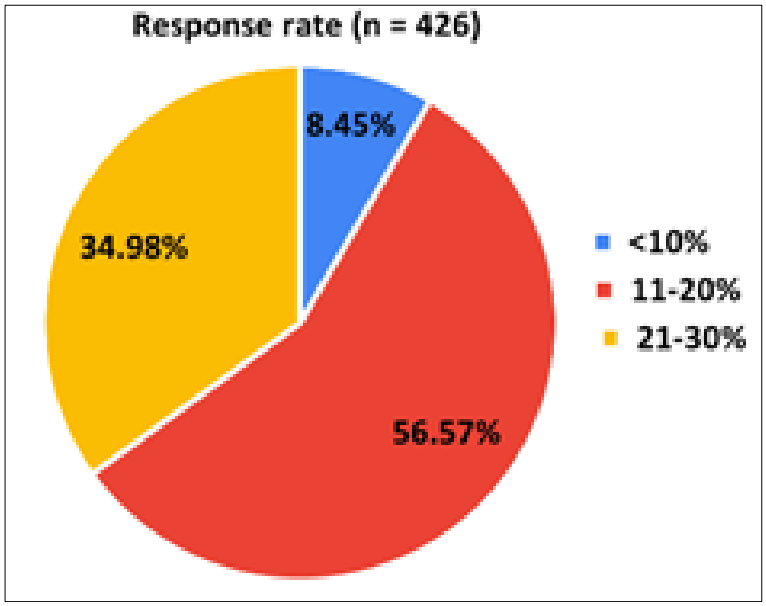

Fig 2: Distribution of response on the percentage of diabetic individuals on voglibose + glimepiride + metformin triple drug FDC therapy in PGA1c management

Around 77% of the clinicians reported that the most important factors influencing the decision to achieve PGA1c goals are age, duration of diabetes, treatment cost, comorbidities, and therapy non-compliance. About 46% of

the clinicians reported that achieving early PGA1c goals yields better clinical outcomes with end-organ protection. Almost 45% of the clinicians reported observing a weight reduction of about 2 to 3 kg with voglibose + glimepiride + metformin FDC therapy (Fig. 3). Around 61% of the clinicians reported recommending voglibose + glimepiride + metformin triple-drug FDC therapy in diabetic individuals with high PGA1c (Table 2).

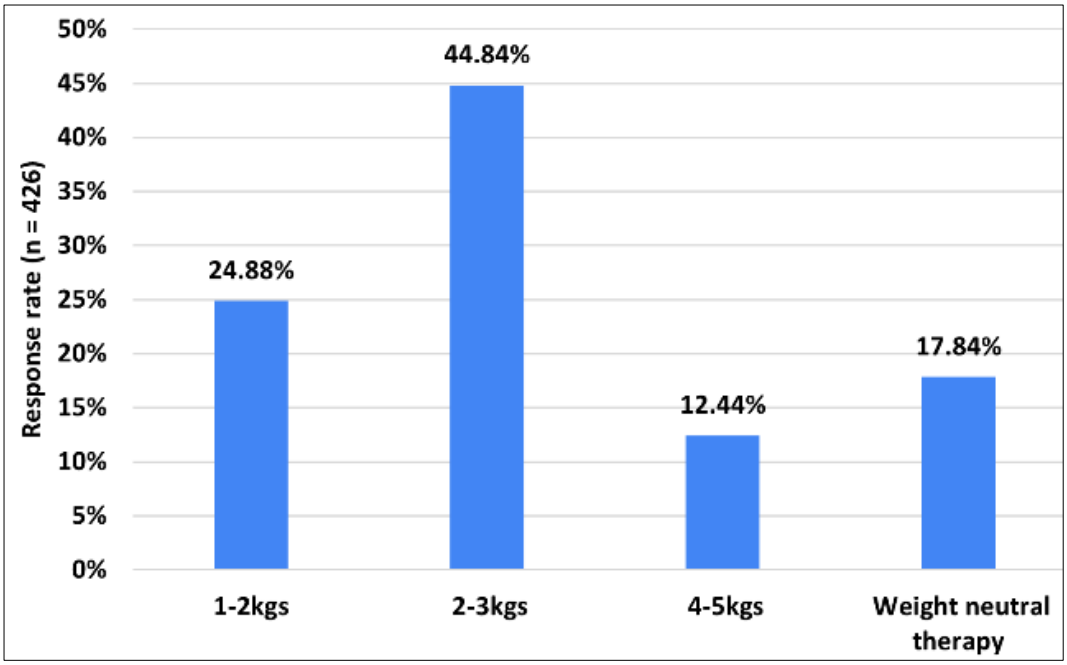

Fig 3: Distribution of response on the weight reduction observed with voglibose + glimepiride + metformin FDC therapy

Table 2: Distribution of response to the recommendation for voglibose + glimepiride + metformin triple drug FDC therapy in diabetic patient subsets

Subset of diabetic patients	Response rate (n = 426)
High HbA1c (PGA1c)	259 (60.8%)
High cardiovascular (CV) Risk	79 (18.54%)
High body mass index (BMI)	48 (11.27%)
Unwillingness to Use Insulin	40 (9.39%)

Discussion

According to the current survey results, voglibose + glimepiride + metformin FDC therapy is highly preferred for managing T2DM in various settings. It effectively controls both FBG and PPBG, as well as helps in managing HbA1c levels. Based on the survey findings, the triple FDC of voglibose + glimepiride + metformin plays a crucial role in effectively managing all parameters of the glycemic hexad. Studies have reported that the glycemic pentad, comprising FBG, PPBG, HbA1c, avoidance of hypoglycemia, avoidance of nocturnal hypoglycemia, and minimization of glycemic variability, is closely linked to cardiovascular outcomes. Therefore, it is imperative to give equal attention to all these parameters when devising strategies and selecting medications for T2DM management [8]. Kalra *et al*. reported that the triple fixed-dose combination of metformin, glimepiride, and voglibose emerges as an essential commodity in achieving the targets of the glycemic parameters, effectively controlling all parameters of glycemic control, and holding a prominent position in T2DM management [9].

The current survey respondents expressed a preference for the voglibose triple drug FDC over bolus insulin for managing post-meal hyperglycemia due to its noted advantages in compliance and glycemic control. John *et al*. emphasized the efficacy of voglibose, an α-glucosidase inhibitor, in regulating postprandial blood glucose (PPBG) levels by modulating glucose absorption [7]. TJ *et al*. found that the voglibose triple drug FDC is a safe and effective anti-hyperglycemic agent that not only effectively controls blood glucose levels but also promotes weight loss. Furthermore, comparative analysis indicates its superiority to metformin concerning various key glycemic parameters, without increasing the risk of hypoglycemia [10]. In another study, patients with T2DM whose blood sugar levels were not controlled with two oral hypoglycemic agents (metformin and glimepiride) were given a third drug called voglibose in the form of FDC. The study observed the effect of voglibose as a third agent on various parameters. It was observed that there was no significant change in the body weight of patients at the end of the study [11].

Many T2DM patients in India are prescribed FDC voglibose, glimepiride, and metformin as part of their PGA1c management. Bantwal *et al*. found that this triple FDC therapy effectively reduces HbA1c levels and helps patients achieve their target glycemic control. Additionally, the treatment was well-tolerated and resulted in weight loss. The study showed a compliance rate of 92%, indicating good adherence among patients. Therefore, the triple FDC of glimepiride, metformin, and voglibose is a promising treatment option for the clinical management of T2DM among the Indian population [12]. According to Shamanna *et al*. the triple drug FDC consisting of 1 mg glimepiride, 500 mg metformin, and 0.2 mg voglibose, taken once daily for one to three months, is the most commonly used treatment for both newly diagnosed and long-standing diabetes patients in routine clinical practice in India [13].

The triple-drug combination of voglibose, glimepiride, and metformin can potentially improve glycemic control and can delay or postpone microvascular and CV complications in T2DM patients [4]. Rao and Faruqui showed that the triple-drug FDC of voglibose, glimepiride, and metformin significantly decreased the HbA1c value, fasting plasma glucose level and PPBG level at the end of the treatment [14]. Arif A. Faruqui found that after three months of treatment

with the triple FDC of voglibose, glimepiride, and metformin, the HbA1c levels decreased significantly from 10.6 to 6.6%, FPG levels decreased significantly from 208.33 mg/dL to 118.06 mg/dL, and postprandial hyperglycemia (PPHG) levels decreased significantly from 360.14 mg/dL to 168.36 mg/dL [11].

Numerous studies have shown that the combination of glimepiride, metformin, and voglibose as a triple FDC can offer a significant advantage in reducing the risk of weight gain. This is attributed to the efficacy of voglibose in reducing body weight, while also effectively controlling PPBG levels [11, 12, 4]. In the present study, clinicians also reported observing a 2 to 3 kg reduction in weight with voglibose + glimepiride + metformin FDC therapy.

The current clinicians recommended the use of voglibose + glimepiride + metformin triple drug FDC therapy in diabetic individuals with high PGA1c. In line with these findings, a consensus study by Das *et al*. reported that the triple combination FDC is effective in reducing the PGA1c level in T2DM patients [4]. Similarly, Faruqui AA also observed that the PPHG level was reduced throughout the study period of 3 months of use of a triple-drug combination in patients with T2DM [11].

The survey findings underscored the significance of triple combination FDC therapy for glycemic control and shed light on notable trends in prescription practices for diabetes management. A significant strength of the survey lies in its utilization of a well-designed and validated questionnaire for data collection from clinicians. However, it is essential to acknowledge certain limitations inherent to the survey methodology. Relying solely on expert opinions introduces the potential for bias, given the diverse perspectives and preferences among clinicians, which may have influenced the reported results. Hence, it is crucial to consider these limitations when interpreting the findings. Furthermore, the survey may not capture emerging trends or new evidence in diabetes management. Therefore, prospective trials or real-world observational studies are needed to validate the survey results and offer a more comprehensive understanding of optimal treatment approaches.

Conclusion

The survey highlighted clinicians' preference for voglibose + glimepiride + metformin as a triple-drug FDC therapy, citing its effectiveness in addressing all aspects of the glycemic hexad. The experts also noted the superior efficacy of voglibose + glimepiride + metformin compared to bolus insulin in controlling post-meal hyperglycemia, and its preference as FDC therapy for individuals with high PGA1c levels.

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Author's Contribution

Not available

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