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Expert opinion on fixed-dose combinations of Sitagliptin + metformin and the triple drug combination of Voglibose + Glimepiride + 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 + metformin and the triple drug combination of voglibose + glimepiride + metformin for managing type 2 diabetes mellitus (T2DM) in Indian settings.
Methodology: The cross-sectional multiple-response questionnaire-based survey was conducted among experts from various states across India. The questionnaire, comprising 25 questions, addressed feedback, clinical observations, and experience in managing T2DM using FDCs. Descriptive statistics was used for data analysis, presenting categorical variables as percentages. Graphs were created using Microsoft Excel 2013.
Results: The survey included 879 clinicians from diverse clinical settings in India. Approximately 38% reported a monthly incidence of new-onset diabetes as 25-30, with 55-60% of patients failing to achieve the HbA1c goal of ≤7%. Sedentary lifestyles, poor dietary habits, and family history were cited as major contributors to early-onset diabetes (84%). Regarding sitagliptin + metformin therapy, 28% of clinicians reported >40% of patients achieving the target HbA1c goal (≤7%) over 4 years. Approximately 61% of clinicians regarded this combination as ideal for newly diagnosed T2DM patients with HbA1c >7.5%. Nearly 56% of the respondents observed a reduction of 1-1.5% in HbA1c with this combination therapy, highlighting the advantages such as HbA1c control, absence of hypoglycemia and weight gain, and cardio protective effects. In real-world clinical settings, the FDC of voglibose, glimepiride, and metformin demonstrated a 1.5%-1.8% reduction in HbA1c, as reported by 45% of clinicians. Adherence rates of 60%-70% were observed for this FDC, and it was recommended for the duration of one year (39%) and 6-8 months (33%).
Conclusion: Sitagliptin-metformin combination was preferred due to multitude of benefits including superior HbA1c control, absence of hypoglycemia and weight gain, along with enhanced cardiac safety. The triple-drug combination of voglibose, glimepiride, and metformin was also highly effective in reducing HbA1c levels, demonstrating greater adherence and robust efficacy.

Keywords: Sitagliptin, metformin, voglibose, type 2 diabetes mellitus, glycated hemoglobin

Introduction
Diabetes ranks among the top 10 global causes of mortality, contributing to cardiovascular disease, respiratory problems, and cancer [1-3]. By 2035, the projected global count of diabetes-related deaths was expected to reach 592 million. Additionally, the global prevalence of Type 2 diabetes mellitus (T_2DM) was estimated to increase to 7079 cases per 100,000 individuals by 2030 in all geographic areas [4, 5]. India ranks second highest in the global diabetes epidemic. Within the age group of 20-79 years, India recorded 74.9 million individuals with diabetes in 2021, a figure projected to rise to 124.9 million by 2045 [6, 7].
In India, more than half of the patients with T_2DM fail to achieve the recommended glycated hemoglobin (HbA1c) level of 7% [8, 9]. In such patients, the use of fixed drug combinations (FDCs) offers several advantages, including improved adherence to treatment regimens, simplified dosing schedules, and potentially enhanced efficacy [10]. Numerous studies have validated the effectiveness of the combination therapy of sitagliptin with metformin in the treatment of diabetes.

Sitagliptin is a potent, highly selective oral DPP-4 inhibitor with an oral bioavailability of 87% and a terminal half-life of 10 to 12 hours. It acts through the incretion pathway and has a glucose-dependent mode of action. The complementary hypoglycemic properties of sitagliptin and metformin make the FDC treatment an attractive prospect [11, 12].

Sitagliptin and metformin combination is a preferred, cost-effective first-line treatment for T_2DM in India, offering better glycemic control, weight reduction, and fewer adverse effects over 30 weeks, especially for patients with HbA1c levels above 7.5% at diagnosis [13-15].

Triple-drug combination is a promising option in the management of T_2DM, which controls both fasting and post-prandial blood glucose and ultimately HbA1c values [16-18]. The triple-drug combination of voglibose + glimepiride + metformin can potentially improve glycemic control and delay or prevent microvascular and cardiovascular complications. Voglibose, an α-glycosidase inhibitor, was commonly prescribed for type 2 diabetes, reducing HbA1c levels by 0.5% to 1.4%. Combining metformin with voglibose further lowers HbA1c and fasting plasma glucose. Glimepiride, a second-generation sulfonylurea, improves glycemic control in adults with type 2 diabetes, particularly in those with residual pancreatic beta-cell activity [16-20].

The present survey is intended to gather clinicians' perspectives regarding the prescription practice of the FDCs of sitagliptin + metformin and the triple drug combination of voglibose + glimepiride + metformin for T_2 DM treatment in Indian settings.

Methods

A cross sectional, multiple-response questionnaire based survey among physicians specialized in managing T_2DM in the major Indian cities from June 2022 to December 2022.

Questionnaire

The questionnaire booklet titled VICTORY-3 (A Report on Views in Current Treatment Options & Recent trends in Diabetolog Y-3) study was sent to the doctors who were interested to participate. The VICTORY-3 study questionnaire included 25 questions about the current opinion, clinical observations, and clinical experience of specialists in managing T2DM using the 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 2022 for participation in this Indian survey. About 879 clinicians from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. They were explicitly instructed to provide individual responses without consulting their colleagues. Before commencing the study, written informed consent was obtained from all survey participants.

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 were created using Microsoft Excel 2013 (Version 16.0.13901.20400).

Results

The present survey study involved 879 clinicians from various clinical settings across India. According to 38% of the responders, the monthly average incidence of new-onset diabetes was 25-30 and half of them reported that 55-60% of patients failed to achieve the HbA1c goal of ≤7%. Majority (84%) of the respondents cited sedentary lifestyle, high consumption of junk foods, and family history as reasons for the onset of diabetes at a young age. Approximately 42% of the clinicians noted that obese individuals with T_2DM had high, uncontrolled postprandial blood glucose (PPBG). Around 32% indicated that the risk of 'glycemic variability' in uncontrolled PPBG individuals was 60-70%. Majority (91%) of the respondents observed that uncontrolled PPBG was correlated with high HbA1c levels in T_2DM individuals.

The majority of respondents (52%) advocated for combining gliptins with metformin to address glycemic variability, while other combinations such as voglibose + glimepiride + metformin, sulfonylureas + metformin, and Insulin + metformin were recommended by 37%, 6%, and 5% of clinicians, respectively. Notably, 55% of clinicians favored the Gliptins + metformin combination specifically for controlling high postprandial blood glucose levels.

Regarding safety considerations, a significant 90% of clinicians reported sitagliptin as safe for individuals dealing with type 2 diabetes mellitus (T_2DM) and concurrent conditions like non-alcoholic fatty liver disease (NAFLD). Moreover, more than half of the clinicians affirmed that sitagliptin monotherapy does not lead to an increase in uric acid levels in individuals with T_2DM. Impressively, the outcomes of the Trial Evaluating Cardiovascular Outcomes with Sitagliptin (TECOS) trial influenced clinical practice, with 88% of respondents indicating that these results, affirming the cardiovascular safety of sitagliptin, contributed to an increased utilization of the drug.

Around 60% of clinicians highlighted sitagliptin's notably high DPP4 inhibition selectivity compared to other inhibitors, while 33% and 5% reported moderate and low selectivity, respectively. Additionally, 84% of respondents indicated that sitagliptin provides extended DPP4 inhibition for 24 hours, surpassing gliptin. However, a minority (7%, 6%, and 2%) identified vildagliptin, linagliptin, and teneligliptin as competitors in this aspect. In terms of advantages, a consensus among almost all clinicians emerged: sitagliptin outperforms other oral antidiabetic agents in several key areas. These include better HbA1c reduction, safety in patients with cardiovascular risk factors and NAFLD, easy dosage regimen, and proven clinical efficacy.

Regarding treatment outcomes, 28% of clinicians noted that over a 4-year period, more than 40% of patients achieved the target HbA1c goal (≤7%) with sitagliptin and metformin therapy. Varied percentages were reported, with 27%, 26%, and 18% indicating success rates surpassing 70%, 60%, and 40%, respectively. Findings from the Cosmic Landmark study underscore the efficacy of combining sitagliptin and

metformin, showcasing a substantial 1.5% reduction in HbA1c levels. Notably, approximately 89% of clinicians confirmed observing this reduction in their routine practice. However, 10% disagreed with this observation, while 1% refrained from providing an answer. For 61% of clinicians, sitagliptin and metformin combination therapy was considered as the most suitable option for newly diagnosed individuals with T_2DM where HbA1c was >7.5% (Table 1).

Table 1: Distribution of response to a group of T_2DM individuals most suitable for sitagliptin and metformin combination therapy

Group	Response rate (n = 879)
Newly diagnosed T_2DM, with HbA1c >7.5%	537 (61.09%)
Uncontrolled T2DM individuals on sulfonylureas + metformin combination	145 (16.5%)
Elderly T_2DM individuals	58 (6.6%)
Long-standing diabetic individuals	109 (12.4%)
All the above	23 (2.62%)
Not attempted	7 (0.8%)

Most clinicians (56.09%) observed a 1-1.50% reduction in HbA1c with sitagliptin and metformin combination therapy (Figure 1). Nearly all clinicians reported HbA1c control, no risk of hypoglycemia and weight gain, and safety in cardiac patients as the advantages of sitagliptin + metformin therapy over glimepiride + metformin combination (Figure 2). Majority of clinicians (45%) reported a 1.5%-1.8% reduction in HbA1c with the FDC of voglibose, glimepiride, and metformin therapy in the real-world clinical settings (Table 2).

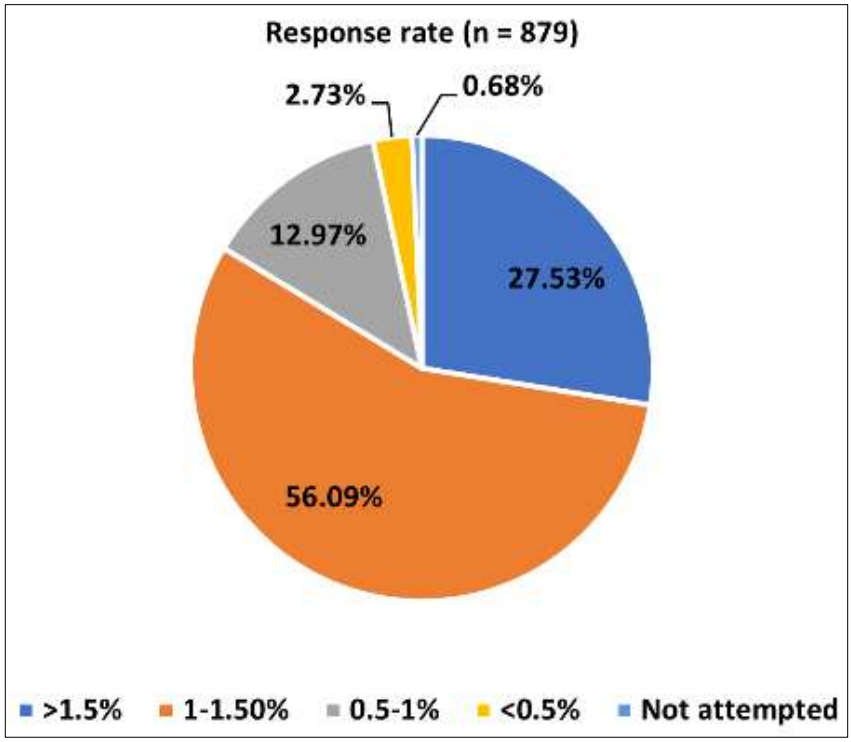

Fig 1: Distribution of response to proportion of HbA1c reduction observed with sitagliptin and metformin combination therapy

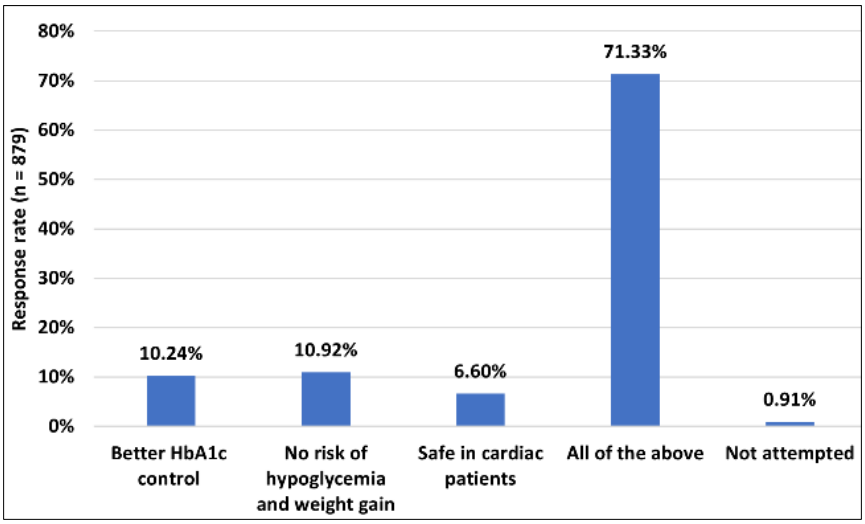

Fig 2: Distribution of response to advantages of sitagliptin + metformin over glimepiride + metformin combination

Table 2: Distribution of response to proportion of maximum HbA1c reduction observed with FDC of voglibose, glimepiride & metformin therapy in real-world clinical settings

Proportion of HbA1c reduction	Response rate (n = 879)
1.50% - 1.80%	397 (45.16%)
1.20% - 1.55%	246 (27.99%)
1% - 1.20%	170 (19.34%)
0.50% - 0.80%	61 (6.94%)
Not attempted	5 (0.57%)

According to 45% of clinicians, 60%-70% of patients adhere to the FDC of voglibose, glimepiride, and metformin triple drug combination (Fig. 3). The FDC of voglibose, glimepiride, and metformin was recommended by 39% and 33% of clinicians for one year and 6–8 months, respectively (Table 3).

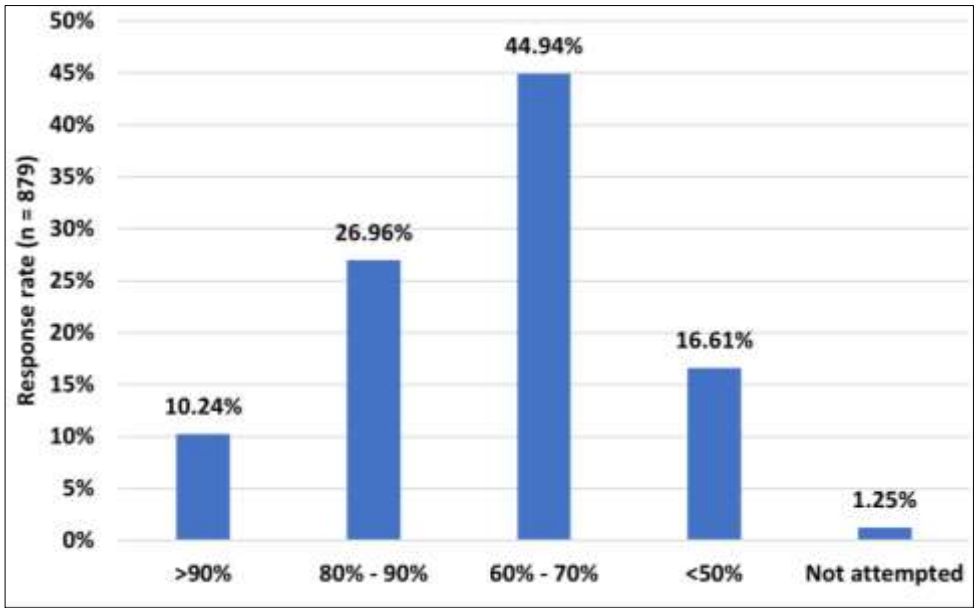

Fig 3: Distribution of response to the percentage of patients adhering FDC of voglibose, glimepiride and metformin triple drug combination

Table 3: Distribution of response to the duration for prescribing the voglibose, glimepiride and metformin triple drug combination

Duration	Response rate (n = 879)
1 year	343 (39.02%)
6-8 months	289 (32.88%)
5-6 months	148 (16.84%)
<3 months	94 (10.69%)
Not attempted	5 (0.57%)

According to 32% of the respondents, 60%-70% of individuals with T_2DM are at the risk of developing lipitension whereas 29%, 19% and 19% clinicians reported it to be 50%-60%, 70-80% and less than 50%. The survey revealed that 92% of clinicians found pill burden to be a significant limiting factor in managing lipitension, while 6% did not consider it and 2% did not answer the question. However, almost all clinicians reported that a combination of telmisartan and rosuvastatin can effectively manage lipitension by reducing pill burden, lowering cardiovascular risk in T2DM, and improving therapy compliance, resulting in better treatment outcomes.

Discussions

This study emphasized the substantial preference for sitagliptin, especially the combination of sitagliptin and metformin in the treatment of T_2DM. The findings also underscore the effectiveness and prescription pattern of the FDC of voglibose, glimepiride and metformin therapy in T_2DM.

Majority of the clinicians in this survey recommended sitagliptin and metformin combination therapy for newly diagnosed T_2DM with HbA1c >7.5%. They also noted that patients achieved the target HbA1c goal of ≤7% over 4 years with a 1-1.50% reduction in HbA1c. In line with this, a 24-week randomized trial showed that initial combination therapy of sitagliptin (50 mg) + metformin (1000 mg) twice daily resulted in a maximum reduction of HbA1c levels by 2.1%, fasting glucose levels by 3.8 mmol/l, and post-prandial glucose levels by 15.9 mmol/l, with 66% of patients achieving HbA1c levels below 7.0% [21]. Lim *et al.* also demonstrated significant glycemic improvement with sitagliptin and metformin combination therapy in treatment-naive T_2DM patients, showing reductions in HbA1c levels, fasting, and post-load 2-hour glucose levels after 52 weeks of treatment [22]. Another study by Reasner *et al.* found that initial treatment with sitagliptin/metformin FDC provided superior glycemic improvement compared to metformin monotherapy, with a greater proportion achieving an HbA1c value <7% [23].

In addition, a randomized controlled trial by Williams-Herman *et al.* found that the combination therapy of sitagliptin and metformin, as well as either therapy alone, led to significant and persistent improvements in glycemic control and β-cell function for two years in patients with T2DM [24]. The COSMIC study indicated that initial combination therapy with sitagliptin and metformin demonstrated a persistent glucose-reducing effect over four years in real-world follow-up studies. After the first year,

72% of the patients demonstrated a reduction in HbA1c by at least 0.8% or achieving the target HbA1c of 7.0% or less. After four years, 35% of the patients still exhibited a response, maintaining an HbA1c level of 7.0±0.9% [25]. Moreover, Charbonnel *et al*. also demonstrated the efficacy and tolerability of adding once daily sitagliptin 100 mg to ongoing metformin therapy in T_2DM patients with inadequate glycemic control on metformin monotherapy. A significantly higher percentage of patients achieved an HbA1c level <7% with sitagliptin (47.0%) compared to placebo (18.3%) [26]. Several other studies have also revealed better improvements in glycemic control with a combination of sitagliptin and metformin [27, 28].

Majority of the clinicians preferred the combination of sitagliptin and metformin over glimepiride + metformin combination due to benefits such as better HbA1c control, no risk of hypoglycemia and weight gain, and safety in cardiac patients. A double-blind study in Korean patients with T_2DM demonstrated that sitagliptin/metformin FDC treatment was more effective than glimepiride in reducing HbA1c and FPG levels after 30 weeks of initial treatment. A significantly higher proportion of patients in the sitagliptin/metformin FDC group achieved the target HbA1c level of <7.0%. Glimepiride treatment resulted in weight gain, while sitagliptin/metformin FDC led to slight weight loss and fewer cases of hypoglycemia [13]. Tahashildar *et al*. noted that the combination of sitagliptin and metformin resulted in better glycemic control and fewer incidences of hypoglycemic episodes, gastrointestinal adverse events, and weight gain compared to glimepiride [14]. According to Chung *et al*., the treatment of T2DM with 100 mg sitagliptin once daily has shown promising results in Korean patients. The treatment was found to be effective and well-tolerated in patients who experienced inadequate glycemic control with metformin alone, or in combination with glimepiride, and acarbose [29].

The physicians also recommended the triple drug combination of voglibose, glimepiride and metformin therapy for its effectiveness and reduction in HbA1c in T_2DM patients. A survey conducted by Das *et al*. in Indian context demonstrated a robust consensus (80.7%) among clinicians who strongly advocated for its potential to delay the initiation of insulin therapy. Moreover, a significant majority of the clinicians (72.7%) expressed confidence in the cardiovascular neutrality of the glimepiride/metformin /voglibose combination. The survey findings exhibited an overwhelming consensus (86.8%) among clinicians who believed in the efficacy of early intensification with the glimepiride/metformin/voglibose triple combination in achieving target HbA1c levels, particularly in cases where the baseline HbA1c levels were elevated (1.5–2.0% above the target). Furthermore, a substantial proportion of clinicians (70.2%) noted that this combination therapy might potentially reduce the risk of both macrovascular and microvascular complications [17].

Some studies also corroborated the potential of the triple-drug combination of voglibose, glimepiride and metformin in effectively managing T_2DM by controlling fasting and postprandial blood glucose levels. The combination was well-tolerated and showed a significant decrease from baseline in HbA1c value, FPG levels, and PPBG levels after three months of treatment. Overall, the combination was found to be effective in controlling both fasting and postprandial glucose levels [18, 30].

The current study offers valuable insights into the perspectives of experts on the treatment of T_2DM in an Indian context. The study's major strength lies in the collection of expert opinions through a meticulously created and validated questionnaire-based survey. The survey findings can assist in making informed decisions to achieve optimal treatment outcomes in T_2DM patients. However, it is important to note that the study has several limitations. Since the conclusions were drawn from expert opinions, there was a possibility of bias affecting the findings. Therefore, further research with larger sample sizes and randomized controlled procedures was essential to validate the survey findings.

Conclusion

In conclusion, clinicians widely endorse the combination therapies of sitagliptin and metformin, as well as voglibose, glimepiride, and metformin, for the effective management of T_2DM. Notably, the sitagliptin and metformin combination emerges as the preferred option, showcasing superior control over HbA1c levels, absence of hypoglycemia and weight gain, and enhanced cardiac safety. Furthermore, the triple-drug combination of voglibose, glimepiride, and metformin exhibits significant efficacy in reducing HbA1c levels among T_2DM patients, underscoring its robust and sustained effectiveness in clinical practice.

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