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Original Research Article

Expert opinion on the prescription practice of vildagliptin and its combinations in managing type 2 diabetes mellitus in Indian settings

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ABSTRACT

Background: The aim of the study was to gather expert opinion regarding the use of vildagliptin and its combinations in T2DM in Indian settings.
Methods: This cross-sectional study involved 24 questions and collected perspectives of experts across various clinical settings in India regarding the use of vildagliptin and its combinations for the management of type 2 diabetes mellitus (T2DM) in their clinical practice.
Results: Among 195 participants, most clinicians (73%) advocated vildagliptin once-daily formulation for newly diagnosed young diabetics, elderly patients with long-standing diabetes, and those with uncontrolled diabetes as an add-on therapy. Around 92% favored vildagliptin for its weight-neutral nature, preservation of beta-cell function, minimal glycemic variation, and low risk of adverse effects. Most clinicians (66%) preferred initiating vildagliptin and metformin combination therapy in diabetic individuals aged 40 to 50 years, with 53% opting for it when HbA1c levels exceeded 8%. Approximately 83% favored this combination for young, elderly, and long-standing diabetic individuals. More than half (54%) of the clinicians preferred prescribing the fixed-dose combination (FDC) of vildagliptin and dapagliflozin to 11-25% of the patients.
Conclusions: The survey underscored the effectiveness of vildagliptin and its combinations in managing T2DM. Clinicians widely endorsed vildagliptin once-daily formulation and vildagliptin and metformin therapy for diverse diabetic populations due to their efficacy and tolerability. They also advocated the use of vildagliptin and dapagliflozin therapy, especially in patients with specific comorbidities or higher HbA1c levels, citing its benefits in achieving better glycemic control and reducing disease progression.

Keywords: Type 2 diabetes mellitus, Glycemic control, Vildagliptin, Dapagliflozin, Metformin

INTRODUCTION

Diabetes stands as one of the paramount global health crises of the twenty-first century, alongside cardiovascular disease (CVD), respiratory disease, and cancer, ranking among the top 10 causes of mortality.[1] The 10th edition of the International Diabetes Federation (IDF) Diabetes Atlas underscores the escalating global prevalence of diabetes, posing a substantial challenge to global health and well-being. According to reports, currently, 537 million adults aged 20-79 years worldwide are living with diabetes, representing 1 in 10 adults. Projections suggest a further rise to 643 million by 2030 and a staggering 783 million by 2045.[2]

The global burden of diabetes is substantial in developing economies such as India, largely driven by escalating rates of overweight/obesity and unhealthy lifestyle choices. According to 2019 estimates, India had 77 million individuals with diabetes, a figure projected to surge to over 134 million by 2045.[3] As per the IDF, one out of every seven adults diagnosed with diabetes globally resides in

India. Additionally, it is reported that one in every third households in India has at least one member diagnosed with diabetes, further emphasizing the widespread prevalence of the condition.[4]

Dipeptidyl peptidase-4 (DPP-4) inhibitors constitute an oral pharmacological approach for managing adults with type 2 diabetes mellitus (T2DM). They leverage the glucose-lowering effects of the gastrointestinal hormone glucagon-like peptide-1 (GLP-1). These orally active small molecules enhance endogenous incretin levels, thereby improving glycemic control in individuals with T2DM.[5] In a real-world study conducted by Hasnani et al. in India, DPP-4 inhibitors emerged as the most frequently prescribed oral antidiabetic agents (OAD) among the elderly population (>60 years), accounting for 91% of the prescriptions, followed by metformin at 75%. Furthermore, DPP-4 inhibitors ranked as the second most commonly prescribed OAD after metformin for patients with chronic kidney disease (CKD) or CVD.[6]

Vildagliptin, a DPP-4 inhibitor, effectively reduces HbA1c levels in patients with T2DM when used as monotherapy, dual, or triple combination therapy. In India, vildagliptin is commonly prescribed for T2DM patients due to its ability to decrease the mean amplitude of glycemic excursion, its lower risk of hypoglycemia, and its weight-neutral profile. As a novel oral antidiabetic agent, Vildagliptin enhances pancreatic islet cell responsiveness to glucose.

Extensive clinical trials involving approximately 22,000 patients and 7000 patient-years of vildagliptin exposure have demonstrated its favourable tolerability and efficacy in improving glycemic control in T2DM patients. Monotherapy trials have shown significant reductions in HbA1c levels, alongside neutral effects on body weight and lipids, as well as a low risk of edema and hypoglycemia. These attributes position vildagliptin as a favourable option for combination therapy in T2DM management.[7,8]

The unmet requirement to attain or improve glycated haemoglobin (HbA1c) levels is closely linked to the necessity for diverse therapeutic interventions, particularly for tailoring treatment to individual needs. The objective of the current expert opinion paper was to understand the utilization and prescription practice of vildagliptin and its combinations in the management of patients with T2DM within routine clinical practice settings in India.

METHODS

This cross-sectional, multiple-response questionnaire-based survey was conducted among clinicians with expertise in managing diabetes across the major cities in Indian from June 2023 to December 2023. The study was conducted after receiving approval from Bangalore Ethics, an Independent Ethics Committee which was recognized by the Indian Regulatory Authority, Drug Controller General of India.

An invitation was sent to leading clinicians in managing diabetes in the month of March 2023 for participation in this Indian survey.

About 195 diabetologists from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. Further, we excluded those who were not interested to participate in this study. The questionnaire booklet named VERDICT (Vildagliptin ExpeRience in T2DM Patients in Indian ConText) study was sent to the physicians and it comprised 24 questions addressing current feedback, clinical observations, and specialists' experiences regarding the use and prescription patterns of vildagliptin and its combinations in the management of T2DM. Clinicians were instructed to answer the questionnaire on their own, without contacting any of their colleagues. Prior to the study's implementation, each doctor provided their written informed permission before the initiation of the study.

The data were analysed using descriptive statistics. Categorical variables were presented as percentages to provide a clear understanding of 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, pie, and bar charts were created using Microsoft Excel 2013.

RESULTS

The survey involved a total of 195 experts. Majority of the clinicians (77%) favoured all the mentioned diet restrictions namely intermittent fasting, ketogenic diet, and low-fat diet for diabetes individuals. A significant number of clinicians (78%) recommended aerobic exercises, strength/resistance training, and yoga for diabetes individuals. According to 51% of clinicians, 40-50% of diabetic individuals are reluctant to intensify pharmacotherapy. The majority of the clinicians (78%) attributed clinical inertia to poor communication about the disease and lack of awareness of diabetic-related complications. Approximately 85% of the clinicians considered HbA1c as the primary indicator of glycemic control after initiation of pharmacotherapy. A significant proportion of clinicians (95%) opined against using continuous glucose monitoring for initiating pharmacotherapy.

Mass education through social media emerged as the most favoured option (30%) for educating patients with diabetes, while individual one-to-one sessions were also highly favoured (28%). The predominant factor linked to medication non-adherence among T2DM patients was the lack of patient education, representing 63% of responses. In clinical practice, dapagliflozin emerged as the most commonly prescribed SGLT2 inhibitor, with 96% of

clinicians endorsing its use. Dapagliflozin was preferred by 57% of clinicians as an add-on to DPP4 inhibitors. Majority (42%) of the clinicians observed a 25-50% reduction in insulin usage following recent advancements in OADs such as DPP4 inhibitors and SGLT2 inhibitors.

Majority of the clinicians (73%) recommended using vildagliptin once-daily formulation in newly diagnosed young diabetic individuals, elderly long-standing diabetic individuals as add-on therapy, and uncontrolled diabetic individuals as add-on therapy (Figure 1). Most of the respondents (92%) preferred vildagliptin due to its weight-neutral property, its ability to help preserve beta cell function, its tendency to cause less glycemic variation, and its low risk of adverse effects (Table 1).

Majority of the respondents (38%) indicated that they initiate combination therapy in 40-50% of newly diagnosed individuals with T2DM. Approximately 81% cited ease of achieving glycemic goals, fewer adverse events, and delaying progression of the disease as reasons for starting combination therapy. A substantial majority, representing 92% of respondents, highlighted their consideration of factors such as safety, affordability, efficacy, availability, and scientific information when selecting fixed-dose combinations (FDCs). Around 48% reported that the most common timing for initiating DPP4i and SGLT2i combination therapy in clinical practice is after one drug failure.

Majority of the clinicians (65.64%) preferred initiating vildagliptin and metformin combination therapy in diabetic individuals aged 40 to 50 years. Furthermore, 29% of the respondents opted for this therapy in the age group of 50 to 60 years (Table 2). Majority (53%) of the clinicians preferred to initiate vildagliptin and metformin combination therapy in patients with HbA1c levels >8%, while 38% indicated a preference for initiating this therapy when HbA1c level >7% (Figure 2). Majority (82.56%) of the respondents preferred patient groups for initiating the FDC of vildagliptin and metformin for young, elderly, and long-standing diabetic individuals (Table 3).

About 54% of the clinicians indicated a preference for prescribing the FDC vildagliptin and dapagliflozin to 11-25% of the patients, while 38% preferred it for 26-50% of the patients (Figure 3). Majority of the clinicians (64%) reported prescribing the combination of vildagliptin and dapagliflozin for better glycemic control, followed by 24% of clinicians who cited pleiotropic benefits as the reason (Table 4).

Approximately 79% indicated that diabetic patients with atherosclerotic cardiovascular disease (ASCVD), CKD (up to stage 3), and those with HbA1c levels ≥7.5% at diagnosis would benefit from the FDC of vildagliptin and dapagliflozin (Figure 4). Most clinicians (85%) reported benefits such as achieving rapid and sustained glycemic goals and reducing disease progression with vildagliptin and dapagliflozin and metformin FDC therapy (Table 5).

Table 1: Distribution of response to reasons for preferring vildagliptin over other oral antidiabetic drugs.

Reasons	Response rate (n=195) N (%)
Weight neutral property	3 (1.54)
Helps in preserving beta cell function	2 (1.03)
Cause less glycemic variation	8 (4.1)
Possess low risk of adverse effects	2 (1.03)
All the above	180 (92.31)

Table 2: Distribution of response to preferred age groups for vildagliptin and metformin combination therapy.

Age group (years)	Response rate (n=195) N (%)
40-50	128 (65.64)
50-60	57 (29.23)
60-70	7 (3.59)
Above 70	3 (1.54)

Table 3: Distribution of response to preferred patient groups for initiating FDC of vildagliptin and metformin.

Patient group (years)	Response rate (n=195) N (%)
Young diabetic individuals	11 (5.64)
Elderly diabetic individuals	9 (4.62)
Long-standing diabetic individuals	14 (7.18)
All of the above	161 (82.56)

Table 4: Distribution of response to reasons for prescribing a combination of vildagliptin and dapagliflozin.

Reason	Response rate (n=195) N (%)
For better glycemic control	125 (64.1)
For pleiotropic benefits	47 (24.1)
For patient compliance	20 (10.26)
All of the above	3 (1.54)

Table 5: Distribution of response to benefits of vildagliptin and dapagliflozin and metformin FDC therapy.

Benefits	Response rate (n=195) N (%)
Rapid and sustained glycemic goal	20 (10.26)
Reduces diseases progression	8 (4.1)
All of the above	167 (85.64)

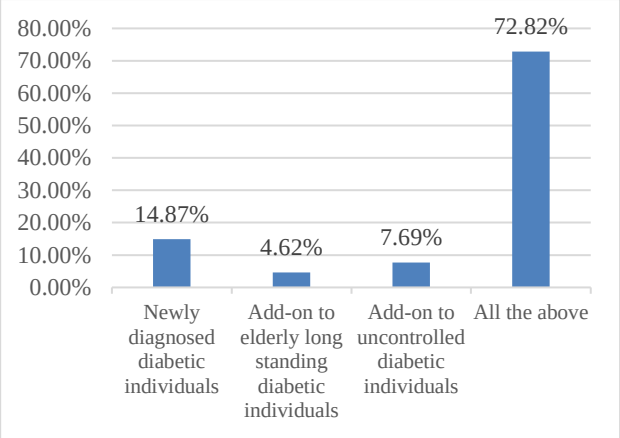

Figure 1: Distribution of response to preference for using vildagliptin once-daily formulation in different diabetes individuals.

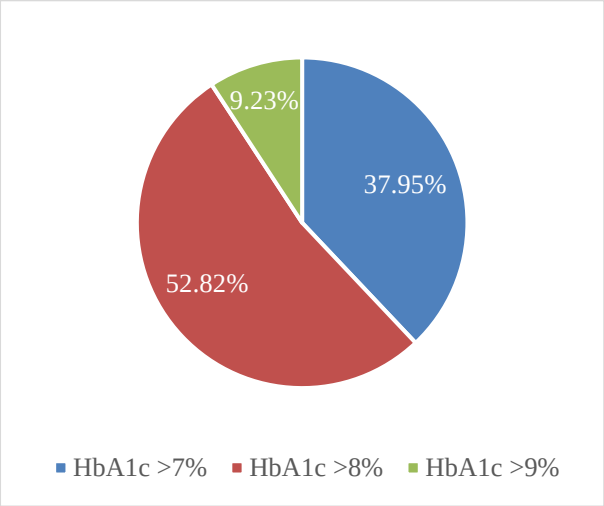

Figure 2: Distribution of response to preferred HbA1c levels for initiating vildagliptin and metformin combination therapy.

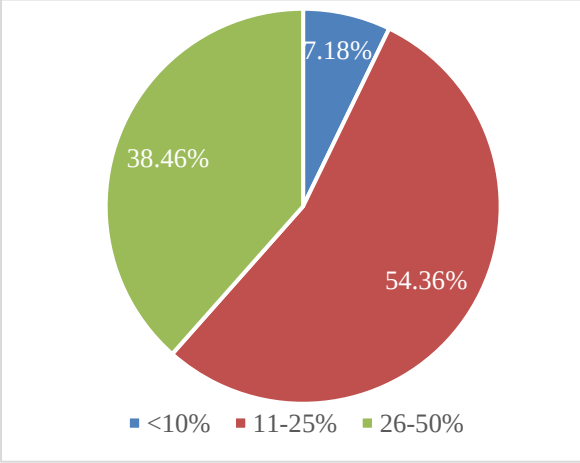

Figure 3: Distribution of response to preference for prescribing an FDC of vildagliptin and dapagliflozin.

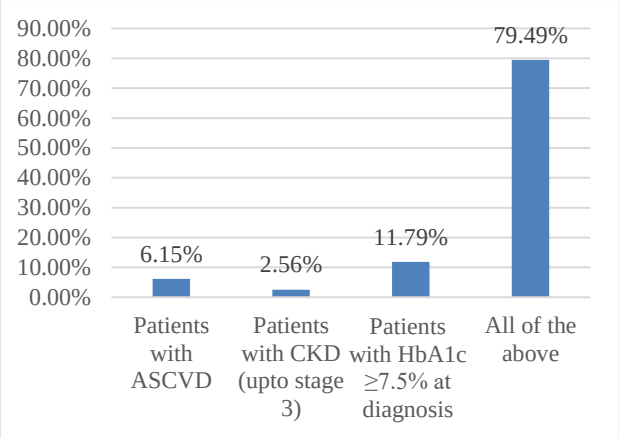

Figure 4: Distribution of response to categories of diabetic individuals benefiting from FDC of vildagliptin and dapagliflozin therapy.

DISCUSSION

The current survey, based on expert opinion, was intended to understand the prescription practice of vildagliptin and its combinations, aiming to aid clinicians in making informed clinical decisions regarding their use in T2DM management. The consensus among clinicians leaned towards recommending vildagliptin once-daily formulation for a range of diabetic populations, including newly diagnosed young individuals, elderly patients with long-standing diabetes, and those with uncontrolled diabetes who require add-on therapy. Majority of the clinicians favored vildagliptin owing to its weight-neutral characteristic, ability to preserve beta cell function, and minimal risk of adverse effects.

Bosi et al demonstrated that vildagliptin is well-tolerated and leads to clinically significant, dose-dependent reductions in HbA1c and fasting plasma glucose (FPG) levels when used as an add-on therapy in patients with T2DM who have inadequate control with metformin.[9] A randomized study spanning 24 months, conducted among T2DM patients treated with insulin, the use of vildagliptin as an adjunct to insulin therapy for the entire duration, demonstrated excellent tolerance and resulted in sustained decrease in HbA1c levels, insulin dosage, injection frequency, and the likelihood of experiencing hypoglycemia.[10] Fonseca et al demonstrated that vildagliptin effectively reduced HbA1c levels in patients with T2DM who have poorly controlled blood sugar, despite receiving high doses of insulin.[11]

In a systematic review and meta-analysis conducted by Bekiari et al comprising sixty-nine studies involving 28,006 patients, vildagliptin emerged as an effective and safe therapeutic option for individuals with T2DM, both as monotherapy and as an add-on treatment. The study revealed that compared to placebo, vildagliptin significantly reduced HbA1c levels, and it exhibited comparable efficacy to other antidiabetic agents, without increasing the risk of hypoglycemia.[12] Lauster et al

concluded that vildagliptin has demonstrated efficacy in reducing HbA1C, FPG levels, prandial glucose levels, and prandial glucagon secretion, while also enhancing beta-cell function.[13] Pan et al found that vildagliptin, whether used alone or alongside other OADs, effectively improves glycemic control while preserving both α- and β-cell function. Additionally, it reduces lipotoxicity and insulin resistance. This medication was well-tolerated, weight-neutral, and carries a low risk of adverse effects, including hypoglycemia and CV/cerebrovascular events.[14]

The majority of the clinicians confirmed a clear preference for initiating vildagliptin and metformin combination therapy in diabetic individuals aged 40 to 50 years and when HbA1c levels exceed 8%. This choice is consistent across patient demographics, including young, elderly, and long-standing diabetic individuals. In a meta-analysis conducted by Ding et al., incorporating 11 randomized controlled trials and involving 8533 patients, it was found that when compared to metformin alone, the combination of vildagliptin with metformin led to significant reductions in FPG, HbA1c, and body weight. Specifically, when the dose of metformin in the vildagliptin and metformin combination group was equal to or greater than 1500mg per day, notable reductions in HbA1c and FPG were observed.[15] The VICTORY Study, conducted by Suh et al., demonstrated that the vildagliptin/metformin combination effectively reduced HbA1c levels to the target of ≤7.0%.[16] In a real-world study conducted by Van et al vildagliptin emerged as an effective and safe treatment option for patients with T2DM who were already undergoing metformin therapy. Moreover, the single-pill combination of vildagliptin and metformin offers a convenient alternative, ensuring comparable effectiveness and tolerability.[17] Initiating early intervention with combination therapy of vildagliptin alongside metformin yields superior and enduring long-term advantages when compared to the prevailing standard of care, which typically involves initiating treatment with metformin monotherapy for patients recently diagnosed with T2DM.[18,19]

Most clinicians preferred prescribing the FDC vildagliptin and dapagliflozin to 11-25% of their patients. The primary rationale cited by the majority of clinicians is its efficacy in achieving better glycemic control. Additionally, a substantial proportion of the clinicians believed that diabetic patients with ASCVD, CKD (up to stage 3), or initial HbA1c levels ≥7.5% could benefit from this combination therapy. In the Indian context, an opinion-based consensus conducted by Garg et al presented vildagliptin-dapagliflozin FDC as the preferred first-line treatment for obese and hypertensive patients with T2DM, achieving a moderate consensus level (C). Additionally, the same combination was recommended as a second-line treatment for obese and hypertensive T2DM patients who remain uncontrolled on metformin, garnering a strong consensus level (B) from experts. Furthermore, clinical experts also agreed that T2DM patients inadequately controlled on two OADs with HbA1c levels >8% could be suitable candidates for initiating vildagliptin-dapagliflozin FDCs.[20]

Most respondents cited various benefits associated with vildagliptin and dapagliflozin and metformin FDC therapy, including the attainment of rapid and sustained glycemic goals and the reduction of disease progression. Vildagliptin is effective in reducing HbA1c levels in patients with T2DM when administered as monotherapy, dual or triple combination therapy.[7] In clinical investigations involving individuals with T2DM, dapagliflozin has demonstrated a notable reduction in HbA1c levels (approximately 0.5%-1%, from a baseline range of 8%-9%) and body weight (approximately 2-3 kg), while posing no elevated risk for hypoglycemia.[21] Metformin has served as the cornerstone in the management of T2DM for decades. This biguanide agent is commonly employed as a first-line treatment for T2DM, demonstrating efficacy both as monotherapy and in conjunction with other glucose-lowering medications, effectively reducing HbA1c levels.[22,23]

The present study offers valuable insights into clinicians' perspectives on the utilization of vildagliptin and its combinations in the management of T2DM within an Indian context. The findings, obtained from a meticulously designed and validated questionnaire-based survey, hold significant relevance in making informed decisions regarding optimal treatment options, thereby improving patient outcomes in T2DM management. However, it is essential to acknowledge certain limitations of the study. Relying on expert judgments may introduce bias, as individual viewpoints and preferences could have influenced the reported conclusions. Therefore, it is imperative to interpret the results with these limitations in mind and consider further research to validate and expand upon the findings.

CONCLUSION

The current study adds to the existing literature evidence on the use of vildagliptin and its combinations for the management of T2DM in clinical practice. Consensus among the clinicians strongly corroborated the use of vildagliptin once-daily formulation as a preferred treatment option for various diabetic populations, offering benefits such as weight neutrality, preservation of beta cell function, and minimal adverse effects. Additionally, they advocated for the use of vildagliptin + dapagliflozin combination therapy, particularly in patients with specific comorbidities or higher HbA1c levels, citing its benefits in achieving better glycemic control and reducing disease progression.

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