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Original Research Article

Role of vildagliptin and its combination in type 2 diabetes mellitus management: a knowledge, attitude, and practice survey among Indian healthcare professionals

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) is a prevalent condition, with a significant burden in India, affecting approximately 74.2 million individuals. Vildagliptin, a selective dipeptidyl peptidase 4 (DPP-4) inhibitor, is approved globally for monotherapy and combination therapy. Recently, it became available as a generic product, which increased its accessibility to patients. This study aimed to assess the knowledge, attitude, and practice (KAP) regarding vildagliptin and its combination in T2DM management.
Methods: A pan-India cross-sectional KAP survey was conducted from February 2022 to March 2023. The survey utilized a specially designed questionnaire focusing on various aspects of vildagliptin treatment. A total of 1,440 healthcare professionals (HCPs) with recognized qualifications and experience in diabetes management participated. Descriptive statistics were employed for data analysis.
Results: HCPs reported initiating Vildagliptin monotherapy at an HbA1c 6.5-7.5%, while combination therapy with vildagliptin and metformin at HbA1c 7-8%. Vildagliptin was primarily preferred as an add-on to metformin. Inadequate HbA1c control with existing therapy emerged as the primary trigger for switching to vildagliptin and metformin combination. Treatment-naïve T2DM patients with HbA1c 1.5% above target and those uncontrolled on metformin monotherapy or dual therapy were reported to benefit most from combination therapy. Combination therapy was reported to result in a glycemic reduction of 1.0-1.5%. HCPs perceived vildagliptin better than other DPP4 inhibitors due to its efficacy in reducing HbA1c and a lower risk of hypoglycemia.
Conclusions: The KAP survey highlights the value Indian HCPs place on the effectiveness and tolerability of vildagliptin and their attitudes and practices in its use, highlighting its clinical utility in routine practice.

Keywords: Diabetes, KAP survey, Vildagliptin, Metformin, DPP4 inhibitors, India

INTRODUCTION

Diabetes represents one of the most pressing global health issues in the 21st century, standing among the top 10 causes of mortality alongside cardiovascular disease (CVD), respiratory issues, and cancer.[1,2] According to the World Health Organization (WHO), non-communicable diseases (NCDs) were responsible for 74% of global deaths in 2019, with diabetes contributing to 1.6 million fatalities, making it the ninth leading cause of death worldwide.[2] Projections indicate that by 2035, nearly 592 million individuals may die due to diabetes.[3]

Type 2 diabetes mellitus (T2DM), which accounts for 90% of all diabetes cases, significantly impacts individuals across various age groups and regions.[4] Moreover, it has attained epidemic proportions in several developing economies like China and India.[4,5] In India, approximately 74.2 million individuals are affected by diabetes. In other terms, India accounts for 1 in 7 of all adults living with diabetes worldwide.[6]

In response to food intake, the gut releases incretin hormones like glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic peptide, which stimulate insulin secretion in a glucose-dependent manner, inhibit glucagon secretion, and slow gastric emptying. However, these hormones are deactivated by dipeptidyl peptidase-4 (DPP-4).[7,8] The impaired incretin effect observed in patients with T2DM led to the development of incretin-based treatments, including DPP-4 inhibitors and GLP-1 receptor agonists, which respectively inhibit DPP-4 activity and resist breakdown by DPP-4.[7]

Vildagliptin is a selective and reversible inhibitor of DPP-4.[8] It is approved in more than 110 countries globally as monotherapy and combination therapy for T2DM. Additionally, there is a fixed-dose combination of vildagliptin/metformin that is also available.[7]

Vildagliptin increases the functioning of beta cells by improving insulin secretion rate, and alpha-cell function by restoring glucose-related glucagon suppression.[8-10] Long-term therapy can delay beta-cell deterioration in T2DM.[9] It exhibits synergism with metformin, leading to increased active GLP-1 levels, which contributes to long-term improvements in beta-cell activity. Vildagliptin treatment improves peripheral insulin sensitivity and postprandial triglyceride-rich lipoprotein metabolism.[8,9]

Vildagliptin can be used as monotherapy in metformin-intolerant patients, for treatment intensification in patients with inadequately controlled T2DM, as a part of dual or triple combination therapy, in patients with co-morbidities like cardiovascular disease, in obese patients, and patients who want to avoid weight gain. Furthermore, its acceptance by physicians suggests the wide use of vildagliptin for each subgroup of the diabetic continuum in Indian settings.[11]

Vildagliptin is commonly prescribed in Indian T2DM patients because it reduces the mean amplitude of glycemic excursion, has a lower risk of hypoglycemia, and is weight-neutral.[10] Recently, the vildagliptin patent expired, resulting in the introduction of generic versions, making it more accessible to patients for regular use.[12]

Given the existing evidence and the place in therapy of Vildagliptin and its combination in T2DM management, it is crucial to understand its use, attitude towards its initiation, treatment intensification, and the patient groups that benefit in the clinical practice.

Knowledge, attitude, and practice (KAP) surveys evaluate the beliefs and perceptions of a population on a specific topic and how they implement it.[13] The objective of the present study was to assess the knowledge, attitude, and practice of Indian healthcare professionals (HCPs) towards the use of vildagliptin in routine clinical practice, which refers to situations in real-life scenarios or day-to-day outpatient department (OPD) clinics, ruling out standardized regulations of a clinical trial.

METHODS

Survey design and setting

This was a cross-sectional, descriptive, observational questionnaire-based KAP survey across India from February 2022 to March 2023. The flow of the study was: sharing the questionnaire with participants i.e., HCPs who gave consent, followed by filling of the questionnaire based on experience and clinical use in the past, collection of questionnaires, compilation, analysis, and presentation of data.

Survey participants

Survey participants were registered medical practitioners, including diabetologists, endocrinologists, cardiologists, physicians, and nephrologists with recognized qualifications, working in OPDs of privately run clinics/hospitals in a tertiary care setting and using vildagliptin and vildagliptin-metformin combination.

Survey instrument

The questionnaire was a specially designed, self-completion, and structured questionnaire, which included 12 multiple-choice questions. Questions were related to the knowledge, attitude, and practice in the use of vildagliptin and vildagliptin-metformin combination among healthcare professionals. These included 4 knowledge, 6 attitude, and 2 practice-based questions. Since the survey was voluntary, respondents were not obligated to answer every question. Additionally, participants were free to select more than one response to a question if they deemed it appropriate or desirable.

Knowledge-based questions were as follows: level of HbA1c for initiating monotherapy and combination therapy, advantages of vildagliptin over other DPP4 inhibitors, and preferred class of drugs added to vildagliptin.

Attitude-based questions were as follows: patient profiles that would benefit from vildagliptin monotherapy and combination therapy with metformin, factors responsible for switching to vildagliptin from other treatments, factors responsible for switching to vildagliptin and metformin from vildagliptin, a preferred class of drug in patients uncontrolled on metformin and sulfonylurea, and potential to replace other drugs.

Practice-based questions were as follows: most-prescribed vildagliptin dose and percent reduction in glycemic parameters.

Ethical considerations

This was a survey through which no patient-related data was captured and therefore ethics committee approval was not necessary and hence not obtained. As this was not a clinical trial, no clinical trial registration was required.

Data analysis

Descriptive statistics were used to summarize the qualitative data by number and percentage for each category in each question. Many participants responded to more than one option for some questions if desired and suitable. The denominator for calculating the proportion for a particular question was the total number of participants who replied to a particular question. Data has been summarized and presented in tables and graphs.

RESULTS

A total of 1, 440 healthcare professionals participated in this survey across India and all completed the survey.

Knowledge about vildagliptin and its combination

Half of the participants reported initiating monotherapy of vildagliptin at an HbA1c of 6.5-7%. Another significant proportion reported initiating monotherapy of vildagliptin at an HbA1c of 7.5-8.5% (Table 1). Furthermore, the majority of participants reported that would prefer initiating vildagliptin and metformin combination at an HbA1c level of 7-8% in newly detected T2DM patients (Table 1).

Participants reported better HbA1c reduction (64%) as the primary factor that makes vildagliptin better than other DPP4 inhibitors like sitagliptin and teneligliptin, followed by a reduced likelihood of causing hypoglycemia (50%) (Table 1).

When asked about their preference for adding vildagliptin with OADs, participants preferred adding it mainly to metformin (3.1), followed by metformin and SGLT2 inhibitor combination (4.0). Vildagliptin addition to metformin, sulfonylurea, and pioglitazone combination was the least preferred (6.8) (Figure 1).

Attitude or perception about vildagliptin and its combination

Most participants (75%) indicated that insufficient HbA1c control was the primary reason for switching to vildagliptin from other oral-antidiabetic (OAD) agents. Additionally, some of them (36%) reported hypoglycemia with existing treatment as another factor for switching to vildagliptin from other OADs (Table 2).

Table 1: Knowledge among HCPs about vildagliptin.

S. no.	Questions	Percentage of HCPs
1	At what level of HbA1c do you initiate only monotherapy of vildagliptin?	
	6.5 to 7.5	50
	>7.5 to 8.5	46
	>8.5 to 9.5	4
	7-8	0
2	Which HbA1c range would you consider to start vildagliptin and metformin for a newly detected T2DM patient?	
	7 to 8	79
	>8 to 9	18
	>9 to 10	0
	7.5 to 8.5	7
3	In your opinion how is vildagliptin better than other DPP-4 inhibitors e.g. sitagliptin and teneligliptin?	
	Better HbA1c reduction	64
	Less chance of hypoglycemia	50
	Cost of therapy	39
	More inhibition of DPP4 enzyme	14
	Less chance of secondary failure	0
	Others	0

DPP4: Dipeptidyl peptidase 4, HbA1c: glycated hemoglobin; T2DM: type 2 diabetes mellitus

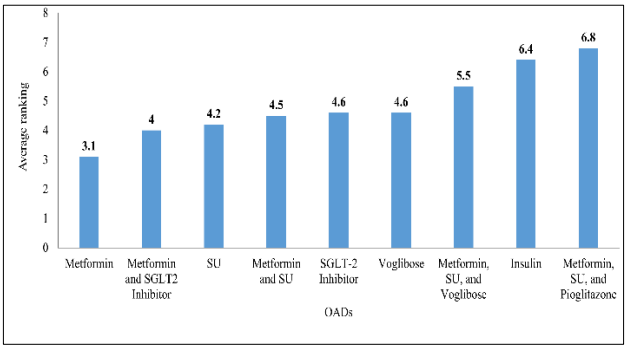

Figure 1: Order of preference to add vildagliptin with other OADs.

Ranked on a scale of 1 -9 as per their preference, where preference decreased from 1 to 9. SGLT-2: sodium-glucose transporter-2, SU: sulfonylurea

Most participants (64%) reported that inadequate HbA1c control is the most common trigger for switching to vildagliptin and metformin or other combinations from vildagliptin (Table 2).

When asked about which patient profile would benefit the most from vildagliptin monotherapy, the participants reported treatment-naive T2DM patients (64%), patients with uncontrolled T2DM with metformin monotherapy (54%), and patients with uncontrolled T2DM on dual therapy of sulfonylurea and metformin (50%) were among those likely to benefit (Table 2).

Table 2: Attitude or perception about vildagliptin.

S. no.	Questions	Percentage of HCPs
1	What are the trigger factors that make you switch to vildagliptin from other treatments patients are on?	
	Inadequate HbA1c control	75
	Hypoglycemia	36
	High-age patients	18
	Comorbidity	14
	Low-age patients	7
2.	What are the trigger factors that make you switch from vildagliptin to vildagliptin-metformin or any other combination?	
	Inadequate HbA1c control	64
	Hypoglycemia	36
	High-age patients	14
	Comorbidity	7
	Low-age patients	0
3.	Which patient type would benefit from vildagliptin monotherapy?	
	Treatment-naïve T2DM patients	64
	Uncontrolled T2DM patient on dual therapy of SU + metformin	54
	T2DM patients uncontrolled on metformin monotherapy	50
	Obese T2DM patients	11
4	Which patient type would benefit from vildagliptin and metformin combination therapy?	
	Treatment-naive T2DM patients with HbA1c 1.5% above target	61
	Uncontrolled T2DM patients on dual therapy of SU and metformin	54
	T2DM patients uncontrolled on metformin monotherapy	54
	Obese T2DM patients	11
5	Which class of drug would you like to add in patients uncontrolled on metformin and SU?	
	DPP4 inhibitors	89
	SGLT2 inhibitors	18
	Pioglitazone	7
	Voglibose	7
	GLP-1 analogues	7
6.	Do you think vildagliptin can replace any oral anti-diabetic in the future?	
	Teneligliptin	46
	Sitagliptin	39
	Glimepiride	32
	Gliclazide	29
	Metformin	25
	Voglibose	25
	Linagliptin	25
	Dapagliflozin	7
	Empagliflozin	7
	Remogliflozin	4

Similarly, when asked about which patient profiles would benefit from the vildagliptin and metformin combination, the participants reported that treatment-naïve T2DM patients with HbA1c 1.5% above target (61%), patients with uncontrolled T2DM either on dual therapy of sulfonylurea and metformin (54%) or on metformin monotherapy (54%) were among those likely to benefit (Table 2).

The majority of participants (89%) reported that they would prefer adding DPP-4 inhibitors for patients with uncontrolled T2DM on metformin and sulfonylurea therapy followed by SGLT2 inhibitors (18%), pioglitazone (7%), voglibose (7%), and GLP-1 analogs (7%) (Table 2).

In response to inquiries about the potential for vildagliptin to replace other OADs in the future, the majority of participants (46%) indicated it could replace teneligliptin, followed by sitagliptin (39%), and glimepiride (32%). Some also indicated the possibility of other OADs also being replaced by vildagliptin (Table 2).

Practice assessment for vildagliptin and its combination

The majority of participants (57%) prescribed the 50 mg twice daily (BID) dose of vildagliptin, while the rest prescribed the 100 mg once daily (OD) dose (Table 3).

Most participants (61%) noted a glycemic reduction of 1.0–1.5% when using vildagliptin with metformin. Others reported reductions of 0.5 to 1% and 1.5 to 2.5%. Only a proportion reported reductions exceeding 2.5% (Table 3).

Table 3: Practice-related aspects for vildagliptin.

S. no.	Questions	Percentage of HCPs
1	Which vildagliptin dosing form do you prescribe the most?	
	Vildagliptin 50 mg BID	57
	Vildagliptin 100 mg OD	43
2	As per your clinical experience, how much reduction occurs in glycaemic parameters with vildagliptin + metformin from baseline?	
	0.5 to 1%	18
	>1 to 1.5%	61
	>1.5 to 2.5%	21
	>2.5%	4

BID: Twice daily, OD: once daily

DISCUSSION

DPP-4 inhibitors have established themselves as an important class of oral antidiabetic drugs for managing T2DM.[14] These inhibitors have been integrated into the treatment protocols outlined in numerous national and international guidelines for T2DM.[14]

Vildagliptin exerts its effects as a potent and selective inhibitor of the DPP-4 enzyme. The efficacy of vildagliptin in reducing HbA1c levels has been established in clinical studies. Additionally, its safety and tolerability profile has been demonstrated to be superior to that of sulfonylurea or thiazolidinedione therapy.[15] This survey focused on the knowledge, attitude, and practice of healthcare professionals on the use of vildagliptin in routine clinical practice.

Knowledge about vildagliptin and its combination

American Association of Clinical Endocrinologists (AACE) recommends initiating monotherapy when the initial HbA1c is below 7.5%, while dual therapy is suggested for an initial HbA1c level exceeding 7.5%.[16,17] Around 50% of HCPs participating in this survey reported initiating vildagliptin monotherapy at an HbA1c of 6.5-7.5% while another 46% reported initiated it initiating it at HbA1c of 7.5-8.5%. This finding aligns with clinical studies assessing the effectiveness of vildagliptin monotherapy, which also reported that patients included in these studies typically had baseline HbA1c levels ranging from 6.5% to 8.5%.[18,19]

The majority of HCPs prefer to initiate vildagliptin and metformin combination at an HbA1c level of 7–8 in newly detected T2DM patients. Clinical studies assessing the effectiveness of this combination also enrolled patients with a mean baseline HbA1c ranging from 7.3% to 8.1%.[20-22]

Most HCPs find vildagliptin to be better than other DPP4 inhibitors due to its superior efficacy in reducing HbA1c levels. Literature reports also indicate better HbA1c reduction from the baseline with vildagliptin (-0.88%) than sitagliptin (-0.79%), saxagliptin (-0.70%), linagliptin (-0.55%), alogliptin (-0.76%) and teneligliptin (-0.8%-0.9%).[23,24] Additionally, half of the participants indicated a low risk of hypoglycemia as a benefit compared to other DPP4 inhibitors. These inhibitors boost insulin secretion in a glucose-dependent manner, mitigating hypoglycemia risk when used alone or with other antidiabetic agents. Studies indicate that hypoglycemic risk in patients treated with vildagliptin or Alogliptin is similar to placebo when used alone or in combination with other agents like insulin or sulfonylurea. Conversely, studies indicate an increased hypoglycemia risk when patients with background treatment with insulin or sulfonylurea are treated with sitagliptin, saxagliptin, or linagliptin.[25]

Most HCPs prefer adding vildagliptin most commonly to metformin. Literature reports indicate that vildagliptin has been evaluated as add-on therapy with metformin, sulfonylureas, thiazolidinediones, and insulin treatment and in initial combination with pioglitazone.[26, 27] Vildagliptin and metformin demonstrate synergistic effects, with vildagliptin stimulating β-cells in a glucose-dependent manner and metformin enhancing insulin sensitivity. Moreover, the well-established favorable safety profiles of both drugs support their combined use.[28] Several trials have evaluated vildagliptin as an additional therapy to metformin.[26-28]

Most HCPs indicated inadequate HbA1c control with OADs as the most common trigger to switch to vildagliptin followed by a lower risk of hypoglycemia. Several studies have demonstrated the efficacy of vildagliptin as an add-on in patients who were inadequately controlled with metformin monotherapy and the occurrence of hypoglycemia was rare.[27,29,30] The efficacy of vildagliptin in combination with other antidiabetic drugs like pioglitazone and insulin has also been demonstrated in patients with insufficiently controlled T2DM with monotherapy.[30]

Attitudes or perceptions about vildagliptin and its combination

Most HCPs mentioned inadequate HbA1c control as the most common trigger for switching to vildagliptin and metformin from vildagliptin. Vildagliptin, as discussed earlier, can be used to intensify therapy in person uncontrolled on metformin with/without other glucose-lowering drugs.[12,31]

Most HCPs consider that vildagliptin monotherapy will mainly benefit treatment-naive T2DM patients, while some consider that it will also benefit patients with uncontrolled T2DM with metformin monotherapy. Various studies have demonstrated the efficacy of vildagliptin in treatment-naïve patients as well as patients uncontrolled on metformin therapy.[18,19,21]

In the view of most HCPs, the treatment-naïve T2DM patients with HbA1c 1.5% above target benefit the most with the vildagliptin and metformin combination. This aligns with the ADA 2024 guidelines that mention patients with HbA1c ≥1.5% above the glycemic target require dual combination therapy to achieve their target HbA1c level.[32] These guidelines also mention that initial combination therapy is better than the sequential addition of medications for early management.[32] The findings of the VERIFY study indicated that the incidence of initial treatment failure (HbA1c value ≥7%) was lower in the vildagliptin-metformin combination treatment group (43.6%) compared to the sequential treatment group (62.1%).[33] Furthermore, a real-world evidence study from India published in 2021 also demonstrated the efficacy of combination therapy in these patients.[22]

Many HCPs also reported that patients with uncontrolled T2DM either on dual therapy of sulfonylurea and metformin or on metformin monotherapy also benefit from this combination. Various studies have demonstrated that HbA1c reduction with vildagliptin and metformin was similar to sulfonylurea and metformin combination.[21,34,35] Alternatively, based on the findings of a study comparing results from randomized controlled trials (RCTs) with observational studies and real-life data, it appears that the

decrease in HbA1c from baseline with sulfonylurea treatment is smaller in real-life settings compared to RCTs. In contrast, the reduction observed with vildagliptin when added to metformin remains essentially the same, indicating that vildagliptin retains its full treatment efficacy in real-life scenarios, unlike sulfonylureas, potentially due to concerns regarding hypoglycemia.[36] Likewise, clinical evidence supports the finding from this survey that vildagliptin and metformin offer better glycemic control in patients inadequately controlled with metformin monotherapy.[22,28,36]

The majority of HCPs reported that they would prefer adding DPP-4 inhibitors for patients with uncontrolled T2DM on metformin and sulfonylurea therapy. This finding is supported by the literature reports where the combination of DPP-4 inhibitor, metformin, and a sulfonylurea is effective in achieving glycemic control.[37,38]

The majority of HCPs reported that vildagliptin may replace teneligliptin in the future while some reported that it may replace glimepiride as well. Although it is difficult to comment on whether vildagliptin can replace these drugs, there are some advantages that vildagliptin offers over them. For example, vildagliptin offers a slightly better reduction in HbA1c compared to teneligliptin.[23,24] Furthermore, vildagliptin has a low risk of hypoglycemia and is weight-neutral, unlike sulfonylureas which are associated with hypoglycemia and weight gain.[7]

Practice assessment for vildagliptin and its combination

Vildagliptin dosage is either 50 mg BID or 100 mg OD. Both dosage regimens result in a similar glycemic reduction.[39] In this survey, the preference for either dose did not differ much, but 50 mg BID was prescribed by more HCPs.

Several studies have demonstrated the efficacy of the vildagliptin and metformin combination.[34] The findings of the present survey indicated a 1.0-1.5% glycemic reduction with vildagliptin and metformin. In a study by Gaal et al, the HbA1c reduction was reported to be 0.8% and 1.0% after 105 and 180 days of treatment with the combination, respectively.[15] Furthermore, Hong et al reported that the adjusted mean HbA1c levels decreased by 1.19% after 24 weeks of treatment.[40] Thus, the findings of this survey align with the existing evidence.

Despite limitations like close-ended questions, and recall bias, this survey has highlighted interesting views about the use of vildagliptin and its combination, which mainly align with the existing evidence.

CONCLUSION

This KAP survey was conducted across the country with experienced HCPs responding to the questionnaire. Vildagliptin was perceived favourably due to its efficacy and lower risk of hypoglycemia. Vildagliptin and metformin combination therapy was associated with favourable reductions in glycemic parameters. Vildagliptin as a monotherapy or in combination with metformin is effective in diverse patient groups. Overall, vildagliptin plays an important role in optimizing glycemic control in T2DM management and this survey highlights its clinical utility in routine practice.

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