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Expert opinion on the use of vildagliptin + dapagliflozin + metformin triple combination for managing uncontrolled type 2 diabetes mellitus in Indian settings

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Abstract
Objective: The current survey-based study aims to gather expert opinion regarding the prescription practice of triple combination oral antidiabetic (OAD) treatment for the management of uncontrolled type 2 diabetes mellitus (T2DM) with a special focus on vildagliptin + dapagliflozin + metformin in Indian settings.
Methodology: The cross-sectional survey utilized a 25-item, multiple-response questionnaire to gather expert opinions from specialists with expertise in managing diabetes. The survey encompassed questions pertaining to current prescription practices, clinical observations, preferences, and experiences related to the use of vildagliptin + dapagliflozin + metformin in routine settings for diabetes management.
Results: About 65% of clinicians preferred initiating gliptin + SGLT2i + metformin as a triple-drug fixed OAD combination therapy. According to 28% of the clinicians, the major advantage of the fixed-dose combination of dipeptidyl peptidase-4 inhibitors (DPP4i) + sodium-glucose cotransporter-2 inhibitors (SGLT2i) + metformin was better glycemic control, while 27% reported it as body weight reduction with a lower risk of hypoglycemia, and 25% reported that it offers end-organ protection to patients. As reported by 67% of the respondents, the advantages of vildagliptin + dapagliflozin + metformin over glimepiride + metformin + pioglitazone include better hemoglobin A1C (HbA1c) reduction, less weight gain, fewer hypoglycemia episodes, end-organ protection, and beta-cell preservation. Approximately 40% of clinicians observed a 1 to 1.5% HbA1c reduction with the use of vildagliptin + dapagliflozin + metformin therapy. Around 46% of clinicians reported a weight reduction of 2 to 3 kg following vildagliptin + dapagliflozin + metformin therapy. Approximately 50% of respondents noted that the incidence of glycemic variability with vildagliptin + dapagliflozin + metformin was rare.
Conclusion: The survey findings highlighted clinicians' preference for gliptin + SGLT2i + metformin as a triple-drug fixed oral antidiabetic combination therapy, noting significant advantages such as improved glycemic control, reduced hypoglycemia risk, and enhanced end-organ protection. Moreover, the survey noted the superior efficacy of vildagliptin + dapagliflozin + metformin over alternative combinations, demonstrating notable reductions in HbA1c levels, weight, and incidence of hypoglycemia, along with beta-cell preservation.

Keywords: Diabetes, type 2 diabetes mellitus, vildagliptin, metformin, dapagliflozin

Introduction
The prevalence of type 2 diabetes mellitus (T2DM) has almost doubled since 1980, rising from 4.7% to 8.5% in the adult population [1]. T2DM affects an estimated 462 million people globally, with low- and middle-income countries witnessing the highest growth rates. In India, T2DM poses a significant burden, with 77 million individuals affected, ranking second globally in T2DM cases. This number was expected to surpass 134 million by 2045 [2, 3]. The increasing burden of T2DM was closely linked to the rising prevalence of overweight/obesity and unhealthy lifestyles in developing economies like India. The country faces substantial challenges in diabetes prevention and management, ranging from a lack of multisectoral approaches to limited access to healthcare and affordable medicines [4, 5].

In India, over half of T2DM, patients fail to reach the recommended target HbA1c level of ≤7% (53 mmol/mol), emphasizing the need for improved diabetes management strategies.

Current medications, while effective, often come with drawbacks such as hypoglycemia and weight gain, underscoring the demand for innovative drugs with an improved risk/benefit profile [6]. Combination therapies, integrating various classes of medications such as biguanides, sulfonylureas (SUs), meglitinides, thiazolidinediones (TZDs), dipeptidyl peptidase-4 inhibitors (DPP-4i), sodium-glucose cotransporter-2 (SGLT-2) inhibitors, alpha-glucosidase inhibitors, and oral glucagon-like peptide 1 (GLP-1) receptor agonists, hold significant promise in optimizing T2DM management, offering improved glycemic control and reduced risk of complications [7].

For patients who are intolerant to metformin or experiencing side effects from metformin monotherapy, fixed-dose combinations (FDCs) containing various oral antidiabetic drugs (OADs) are often prescribed. For instance, combining metformin with a DPP-4 inhibitor is a common and safe alternative. Moreover, adding a third agent can enhance treatment efficacy, addressing challenges in T2DM management and ultimately improving patient outcomes [7, 8, 9].

SGLT-2 inhibitors are the latest oral antidiabetic (OAD) medications recommended for patients with T2DM who have heart failure, atherosclerotic cardiovascular disease, and chronic kidney disease. These medications not only reduce hypoglycemia but also improve body weight, blood pressure, dyslipidemia, and fatty liver disease. Dapagliflozin, a commonly prescribed SGLT-2 inhibitor, effectively lowers blood glucose levels by reducing fasting and post-meal glucose levels. Additionally, dapagliflozin is approved for managing heart failure in adults [10, 11].

Vildagliptin, a potent and selective inhibitor of DPP-4, operates through a reversible and competitive mechanism of action. It enhances pancreatic islet cell responsiveness to glucose, thereby increasing the levels of incretin hormones. Vildagliptin has demonstrated efficacy in reducing HbA1c levels in T2DM patients when used in combination with metformin, pioglitazone, or insulin. Furthermore, it is generally well tolerated whether administered alone or in combination with other antidiabetic treatments [12].

The integration of a triple-drug combination has emerged as a promising strategy in the effective management of T2DM, aiming to address both fasting and post-prandial blood glucose levels, ultimately influencing HbA1c values.[13,14] Guidelines suggest a triple combination of OADs as an effective alternative before the initiation of insulin for the treatment of T2DM. The triple-drug combination of vildagliptin + dapagliflozin + metformin holds the potential to improve glycemic control and delay or prevent microvascular and cardiovascular complications.[15] The present survey was intended to gather clinicians' perspectives regarding the prescription practice of the OAD of the triple combination of vildagliptin + dapagliflozin + metformin 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 OPTIMUM (OAD perspectives of Indian Clinicians in Managing Uncontrolled Diabetes Mellitus) study was sent to the doctors who were interested to participate. The 25-question survey focused on gathering expert opinions regarding current feedback, preferences, clinical observations, and experiences of specialists in managing uncontrolled T2DM, with a particular emphasis on the fixed-dose combination of oral antidiabetic drugs, especially the triple combination of vildagliptin + dapagliflozin + metformin. 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 616 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. Written informed consent was obtained from all participants before the study commenced.

Statistical analysis

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

Results

The survey involved 616 clinicians, with 43% of them reporting that 20 to 25% of diabetic individuals have HbA1c levels (>10%). The majority (74.51%) of clinicians opined that the lack of awareness of early screening among patients contributes to high HbA1c levels at the time of diagnosis. According to 52% of clinicians, both genders exhibit high HbA1c levels. About 34% of clinicians reported high HbA1c levels in the rural population, while 37% reported the same in the urban population. Around 46% of clinicians responded that the incidence of high HbA1c levels among young T2DM individuals at the time of diagnosis was 20%, while 40% of clinicians responded to it as 30%. According to 46% of clinicians, around 30% of elderly T2DM patients have high HbA1c levels at the time of diagnosis.

Majority (64.45%) of the clinicians cited non-adherence to therapy, adverse events related to medication, and medication costs as reasons for uncontrolled HbA1c. Additionally, 80% of respondents expressed that point-of-care instruments for measuring HbA1c are not recommended for individuals with high HbA1c levels. About 74% of clinicians emphasized the importance of achieving good glycemic control in the first year of treatment. Nearly half (49%) of clinicians reported initiating insulin instead of triple fixed-dose combination oral antidiabetic therapy in 11-20% of patients with high HbA1c.

As reported by 63% of clinicians, the limitations of initiating insulin over triple oral antidiabetic therapy include patient non-compliance, risk of hypoglycemia, insulin injections, and therapy costs. Furthermore, approximately 65% of clinicians preferred initiating a triple-drug fixed combination therapy comprising gliptin + SGLT2i + metformin (Figure 1). According to 28% of the clinicians, the advantage of the fixed-dose combination of DPP4i+ SGLT2i+ metformin was better glycemic control, 27% of them reported that it reduces body weight with less risk of hypoglycemia and 25% reported that it offers end-organ protection to the patients (Table 1).

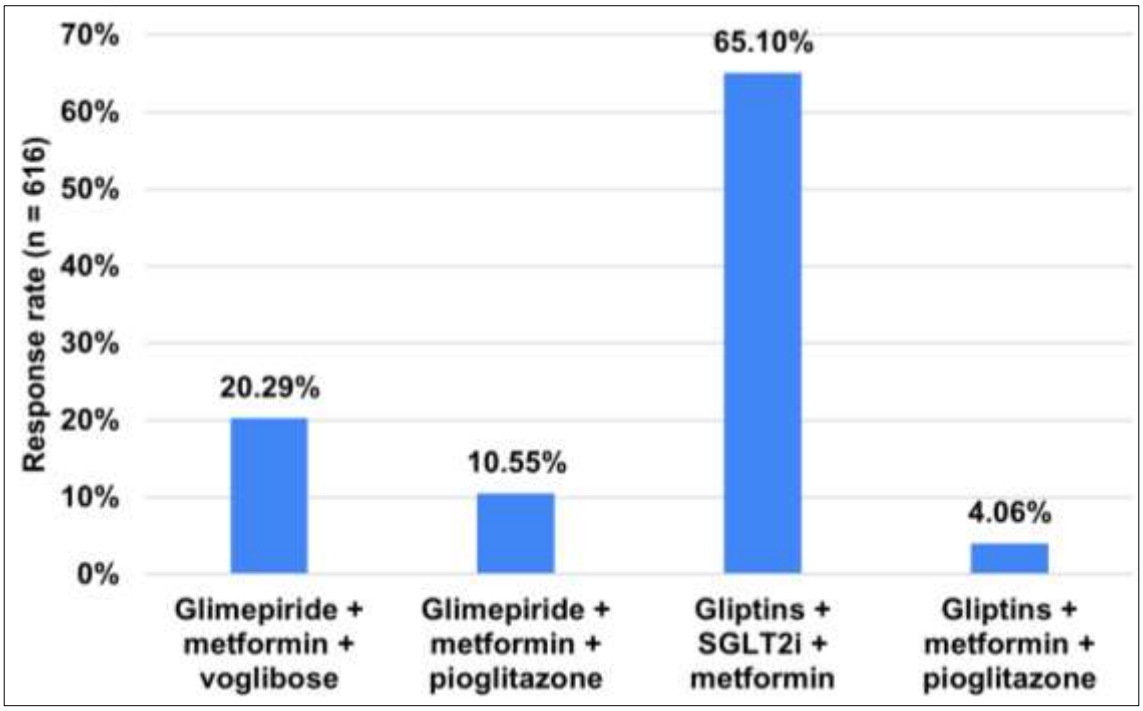

Fig 1: Distribution of responses on the preferences to initiate gliptin+ SGLT2i+ metformin as a triple-drug fixed OAD combination therapy

Table 1: Distribution of responses on the advantages of fixed dose combination of DPP4i+ SGLT2i+ metformin

Advantages	Response rate (n = 616)
Better glycaemic control	28.08%
Reduces body weight with less risk of hypoglycaemia	26.79%
Offers end organ protection	24.84%
Improves patient compliance	16.72%
All of the above	3.41%
Unprescribed	0.16%

About 43% of clinicians reported observing 2 to 3 kg of weight gain in patients after 12 months of treatment with glimepiride + metformin + pioglitazone. Nearly 50% of clinicians opined that after 12 months of treatment with this fixed-dose combination therapy, the incidence of hypoglycemia episodes ranged from 6 to 10% in patients. According to 31% of clinicians, the fixed-dose combination of vildagliptin + dapagliflozin + metformin was preferred for long-standing T2DM in young individuals. Additionally, 76% of clinicians reported that vildagliptin + dapagliflozin + metformin offers good glycemic control in both the genders.

As reported by 67% of respondents, the advantages of vildagliptin + dapagliflozin + metformin over glimepiride + metformin + pioglitazone include better reduction in HbA1c, less weight gain, fewer hypoglycemia episodes, end-organ protection, and beta-cell preservation (Figure 2). Approximately 40% of clinicians observed a reduction in HbA1c ranging from 1 to 1.5% with the use of vildagliptin + dapagliflozin + metformin therapy (Table 2). Around 46% of clinicians reported a reduction in weight ranging from 2 to 3 kg with vildagliptin + dapagliflozin + metformin therapy (Figure 3).

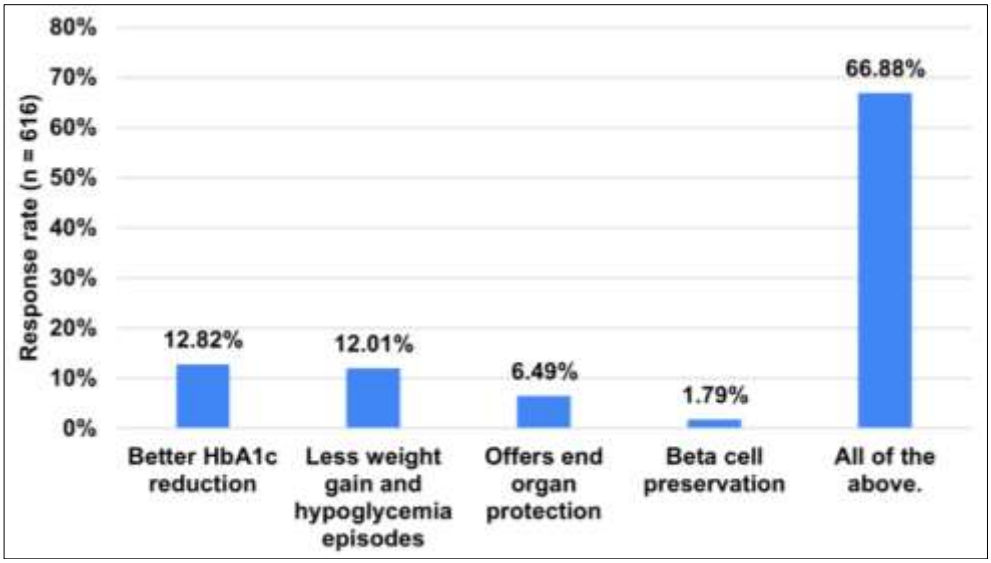

Fig 2: Distribution of responses on the advantages of vildagliptin + dapagliflozin + metformin over glimepiride + metformin + pioglitazone

Table 2: Distribution of responses on the HbA1c reduction observed with vildagliptin + dapagliflozin + metformin therapy

HbA1c level (in percentages)	Response rate (n = 616)
0.5%- 1%	10.06%
1%-1.5%	40.26%
1.5%-2%	35.71%
>2%	13.8%
Do not use	0.16%

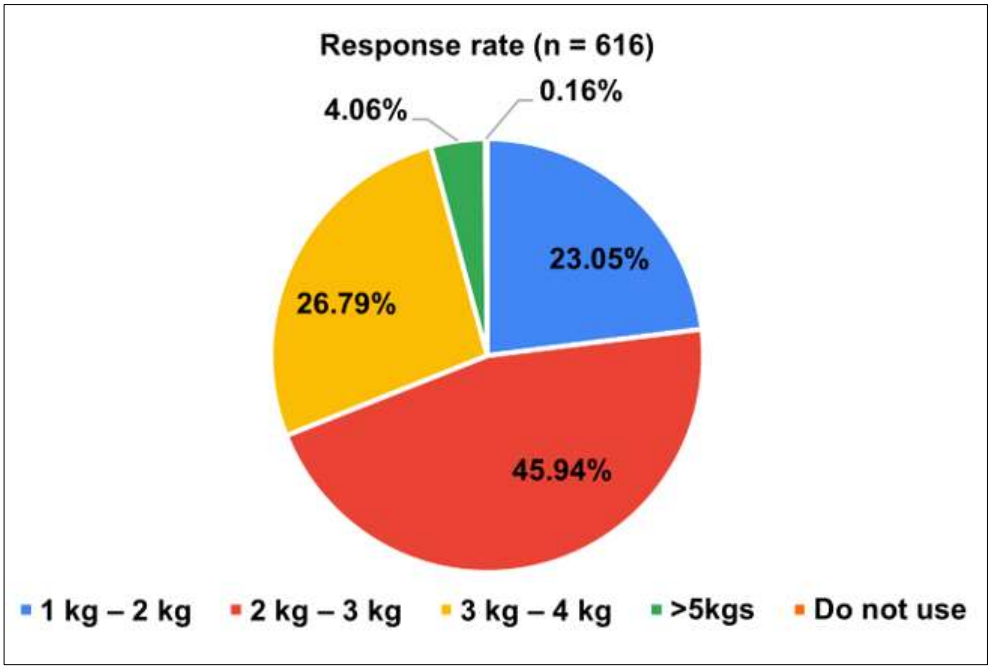

Fig 3: Distribution of responses on the weight reduction observed with vildagliptin + dapagliflozin + metformin

About 38% of clinicians preferred the combination of vildagliptin + dapagliflozin + metformin for patients with stage 2 chronic kidney disease (CKD). Additionally, 35% of clinicians stated that they initiate vildagliptin + dapagliflozin + metformin in approximately 8 to 10 individuals per month. According to 50% of respondents, the incidence of glycemic variability with vildagliptin + dapagliflozin + metformin was rare (Table 3). Furthermore, the majority (63.96%) of respondents reported conducting patient education programs for individuals with high HbA1c (>10%) once a month.

Table 3: Distribution of responses on the incidence of glycemia variability with vildagliptin + dapagliflozin + metformin

Incidence of glycaemic variability	Response rate (n = 616)
Very rare	35.06%
Rare	50.32%
Frequently observed	14.45%
Not used	0.16%

Discussion

The survey findings underscored the preference for the vildagliptin + dapagliflozin + metformin combination in

managing uncontrolled T2DM. The study has also highlighted the importance of achieving target HbA1c levels and the lack of awareness among patients regarding this crucial aspect. HbA1c serves as a reliable indicator of chronic glycemia and was closely linked to the risk of long-term diabetes complications. Therefore, it was currently regarded as the preferred test for monitoring and managing diabetes over the long term. Maintaining HbA1c levels <7% is crucial, as higher levels can indicate the presence of diabetes [16]. Borgharkar *et al*. reported a high burden of uncontrolled diabetes, with 76.6% of patients having poor glycemic control (HbA1c ≥7%; 53mmol/mol) [6]. The present survey has also reported similar findings regarding the increased HbA1c level in T2DM patients.

Majority of the current survey respondents indicated that both genders have high HbA1c levels >10%, with this trend being more prevalent in urban areas. However, there are contradictory findings regarding the association between gender and HbA1c levels. A recent Turkish-based retrospective study by Gülsen *et al*. reported that HbA1c levels were significantly higher in males than females (p<0.001) across all age groups and were positively associated with age for both genders [17]. Conversely, a study conducted by Alzahrani *et al*. found significantly higher levels of HbA1c in women compared to men [18].

Most of the present survey respondents preferred initiating insulin over triple fixed-dose combination therapy. Consistent with this finding, Peyrot *et al*. reported a preference for initiating insulin over triple fixed-dose combination OAD therapy in a specific patient group. The challenges associated with insulin initiation, including non-compliance, the risk of hypoglycemia, discomfort from injections, and treatment costs highlighted by the authors align with the limitations noted in the present survey [19, 20].

Majority of the survey respondents preferred gliptin + SGLT2i + metformin as a triple-drug fixed OAD combination therapy for managing HbA1c among diabetic patients. Similarly, a meta-analysis by Khan *et al*. showed that patients receiving metformin-based combination therapy had greater improvement in glycemic control, as measured by HbA1C, compared to those receiving metformin alone [21]. According to Sahay *et al*., triple combination therapy with gliptin (sitagliptin) + SGLT2i (dapagliflozin) + metformin is significantly more effective in achieving glycemic control compared to dual combination therapy taken once daily. The triple combination therapy did not result in any significant safety concerns [22]. Phung *et al*. found that metformin-based combination therapies with gliptins and SGLT2i significantly reduced HbA1c in T2DM patients [23].

Vashisht *et al*. concluded that metformin combination with SGLT2i and gliptins was associated with lower risks of hypoglycemia. Similarly, Hung *et al*. in a meta-analysis, suggested that combination therapy with metformin + DPP4i+ SGLT2i does not increase the risk of hypoglycemia in patients with untreated T2DM [24]. Additionally, as stated in the study by Chadha *et al*., this combination therapy has been associated with improvements in glycemia and adiposity, as well as a reduction in metabolic and vascular risk [25]. These findings align with similar results reported in the current survey.

The participants in the current survey reported that patients undergoing a 12-month treatment with the combination of glimepiride + metformin + pioglitazone experienced weight gain. Diabetes, being a progressive condition, often requires multiple therapies and combinations for effective blood glucose control. However, the inclusion of pioglitazone in OAD regimens may lead to side effects such as weight gain. In concurrence with this finding, Aghamohammadzadeh *et al*. reported that while pioglitazone significantly decreases HbA1c and triglyceride levels, its association with weight gain could limit its overall utility [26].

The present survey has also highlighted the positive effects of the combination of vildagliptin with metformin and dapagliflozin on HbA1c and weight reduction. Escaño *et al*. concluded that vildagliptin has better glycemic control and weight reduction effects [27]. Similar results were reported by Joen *et al*., where the combination of vildagliptin+ dapagliflozin+ metformin was found to be more effective in reducing HbA1c and weight gain compared to glimepiride, metformin, and pioglitazone [28].

The survey respondents also noted that the incidence of glycaemia variability with vildagliptin + dapagliflozin + metformin is rare. However, there is a lack of studies specifically on the triple combination of vildagliptin with metformin and dapagliflozin. Whereas there are studies on dual therapy showing the effectiveness of vildagliptin in controlling glycemic levels in T2DM patients. For instance, Kalra *et al*. reported that vildagliptin reduces HbA1c levels in T2DM patients, whether used as monotherapy or in dual or triple combination therapy. It also reduces the mean amplitude of glycemic excursion (MAGE), has a lower risk of hypoglycemia, and is weight-neutral. Early combination therapy with vildagliptin and metformin has proven effective and well-tolerated in T2DM patients, irrespective of age or ethnicity [7].

A randomized study by Gautam *et al*. reported that the combination of dapagliflozin and vildagliptin has reduced HbA1c, fasting blood glucose, and postprandial blood glucose levels, with the add-on treatment of vildagliptin showing more pronounced effects than dapagliflozin alone after a 24-week intervention [29]. In another study, Tura *et al*., reported that vildagliptin as monotherapy has improved the glycemic level (p<0.01) [30]. Additionally, Mathew *et al*. found that the dual combination of vildagliptin with metformin provided greater and durable long-term benefits compared to initial metformin monotherapy for patients with newly diagnosed type 2 diabetes [31]. Agrawala *et al*. reported that the vildagliptin-dapagliflozin fixed-dose combination is a promising treatment option for a broad range of Indian T2DM patients. They suggested that patients taking two OADs and experiencing uncontrolled HbA1c levels >8% might be suitable candidates for initiating vildagliptin-dapagliflozin fixed-dose combination therapy [32]. Vildagliptin offers several therapeutic advantages and can serve as an effective combination OAD drug for the management of T2DM. The present study holds significant relevance in understanding prescription patterns, particularly considering the limited literature available on the triple combination of vildagliptin, dapagliflozin, and metformin.

The survey findings underscore the significance of early screening and personalized therapeutic approaches to address the complex challenges associated with glycemic control and shed light on notable trends in prescription practices for diabetes management. A notable 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 gliptin + SGLT2i + metformin as a triple-drug fixed OAD combination therapy, citing significant advantages such as improved glycemic control, reduced hypoglycemia risk, and enhanced end-organ protection. The study also noted the superior efficacy of vildagliptin + dapagliflozin + metformin compared to other combinations, showcasing the advantages such as beta-cell preservation and substantial reductions in HbA1c levels, weight, and incidence of hypoglycemia.

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Author's Contribution

Not available.

Conflict of Interest

Not available.

Financial Support

Not available.

References

1. World Health Organization. Global report on diabetes. Geneva: World Health Organization; c2016 [cited 2024 Mar 12]. p. 83. Available from: https://iris.who.int/handle/10665/204871
2. Chako KZ, Phillipo H, Mafuratidze E, Zhou DT. Significant Differences in the Prevalence of Elevated HbA1c Levels for Type I and Type II Diabetics Attending the Parirenyatwa Diabetic Clinic in Harare, Zimbabwe. Chinese Journal of Biology. 2014 Jan 23;2014:e672980.
3. Anson M, Zhao SS, Essa H, Austin P, Ibarburu GH, Lip GYH, *et al*. Metformin and SGLT2i as First-line Combination Therapy in Type 2 Diabetes: A Real-world Study With a Focus on Ethnicity. Clinical Therapeutics. 2023 Dec 1;45(12):1259-1265.
4. Barman P, Das M, Verma M. Epidemiology of type 2 diabetes mellitus and treatment utilization patterns among the elderly from the first wave of Longitudinal Aging study in India (2017-18) using a Heckman selection model. BMC Public Health. 2023 Apr 14;23(1):699.
5. Pradeepa R, Mohan V. Epidemiology of type 2 diabetes in India. Indian Journal of Ophthalmology. 2021 Nov;69(11):2932-8.
6. Borgharkar S, Das S. Real-world evidence of glycemic control among patients with type 2 diabetes mellitus in India: The TIGHT study. BMJ Open Diabetes Research & Care. 2019 Jul 1;7:e000654.
7. Kalra S, Zargar AH, Sridhar G, Das AK, Ahmed J, Mohan JC, *et al*. Expert eValuation of Efficacy and Rationality of Vildagliptin EVER-Vilda: An Indian Perspective. Clinical Medicine Insights: Endocrinology and Diabetes. 2024 Jan 1;17:11795514231203912.
8. Ballav C, Gough SCL. Safety and Efficacy of Sitagliptin-Metformin in Fixed Combination for the Treatment of Type 2 Diabetes Mellitus. Clinical Medicine Insights: Endocrinology and Diabetes. 2013 Jan 1;6:CMED.S7314.
9. Lee KA, Jin HY, Kim YJ, Kim SS, Cho EH, Park TS, *et al*. Real-world comparison of mono and dual combination therapies of metformin, sulfonylurea, and dipeptidyl peptidase-4 inhibitors using a common data model: A retrospective observational study. Medicine. 2022 Feb 25;101(8):e28823.
10. Hussain M, Elahi A, Iqbal J, Bilal Ghafoor M, Rehman H, Akhtar S, *et al*. Comparison of Efficacy and Safety Profile of Sodium-Glucose Cotransporter-2 Inhibitors as Add-On Therapy in Patients With Type 2 Diabetes. Cureus. 13(4):e14268.
11. Komoroski B, Vachharajani N, Boulton D, Kornhauser D, Geraldes M, Li L, *et al*. Dapagliflozin, a novel SGLT2 inhibitor, induces dose-dependent glucosuria in healthy subjects. Clinical Pharmacology & Therapeutics. 2009 May;85(5):520-526.
12. Kanazawa I, Ichiro TK, Notsu M, Tanaka S, Kiyohara N, Koike S, *et al*. Long-term efficacy and safety of vildagliptin add-on therapy in type 2 diabetes mellitus with insulin treatment. Diabetes Research and Clinical Practice. 2017 Jan 1;123:9-17.
13. Mehta A, Bafna A, Goel S, Trivedi AK, Mishra C, Naik P, *et al*. Diabetes treatment with dapagliflozin and its combinations: Insights from clinical practice. In: Endocrine Abstracts. Bioscientifica; c2023 [cited 2024 Mar 12].
14. Lim S, Ku EJ, Lee SY, Lee JH, Lee JE, Kim KM, *et al*. Therapeutic efficacy and safety of initial triple combination of metformin, sitagliptin, and lobeglitazone in drug-naïve patients with type 2 diabetes: initial triple study. BMJ Open Diabetes Research and Care. 2020 Jan 1;8(1):e000807.
15. Corcoran C, Jacobs TF. Metformin. [Updated 2023 Aug 17]. In: Stat Pearls. Treasure Island (FL): Stat Pearls Publishing; c2024 Jan. Available from: https://www.ncbi.nlm.nih.gov/books/NBK518983/
16. Sherwani SI, Khan HA, Ekhzaimy A, Masood A, Sakharkar MK. Significance of HbA1c Test in Diagnosis and Prognosis of Diabetic Patients. Biomarkers Insights. 2016 Jul 3;11:95-104.
17. Gülsen Ş, Deniz KE, Başak C, Alper G, Yeşil BS, Betül E, *et al*. The effect of age and gender on HbA1c levels in adults without diabetes mellitus. Journal of Medical Biochemistry. 2023 Oct 27;42(4):714-721.
18. India State-Level Disease Burden Initiative Diabetes Collaborators. The increasing burden of diabetes and variations among the states of India: the Global Burden of Disease Study 1990-2016. The Lancet Global Health. 2018 Dec;6(12):e1352-1362.
19. Peyrot M, Rubin RR, Lauritzen T, Skovlund SE, Snoek FJ, Matthews DR, *et al*. Resistance to insulin therapy among patients and providers: results of the cross-

national Diabetes Attitudes, Wishes, and Needs (DAWN) study. Diabetes Care. 2005 Nov;28(11):2673-2679.
20. Chun J, Strong J, Urquhart S. Insulin Initiation and Titration in Patients with Type 2 Diabetes. Diabetes Spectrum. 2019 May;32(2):104-111.
21. Khan RA, Patel N, Folajimi A, Bai BR, Patel V, Komminni PK, *et al*. Comparison of the Efficacy and Safety of Metformin-Based Combination Therapy Versus Metformin Alone in Children and Adolescents With Type 2 Diabetes Mellitus: A Meta-Analysis. Cureus. 2023;15(2):e35014.
22. Sahay RK, Giri R, Shembalkar JV, Gupta SK, Mohan B, Kurmi P, *et al*. Fixed-Dose Combination of Dapagliflozin + Sitagliptin + Metformin in Patients with Type 2 Diabetes Poorly Controlled with Metformin: Phase 3, Randomized Comparison with Dual Combinations. Advances in Therapy. 2023 Jul;40(7):3227-3246.
23. Phung OJ, Sobieraj DM, Engel SS, Rajpathak SN. Early combination therapy for the treatment of type 2 diabetes mellitus: systematic review and meta-analysis. Diabetes, Obesity & Metabolism. 2014 May;16(5):410-417.
24. Hung WT, Chen YJ, Cheng CY, Ovbiagele B, Lee M, Hsu CY, *et al*. Metformin plus a low hypoglycemic risk antidiabetic drug vs. metformin monotherapy for untreated type 2 diabetes mellitus: A meta-analysis of randomized controlled trials. Diabetes Research and Clinical Practice. 2022 Jul 1;189:109937.
25. Chadha M, Das AK, Deb P, Gangopadhyay KK, Joshi S, Kesavadev J, *et al*. Expert Opinion: Optimum Clinical Approach to Combination-Use of SGLT2i + DPP4i in the Indian Diabetes Setting. Diabetes Therapy. 2022 May;13(5):1097.
26. Aghamohammadzadeh N, Niafar M, Dalir Abdolahinia E, Najafipour F, Mohamadzadeh Gharebaghi S, Adabi K, *et al*. The effect of pioglitazone on weight, lipid profile and liver enzymes in type 2 diabetic patients. Therapeutic Advances in Endocrinology and Metabolism. 2015 Apr;6(2):56-60.
27. Escaño AK. Chapter 41 - Insulin, Other Hypoglycemic Drugs, and Glucagon. In: Ray SD, editor. Side Effects of Drugs Annual. Elsevier; c2015 [cited 2024 Mar 13]. p. 521-537.
28. Jeon HJ, Oh TK. Comparison of Vildagliptin-Metformin and Glimepiride-Metformin Treatments in Type 2 Diabetic Patients. Diabetes & Metabolism Journal. 2011 Oct;35(5):529-535.
29. Gautam K, Tripathy R, Meher D, Sahoo JP. Dapagliflozin Versus Vildagliptin as an Adjuvant to Metformin in Patients with Type 2 Diabetes Mellitus: A Randomized, Open-label Study. Cureus. 15(4):e38200.
30. Tura A, Farngren J, Schweizer A, Foley JE, Pacini G, Ahrén B, *et al*. Four-Point Preprandial Self-Monitoring of Blood Glucose for the Assessment of Glycemic Control and Variability in Patients with Type 2 Diabetes Treated with Insulin and Vildagliptin. International Journal of Endocrinology. 2015 Oct 26;2015:e484231.
31. Matthews DR, Paldánius PM, Proot P, Chiang Y, Stumvoll M, Del Prato S, *et al*. Glycaemic durability of an early combination therapy with vildagliptin and metformin versus sequential metformin monotherapy in newly diagnosed type 2 diabetes (VERIFY): A 5-year, multicentre, randomised, double-blind trial. The Lancet. 2019 Oct 26;394(10208):1519-1529.
32. Agrawala RK, *et al*. The Use of Vildagliptin-Dapagliflozin Fixed Dose Combination in Different Patient Profiles in Indian Settings: An Opinion-Based Consensus. International Journal of Clinical and Surgical Research & Reviews. 2023;06(03):2010-2017.

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