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Original Research Article

Preferences and Prescription Practices for Managing Diabetes with a Special Reference to the Clinical Use of Sitagliptin in Indian Settings

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Abstract: ***Background*:** Although there were several clinical studies regarding the effectiveness of sitagliptin, there were dearth of studies on the prescription patterns and practices among clinicians. ***Methodology*:** This cross-sectional study included 19 statements with multiple responses in a pretested questionnaire format to gather and understand the current prescription practices, clinical observation and preferences for managing diabetes with a special reference to the clinical use of sitagliptin in Indian settings. The survey respondents were specialists with expertise in managing diabetes. ***Results*:** According to 49% of clinicians, the preferred drug combination for managing diabetes with hemoglobin A1C (HbA1C) levels >9% is dipeptidyl peptidase 4 inhibitors (DPP4i) + metformin + glimepiride. The majority of clinicians (89.92%) recommended sitagliptin as the preferred gliptin for cardiovascular (CV) protection in diabetic patients. Approximately 38% of clinicians considered established cardiovascular outcome trials (CVOT) and CV benefits as decisive factors in prescribing sitagliptin as a first- or second-line therapy for diabetic patients. Around 72% of clinicians preferred sitagliptin + dapagliflozin as an oral antidiabetic (OAD) combination for type 2 diabetes mellitus (T2DM) patients with chronic kidney disease (CKD). Approximately 42% of respondents reported sitagliptin + metformin as the preferred OAD combination, prescribed as a single pill, for uncontrolled T2DM patients with HbA1c levels >8%. ***Conclusion*:** The study highlighted the prescription trends favoring sitagliptin-based therapies in the management of diabetes, with potential cardiovascular benefits and as first- or second-line OAD therapy. The respondents also emphasized the significance of personalized approaches, such as the sitagliptin + dapagliflozin combination, for T2DM patients with CKD.

Keywords: Cardiovascular Protection, Diabetes, Dipeptidyl Peptidase 4, Metformin, Sitagliptin, T2DM.

INTRODUCTION

Diabetes ranks among the top 10 causes of mortality worldwide, and the associated microvascular and macrovascular complications contribute to organ and tissue damage in approximately one-third to one-half of people [1-4]. According to the World Health Organization (WHO) by 2035, diabetes-related deaths could reach a staggering 592 million, with the global prevalence of type 2 diabetes mellitus (T2DM) expected to rise to 7079 cases per 100,000 individuals by 2030 across all geographical regions [3-5].

According to the International Diabetes Federation (IDF) Diabetes Atlas, the prevalence of T2DM in India has increased tenfold over the past four decades [6]. As per the 2019 estimates, around 77 million individuals in India had diabetes and it is projected to exceed 134 million by 2045 [2]. India ranks second globally in the number of individuals diagnosed with diabetes, with 74.9 million cases among those aged 20-79 as of 2021 and estimates indicate a surge to 124.9 million by 2045. According to the ICMR-INDIAB study encompassing 15 states, diabetes prevalence stands at 7.3%. The study highlights a higher prevalence in urban settings (11.2%) compared to rural areas (5.2%) [7-9].

Achieving the recommended glycemic control in over half of T2DM patients in India remains a challenge, with many failing to maintain the recommended hemoglobin A1C (HbA1c) level of 7%. Due to the progressive nature of T2DM, treatment escalation is often required to maintain glycemic control. However, current medications are not without

drawbacks, such as hypoglycemia and weight gain, underscoring the need for drugs with a more favorable risk/benefit profile [10, 11]. While monotherapy may not suffice over extended periods, combining medications has emerged as a common strategy to achieve optimal glycemic control [12].

In this context, dipeptidyl peptidase 4 (DPP4) inhibitors are increasingly being prescribed in the management of T2DM due to their favorable safety profiles, oral administration, and potential cardiovascular and renal protective effects. These inhibitors function by prolonging the half-life of incretin hormones, such as glucagon-like peptide-1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP), through the inhibition of DPP4 activity. Demonstrating efficacy in reducing HbA1c levels by 0.55–0.88%, DPP4 inhibitors like sitagliptin are effective not only as monotherapy but also when combined with other antidiabetic agents such as metformin, pioglitazone, sulfonylureas (SU), and insulin [13]. Recent studies have shown that sitagliptin alone can reduce HbA1c by 0.5 to 0.7% [14, 15].

Sitagliptin is a highly selective oral DPP-4 inhibitor with an oral bioavailability of 87% and a half-life of 10 to 12 hours. It acts through the incretin pathway in a glucose-dependent manner. The drug has been suggested to be effective and safe for both mono- and combination therapies for older adults with T2DM. Sitagliptin is effective, tolerable, and safe in treating T2DM, either as a monotherapy or in combination with metformin or thiazolidinediones. It helps to lower the levels of HbA1c, fasting, and postprandial glucose and improves beta-cell function [16, 17]. The present survey-based study aims to gather expert opinions regarding the preferences and prescribing patterns for diabetes management, with a special focus on the clinical utilization of sitagliptin within Indian settings.

MATERIALS AND METHODS

This cross sectional, multiple-response questionnaire-based study involved clinicians with expertise in managing diabetes mellitus in the major Indian cities from June 2023 to December 2023. The study was carried out after getting 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 practitioners in treating diabetes mellitus in the month of March 2023 for participation in this Indian survey. About 377 doctors from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provided necessary data. The questionnaire booklet named SIMPLE (Sitagliptin and combinations: Perspective of Indian clinicians in diabetes management) study was sent to the clinicians who were interested to participate. The SIMPLE study questionnaire focused on current feedback, clinical observations, and experiences of specialists in managing diabetes with sitagliptin and its combinations. Clinicians had the option to skip any questions they did not wish to answer and were instructed to complete the survey independently without consulting their colleagues. Written informed consent was obtained from all participants before the study began.

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 included 377 clinicians, with 38% of them reporting that DPP4i is the preferred choice of oral antidiabetics (OAD) in newly diagnosed T2DM patients. Approximately 44% of the respondents opined that 25 to 50% of patients have diabetes with co-morbid conditions such as chronic kidney disorder (CKD), beta-cell dysfunction, peripheral arterial disease (PAD), and coronary artery disease (CAD). Nearly 47% of the clinicians reported that 11 to 20% of patients use continuous glucose monitoring devices.

According to 49% of the clinicians, DPP4i + metformin + glimepiride is the preferred combination choice for diabetes management in patients with HbA1c >9% (Table 1). About 49% of the clinicians agreed that more data is required on the use of statins in diabetic patients, despite numerous guidelines recommending their prescription. Majority of the clinicians (89.92%) opined to use sitagliptin in comparison to the other gliptin for cardiovascular (CV) protection in diabetes patients (Figure 1).

Table 1: Distribution of responses on the preferred choice of combination for diabetes management with HbA1C >9%

Choice of combination	Response rate (n = 377)
Sulfonylureas + metformin	18.04%
Metformin + glimepiride	6.1%
SGLT2i + metformin + glimepiride	24.14%
DPP4i+ metformin + glimepiride	49.07%
DPP4i + metformin	0.8%
Sitagliptin + metformin	0.54%

Choice of combination	Response rate (n = 377)
SGLT2i+DPP4i+metformin	0.54%
Metformin + dapagliflozin + DPP4i	0.27%
SGLT2i + DPP4i + metformin + glimepiride	0.27%

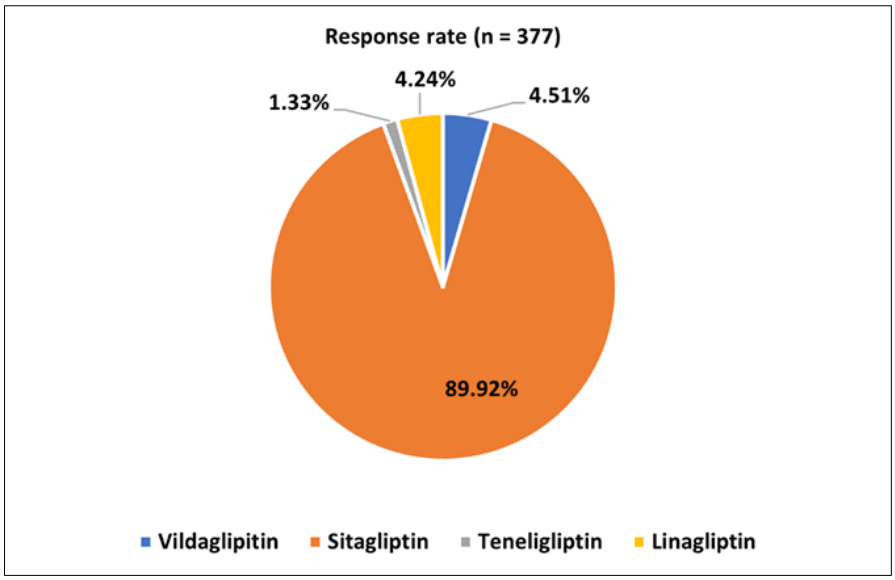

Figure 1: Distribution of responses on the preferred gliptin for CV protection in diabetes patients

About 38% of the clinicians opined that established cardiovascular outcome trials (CVOT) and CV benefits are the characteristics that compel prescribing sitagliptin as the first-line or second-line therapy for diabetic patients (Figure 2). More than half of the clinicians (56.76%) reported gliclazide as the preferred add-on therapy among sulfonylureas (SU) to sitagliptin or dapagliflozin or both, while 42% of them preferred glimepiride. Approximately 58% of the respondents reported using SUs as an add-on therapy to sitagliptin or dapagliflozin or both in patients with HbA1c >9%.

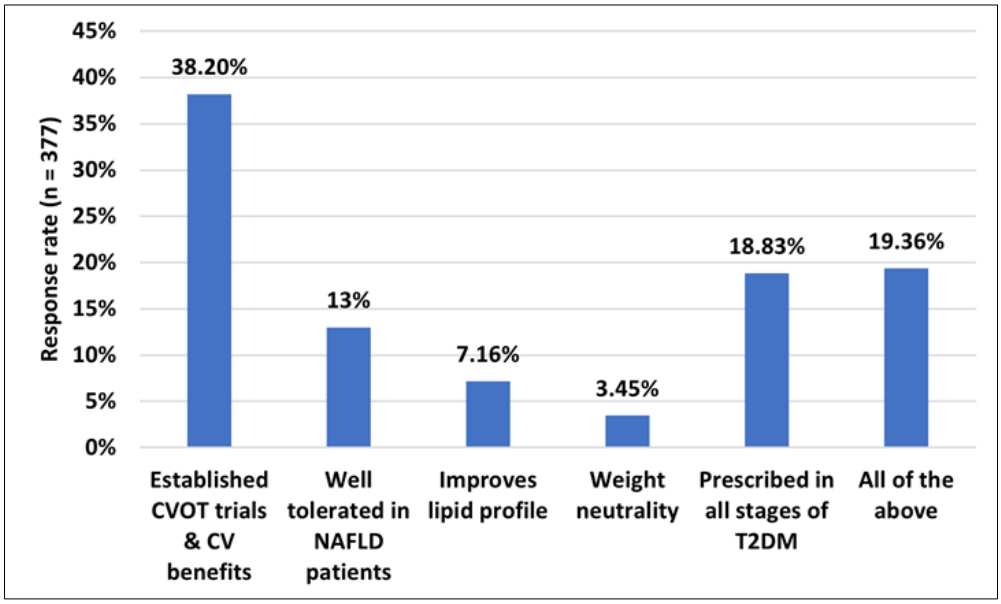

Figure 2: Distribution of responses on the characteristics influencing prescription preference of sitagliptin in T2DM management

About 72% of the clinicians preferred sitagliptin + dapagliflozin as an OAD combination for T2DM patients with CKD (Figure 3). Nearly 62% of the respondents reported that 11 to 25% of patients with T2DM require a triple combination in their clinical practice. As opined by 49% of the clinicians, lifestyle modification is the major factor leading to better therapy outcomes in T2DM patients. More than half (53.05%) of the clinicians responded that 20 to 30% of uncontrolled T2DM patients require multiple classes of drugs to

manage diabetes and other comorbid conditions. According to 42% of the respondents, sitagliptin + metformin is the preferred choice of OAD drug prescribed in combination with sitagliptin as a single pill for uncontrolled T2DM patients with HbA1c >8% (Table 2).

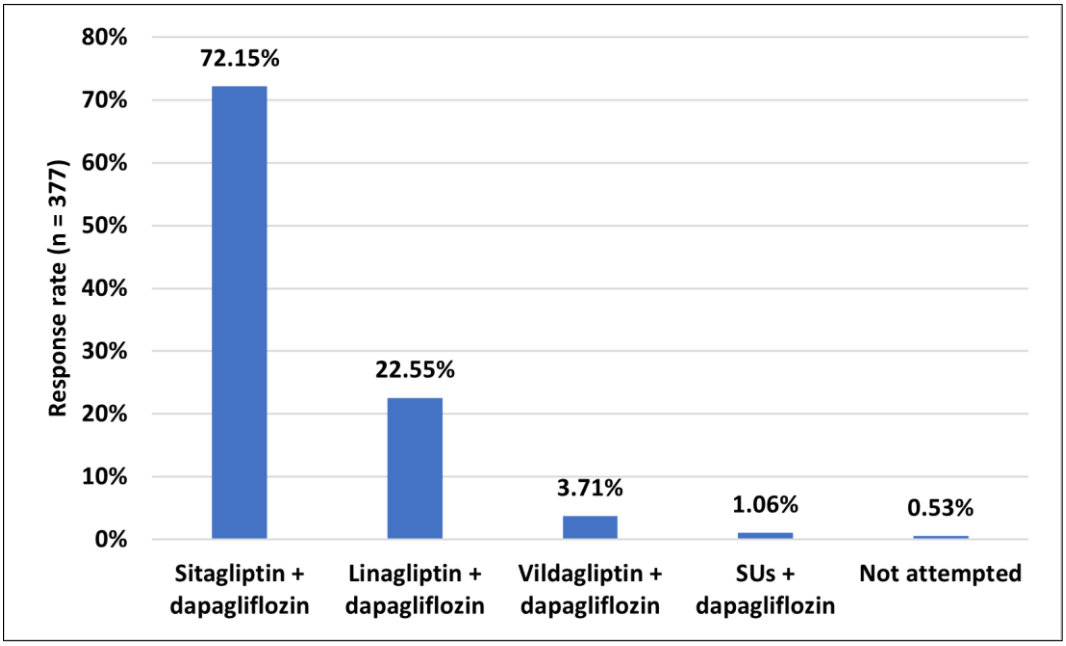

Figure 3: Distribution of responses on preferred OAD combination for T2DM patients with CKD

Table 2: Distribution of responses on the choice of OAD drug to be prescribed in combination with sitagliptin as a single pill in uncontrolled T2DM patients with HbA1c >8% (rank wise)

OAD drugs	Response rate (n = 377)
Sitagliptin + metformin - (Rank 1)	42.44%
Sitagliptin + dapagliflozin - (Rank 2)	15.38%
Sitagliptin + dapagliflozin + metformin - (Rank 3)	29.97%
Sitagliptin + glimepiride + metformin - (Rank 4)	10.61%
Sitagliptin + pioglitazone + metformin - (Rank 5)	1.59%

About 55% of clinicians responded that, in real-world practice, T2DM patients treated with SGLT2 inhibitors typically experience a weight reduction of 2 to 4 kg. Nearly 66% of the clinicians opined that diabetes patients require frequent counseling to reduce the diabetes burden. According to 49% of the respondents, counseling by dietitians is a more beneficial medium for patient awareness and diet charts to control diabetes. About 46% of the respondents moderately agreed, and 33% strongly agreed that telemedicine or teleconsultation is an integral part of diabetes management. As reported by 31% of the clinicians, the most challenging aspect in managing T2DM is compliance with regular diet and exercise, while 30% of them opined compliance with regular consumption of OAD as the challenging aspect.

DISCUSSION

The present survey findings indicated a strong preference for the use of sitagliptin in various contexts of diabetes management, including its use in combination therapies and its role in cardiovascular protection. Additionally, the inclusion of dapagliflozin alongside sitagliptin is favored for T2DM patients with CKD. Most of the clinicians reported DPP4i + metformin + glimepiride as the preferred combination choice of drugs in patients with HbA1C >9%. Similar to this finding, Hermansen *et al*., reported that sitagliptin is effective in reducing HbA1c, fasting glucose, and post-prandial glucose (PPG) when used in dual combination with glimepiride alone and triple combination with glimepiride plus metformin over 24 weeks [18]. Kisioglu *et al*., reported that the addition of DPP4i such as sitagliptin to metformin and glimepiride is an effective and well-tolerated option for patients with T2DM. The study found a significant reduction in HbA1c levels at 3 months (P <0.001), 6 months (P <0.001), and 12 months (P <0.003) [19].

The current survey respondents recommended considering sitagliptin as the preferred gliptin for providing CV protection in individuals with diabetes. A pooled analysis of 25 randomized clinical trials by Engel *et al*., concluded that sitagliptin did not show any risk of CV-related events in T2DM patients [20]. Picatoste *et al*., noted that apart from the antiglycemic effects, sitagliptin treatment helps in improving cardiac function by reducing cardiac apoptosis, fibrosis, and hypertrophy

[21]. Nakamura *et al*., noted that individuals with diabetes and multiple CV risk factors experienced a reduction in blood pressure when treated with sitagliptin. This was accompanied by an improvement in albuminuria, in addition to achieving effective glycemic control [22].

The majority of current survey respondents favored the addition of SUs like gliclazide and glimepiride as add-on therapy with sitagliptin. Furthermore, the study noted that the addition of SUs as add-on therapy to sitagliptin, dapagliflozin, or both is a common practice in patients with HbA1c levels >9%. Harashima *et al*., also found that combining sitagliptin with a low dose of SU (such as glimepiride or gliclazide) is both safe and effective for controlling blood sugar levels, with the glucagon loading test revealing preserved insulin secretion capacity after one year of therapy [23]. Similarly, Zhao *et al*., reported that the combination of glimepiride with sitagliptin is highly effective in the treatment of T2DM patients, which can effectively improve the blood glucose level and oxidative stress [24]. Strojek *et al*., revealed that dapagliflozin added to glimepiride improved glycemic control and body weight [25]. Additionally, Anderson *et al*., reported significant reductions in HbA1c, FPG, and body weight when dapagliflozin was added to oral therapies of glimepiride and sitagliptin compared with placebo [26].

The findings of the trial evaluating cardiovascular outcomes with sitagliptin (TECOS) by Scirica et.al demonstrated that sitagliptin did not increase the risk of major adverse cardiovascular events (MACE) in patients with T2DM and established CV disease [27]. Bethel *et al*., also concluded that sitagliptin had a negative impact on CV among older patients with well-controlled T2DM and CV disease, resulting in no significant safety concerns [28]. The present study also establishes that CVOT and CV benefits make sitagliptin a preferred option as a first- or second-line therapy for diabetic patients.

Majority of the current survey respondents advocated sitagliptin + dapagliflozin as the preferred OAD combination for T2DM patients with CKD. In line with this, Mehta *et al*., also reported their preference to prescribe dapagliflozin+ sitagliptin fixed-dose combinations (FDC) for T2DM patients with CKD [29]. Based on renal safety evidence, Gupta *et al*., also concluded on the therapeutic potential of dapagliflozin and sitagliptin in treating diabetes in CKD patients [29]. A meta-analysis by Liu *et al*., concluded the effectiveness of sitagliptin in reducing proteinuria, improving renal function, and exerting an anti-inflammatory effect in individuals with early-stage diabetic nephropathy [30].

The present survey reported that sitagliptin + metformin is the preferred choice of OAD drug, prescribed as a single pill, in uncontrolled T2DM patients with HbA1c >8%. In concurrence with this finding, Brazg *et al*., in their randomized, double-blind, placebo-controlled, two-period crossover study noted that sitagliptin and metformin resulted in a greater reduction in fasting plasma glucose (FPG) levels [31]. Hayes *et al*., stated that the combination of sitagliptin and metformin has been demonstrated to significantly lower HbA1c to a greater extent. The combination has been found to be safe and well tolerated and with the availability of a single-pill FDC provides ease of use and prescription [32]. Kim *et al*., found that sitagliptin with metformin as an initial treatment resulted in significantly greater improvements in glycemic control and body weight changes, with a lower incidence of hypoglycemia, over 30 weeks [33]. Ballav *et al*., concluded that FDCs of metformin and sitagliptin have a beneficial effect on HbA1c, fasting, and postprandial glucose. The FDC is convenient, well tolerated with minimal side effects, demonstrates a low incidence of hypoglycemia, and does not cause weight gain [34].

The current survey provides valuable insights for clinicians in optimizing treatment strategies and patient care based on the preferences and prescription practices noted in the present survey findings. One of the major strengths of the current survey is the use of a well-designed and validated questionnaire for collecting data from clinicians. However, it is important to recognize certain limitations of the survey. The reliance on expert opinion introduces the possibility of bias, as diverse perspectives and preferences among clinicians may have influenced the reported results. It is essential to consider these limitations when interpreting the findings. The current survey may not capture evolving trends or emerging evidence in diabetes management. To address this limitation, prospective trials or real-world observational studies are warranted to corroborate the survey results and provide a more comprehensive understanding of optimal treatment approaches.

CONCLUSION

The survey findings emphasized significant trends in prescription practices for managing diabetes, with a notable preference for certain drug combinations, particularly sitagliptin-based therapies, among clinicians. The emphasis on sitagliptin for cardiovascular protection and as first- or second-line oral antidiabetic (OAD) therapy underscored its role in holistic diabetes management strategies. Moreover, there were more preference for the sitagliptin + dapagliflozin combination in T2DM patients with CKD highlighted the importance of tailored treatment approaches for specific patient populations.

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Declarations
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