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Original Research Article

Management of type 2 diabetes mellitus: insights into prescribing trends

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ABSTRACT

Background: Recently, management of type 2 diabetes mellitus (T2DM) has changed with advent of novel agents like DPP4i, SGLT2i and GLP-1 agonist. Of these, DPP4i have emerged as promising agents as monotherapy and as an add-on to metformin for improved glycaemic control. This survey was planned to explore current prescribing trends of physicians of India for the management of T2DM.
Methods: This was a prospective, cross sectional, questionnaire-based survey of physicians and endocrinologist across different geographic areas in India. A survey questionnaire consisting of 10 questions related to management of T2DM in real-world clinical settings was prepared, validated in a small group of physicians and then administered to physicians and endocrinologists.
Results: Responses from 502 physicians were received. About 60% physicians prefer DPP4i as first add-on to metformin followed by sulfonylurea (SU) (30%). Amongst DPP4i, vildagliptin and sitagliptin were preferred by 48% and 28% physicians respectively as first add-on to metformin. For patients uncontrolled on metformin + SU therapy, 54 % physicians prefer DPP4i as second add-on. Vildagliptin is perceived to have the better efficacy and safety data, as suggested by 40% and 43% physicians respectively. Large number of physicians (48%) were hesitant to prescribe teneligliptin due to insufficient data. SGLT2 inhibitors are preferred as third add-on by 44% physicians.
Conclusions: DPP4i are being increasingly preferred by physician as an add-on to metformin. Among DPP4i, the survey revealed that vildagliptin is the most preferred DPP4i as an add-on to metformin possibly owing to its established safety and efficacy data.

Keywords: DPP4 inhibitors, Type 2 diabetes mellitus, Vildagliptin

INTRODUCTION

Type 2 diabetes mellitus (Type 2 DM), is a chronic metabolic disorder of complex pathophysiology with worldwide prevalence.[1] There is an expected rise in prevalence of T2DM in Asia over the next 20 years due to a sedentary lifestyle combined with the increase in obesity and overweight resulting from economic development and the changes in diet.[2] Inadequate control of blood glucose in these patients will directly correlate with higher risk for cataracts, retinopathy, neuropathy, and other diabetic microvascular complications.[2] A stepwise treatment approach for diabetes is recommended by various clinical practice guidelines. The primary treatment approach involves lifestyle modifications such as weight reduction, dietary adjustments, and physical exercise followed by initiation of pharmacotherapy.[1] For initiation of monotherapy, metformin is recommended as the preferred oral anti-hyperglycemic agent in most patients with T2DM by American Diabetes Association (ADA).[3] Although monotherapies can provide initial

glycemic control, they have failed to demonstrate effectiveness in maintaining long-term glycemic control because of progressive deterioration of β-cell function.[1,4] This inability of monotherapy to maintain good glycemic control in T2DM provides the rationale for the early use of combination therapy with different classes of drugs.[4] Combination therapy imparts various advantages such as lower doses than those required for individual monotherapies, reduction in adverse effects associated with higher doses of monotherapy and thus improved tolerability.[1]

Advent of novel agents like dipeptidyl peptidase-4 inhibitors (DPP4i), sodium-glucose transport protein 2 inhibitors (SGLT2i) and glucagon-like peptide-1 (GLP-1) agonist have changed the management of diabetes to great extent. Of these, DPP4i have emerged as promising agents as monotherapy and as an add-on to metformin for improved glycemic control. The ADA/European Association for the Study of Diabetes (EASD) position statement and the American Association of Clinical Endocrinologists/American College of Endocrinology algorithm also suggest the use of DPP-4 inhibitors as an add-on when HbA1c target is not achieved with metformin monotherapy.[4] Previous EDGE study has shown that in a 'real-life' setting, vildagliptin can lower HbA1c to target more frequently than comparator oral hypoglycemic agents (OHA) with better safety profile.[5]

However, there is no clarity on which particular class of OHA to be preferred in patients uncontrolled on metformin and which particular drug be selected amongst the class for varying groups of patient population. Therefore, this survey was planned to explore current prescribing trends of physicians in 'real world' for the management of diabetes mellitus considering newer treatment options.

METHODS

This was a prospective, cross sectional, questionnaire-based survey of physicians and endocrinologist seeing patients of T2DM across different geographic areas in India. The survey questionnaire consisted of 10 questions related to management of diabetes in real-world clinical settings, designed to analyze the approach of Indian practitioners for the management of T2DM. The questions were pertaining to preferred oral hypoglycemic agent of choice, preferred sulfonylurea and DPP4i of choice as an add-on to metformin in patients who are uncontrolled on metformin monotherapy; perception about availability of better safety and efficacy data amongst DPP4i; preferred DPP4i in patients with renal failure and heart failure; perception about usage of recently introduced teneligliptin and feedback on current place of newer OHA like SGLT2 inhibitors in the management of T2DM. The questionnaire was later validated in a small group of physicians and then administered to physicians and endocrinologists at the 71st annual conference of the association of physicians of India (APICON) 2016, Hyderabad, Andhra Pradesh, India. Delegates attending APICON conference were approached, explained the objective of doing the study and those willing to provide their opinion were given the questionnaire. No remuneration was given to the participants for filling these survey questionnaires. The completed questionnaire was collected and analyzed. Number of responses to each question was categorized and percentages for all the responses were calculated. Missing data was not considered for calculating percentages. Data were expressed in n (%).

RESULTS

A total of 502 physicians and endocrinologists who were managing T2DM patients in routine clinical practice were surveyed. About 60% physicians preferred DPP4i as first add-on to metformin followed by preference to sulfonylurea (SU) by 31% physicians (Figure 1).

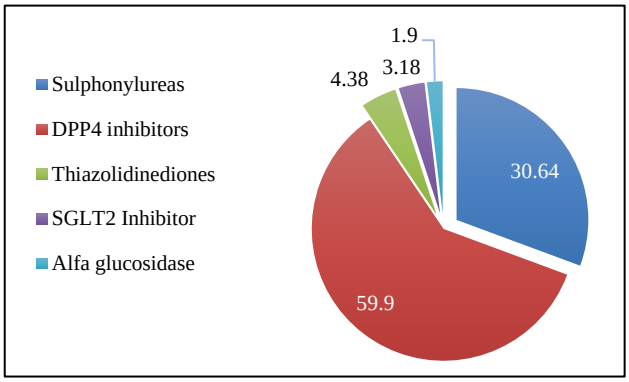

Figure 1: Preferred oral hypoglycemic agents for patients uncontrolled on metformin (%).

Amongst DPP4i, vildagliptin and sitagliptin were preferred by 48% and 28% physicians respectively as first add-on to metformin (Figure 2).

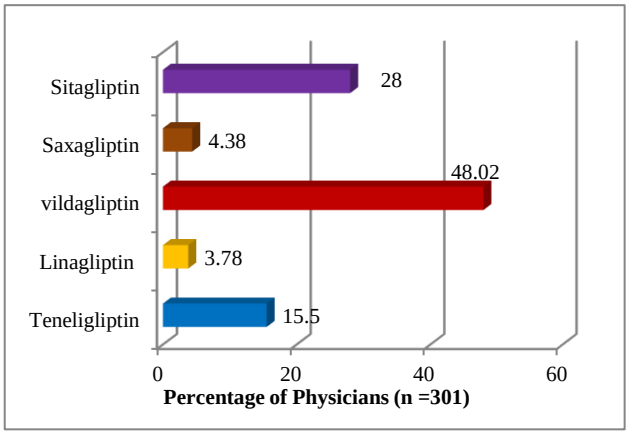

Figure 2: Preferred DPP4i as add-on to metformin.

Whereas, glimepiride (48%) was the most preferred choice amongst sulfonylureas followed by glibenclamide (24%) and gliclazide (18%). DPP4i emerged as the most

preferred second add-on (54%) in the patients uncontrolled on combination of metformin + SU (Figure 3).

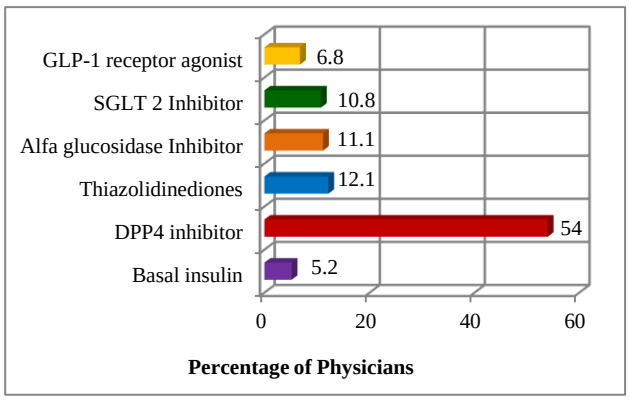

Figure 3: Preferred choice of drug in patient not controlled on combination of sulfonylurea and metformin.

Amongst the DPP4i, vildagliptin has better efficacy and safety data as opined by 40% and 43% physicians respectively. Sitagliptin was ranked second by physicians in terms of efficacy (32%) and safety (37%) (Figure 4).

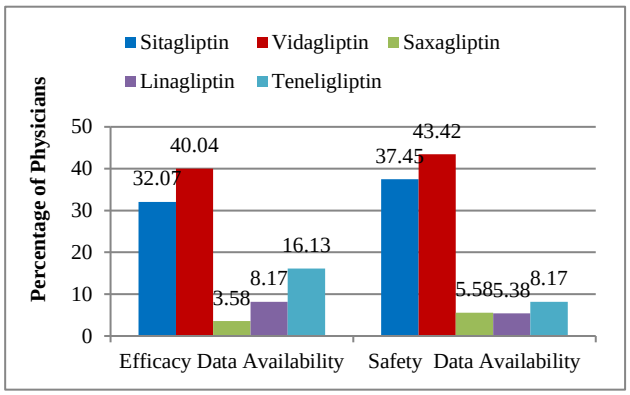

Figure 4: Physician's perception on availability of efficacy and safety data of DPP4i.

Vildagliptin was more preferred by most of the physicians for diabetic patients with heart failure (37%) than sitagliptin (33%). Teneligliptin (15%) and saxagliptin (3%) were the least preferred choices for these subsets of diabetic patients. Similarly, in diabetic patients with renal failure, the most preferred choice of the physicians was vildagliptin (35%) followed by sitagliptin (24%). Teneligliptin (11%) and saxagliptin (7%) were the least preferred choices for these subsets of diabetic patients.

Though teneligliptin usage appears to be slowly increasing because of its low cost, still almost half of the surveyed of physicians (48%) were hesitant to prescribe it due to unavailability of adequate data. Only 9% of physicians were convinced about available efficacy and safety data of teneligliptin. Majority (44%) of the physicians considered the use of SGLT2 inhibitors as a third add-on OHA in management of T2DM rather than first add-on (15%).

DISCUSSION

This study aimed to analyze the current perspective and preferences for different OHA of Indian practitioners in management of T2DM. As recommended by ADA 2016 guidelines, metformin is the initial drug therapy for T2DM.[3,6] However, due to the progressive nature of T2DM, long-term glycemic control is difficult to achieve with a single agent, thus often requiring addition of further agents.[7] SUs, thiazolidinediones (TZDs), DPP4i, GLP-1 receptor agonists, SGLT2 inhibitors and Insulin are the add-on drugs to metformin recommended in case of inadequate glycemic control.[3,6] Although the guidelines has not given any preference for choosing these various agents as an first add-on to metformin in metformin-intolerant patients or those with poor glycemic control, this study has revealed that that most of the physicians preferred DDP4i as the first add-on to metformin.

Currently available anti-diabetic drugs have certain limitations. SUs have short durability of glycemic control with increased risk of weight gain and hypoglycemia, while TZDs are associated with increased risk of weight gain, fractures, edema and heart failure in susceptible individuals as seen in a previous study.[6] Though GLP-1 receptor agonists are associated with low risk of hypoglycemia and weight loss, the frequency of hypoglycemia increases in combination with SU and insulin.[6] Moreover, there is some concern over the safety profile of these drugs due to proliferative effects in the pancreas and continuing report of upper respiratory tract infection.[8] DPP4i is a new class of OHA showing improvement in beta cell function and suppression of glucagon, hence, leading to improvement in post-prandial and fasting hyperglycemia.[9] Gliptins act by enhancing the function of incretin system and reducing metabolism of glucagon-like peptide 1 (GLP-1) and glucose-dependent insulinotropic polypeptide (GIP) by inhibition of dipeptidyl peptidase-4 (DPP-4).[9] Along with being efficacious and safe (low risk of hypoglycemia), they are also weight neutral, making them a unique class of drugs.[9]

The available evidences suggest that combination of DPP-4 inhibitor with metformin provides beneficial effects due to their complementary mechanisms of action along with effective lowering of HbA1C, improvement in beta cell function, low risk of hypoglycemia and low risk of weight gain.[6,10] A meta-analysis by Mishriky et al has shown that while both SU and DPP4i cause a significant reduction in HbA1c, there was a preference for DPP4i over SU from safety point of view and suggested caution in the use of SU.[11] Additional findings in this study suggested that though SU produce greater short-term reduction in HbA1c, this benefit occurs with a

significantly higher risk of hypoglycemia and weight gain and the greater HbA1c reduction may not persist long-term.[11] Also as compared to voglibose, DPP4i has been shown to provide superior HbA1c reduction with better tolerability.[12] Thus, DPP4i owing to its better efficacy and safety than other OHA, was the preferred option as an add-on to metformin amongst the practitioners in case of inadequate glycemic control.

Amongst the DPP4i, vildagliptin was the preferred choice of DPP4i followed by sitagliptin. Various studies have proved that vildagliptin 50mg bid added to metformin improves the glycemic control without any tolerability issues and hypoglycemia.[7,13] Optima study has shown that vildagliptin affords better circadian glucose control than sitagliptin, as an add-on to metformin in moderately controlled T2DM patients.[14] Also, PROVIL study has shown that absolute decrease in HbA1c and fasting blood glucose was significantly more pronounced in patients receiving vildagliptin add-on to metformin than in patients receiving other OHA as add-on to metformin.[15] Thus, better efficacy and safety of vildagliptin over other DPP4i has been well established in controlled clinical trials justifying the choice of surveyed participants.

Amongst SUs, glimepiride was more preferred by physicians than glibenclamide and gliclazide. This preference of physicians is well supported by a study done by González-Ortiz M et al.[16] In this study, it was found that glimepiride/metformin demonstrated being more efficacious than glibenclamide/metformin at reaching the glycemic control goals with less hypoglycemic events in patients with uncontrolled T2DM.[16] Also, it has been observed that glimepiride was associated with fewer episodes of severe hypoglycemia than glibenclamide in routine clinical use and a significantly greater decrease in body weight and body mass index than treatment with glibenclamide.[17,18]

DPP4i were also the most preferred second add-on OHAs in patients uncontrolled on Met + SU. A study has recommended use of DPP4i as an option for add-on therapy to metformin and metformin plus a sulfonylurea, a thiazolidinedione, or Insulin.[6] Amongst DPP4i, Vildagliptin has shown to produce greater reduction in HbA1c levels when used as a second add on in comparison to other gliptins as seen in a previous study.[2] The proclivity in use of vildagliptin would be because of availability of adequate efficacy and safety data through various studies.[7,19-21]

Patients with T2DM are at 2-4 fold increased risk of cardiovascular morbidity and mortality compared to patients without T2DM.[22-24] One of the goals of the ADA/EASD recommendations is to make comprehensive cardiovascular (CV) risk reductions as a major focus of therapy.[6] This definitely highlight the importance of those anti-diabetic drugs that do not increase CV risk but might reduce the risk of CV events. Therefore, careful selection of OHA paying particular attention to CV safety is crucial in optimizing diabetic therapy. In this study, it was observed that majority of the practitioners preferred the use of vildagliptin in heart failure patients. To assess CV safety profile and heart failure (HF) risk of Vildagliptin, a meta-analysis was done by McInnes G et al from a large pool of studies, including trials in high-risk patients with T2DM, such as those with congestive HF and/or moderate/severe renal impairment.[25] Of 9599 patients who received vildagliptin, major adverse CV events (MACEs; myocardial infarction, stroke and CV death) occurred in 83 (0.86%) vildagliptin-treated patients and 85 (1.20%) comparator-treated patients, thereby suggesting that no significant increased risk of HF was seen in vildagliptin-treated patients.[25] SAVOR-TIMI 53 trial showed that more patients in the saxagliptin group than in the placebo group were hospitalized for heart failure (3.5% vs. 2.8%; hazard ratio, 1.27; 95% CI, 1.07 to 1.51; P=0.007), thereby suggesting higher heart failure risk with saxagliptin.[26]

Hyperglycemia is also a major risk factor in development of renal failure and end stage renal disease (ESRD).[27] The problem for the appropriate selection of OHA for patients with diabetes and chronic kidney disease is usual in every day clinical practice. The risk of hypoglycemia, which is higher in subjects with both diabetes and CKD, leads to selection of apt OHA with low risk of hypoglycemia such as metformin and DPP-4 inhibitors. Our study findings suggest that vildagliptin is preferred over other DDP4 inhibitors in diabetic patients with mild to moderate renal failure. Thus, the available data of proven efficacy and safety of vildagliptin in both these conditions (heart failure and renal failure) well support preferences of physicians for vildagliptin in real clinical practice.[19,20,25,27-29]

As outlined with the new recommendations from the ADA/EASD, there is the suggested option of adding SGLT2 inhibitors to the background of metformin or SU plus metformin if glycemic goals are not met. Though this class of drugs are growing in popularity, the FDA issued a number of warnings linking them to serious side effects like ketoacidosis, acute kidney injury and urinary tract infections that could lead to blood infections. In our study, we observed that SGLT2 inhibitors were considered as a third add-on by most of the physicians, which might be due to these raising concerns requiring caution and further evaluation as observed in a recent study.[30]

Teneligliptin being newest DPP4i approved in India and relatively cheaper than other DPP4i, it appears to be tempting the practitioners for widespread use. However, real-life experience suggests that large number of physicians were hesitant to prescribe teneligliptin due to unavailability of adequate efficacy and safety data. The current evidence for cardio-protective effects of teneligliptin is only from short term and small sample size studies.[31] As came out prominently from this study about the need for more efficacy and safety data before

practitioners really start prescribing teneligliptin with confidence, vildagliptin will continue to have an edge over teneligliptin terms of large evidence-based efficacy and safety, convenience of initiating therapy with metformin, good tolerability as dual or triple therapy or in combination with insulin, established renal and cardiac safety, negligible drug interactions and large evidence of safety in Indian patients.

Limitations

The limitation of the present study is that it is based on questionnaire and not data based as in a real-world situation, where the clinic/ hospital based records are analyzed. This data collection is from physicians attending APICON 2016, which is a representation of a group of physicians and not a survey across the country. This survey may not represent primary and tertiary care physicians like diabetologists and endocrinologists.

CONCLUSION

As per the survey findings, DPP4i are the preferred choice amongst OHA as an add-on in patients uncontrolled on metformin/ metformin with SU. Among the DPP4i, the survey revealed that vildagliptin is the most preferred DPP4i as an add-on to metformin possibly owing to its established safety and efficacy data. Further research should continue to document changes in diabetes management trends, especially given the increasing number of medications available.

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