ISSN 2664-3987 (Print) & ISSN 2664-6722 (Online)
South Asian Research Journal of Medical Sciences
Abbreviated Key Title: South Asian Res J Med Sci

| Volume-6 | Issue-1 | Jan-Feb -2024 | **DOI: 10.36346/sarjms.2024.v06i01.003**

Original Research Article

Prescription Trends on the Preference of Hypoglycemic Agents for the Management of Diabetes Mellitus in India

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Article History
Received: 07.01.2024
Accepted: 12.02.2024
Published: 14.02.2024

Abstract: The management of type 2 diabetes requires multifactorial approach in terms of diet, lifestyle modification and pharmacological treatment to prevent or delay complications and maintain the quality of life. Several studies have been conducted to enhance the treatment of type 2 diabetes. However, there was a lack of data regarding the prescription pattern of antidiabetics among clinicians. So, a cross-sectional, questionnaire based study was conducted to gather information about the prevalence, risk factors, and management of diabetes within a population. The data was collected from 551 doctors across all over India. About 44% doctors reported that 5-10 patients per week were newly diagnosed with type 2 diabetes. In this study, 66% of the doctors reported cardiovascular events as a major complication and 28% of the doctors reported renal complications in uncontrolled type 2 diabetes patients. 48% of the 551 clinicians used DPP4 inhibitors as an add on, followed by 30% who reported the use of SGLT2 inhibitors. Notably, 92% of the participants reported urinary tract infection as the most common undesirable effect in their patients, with the usage of dapagliflozin. Nearly 30% of the clinicians in our survey have prescribed SGLT2 inhibitors for patients who are at >50% risk of developing chronic kidney disease. The results from our study, stated that most of the clinicians use DPP4 inhibitors and SGLT2 inhibitors as an add on to metformin in patients with a failure to control the glycaemic index. Dapagliflozin is prescribed not only to control the glycaemic index but also to reduce the hospitalization due to heart failure and other cardiovascular and renal co-morbidities.

Keywords: SGLT2 Inhibitors, DPP4 Inhibitors, Type 2 diabetes mellitus, Cardio-renal complications, Dapagliflozin.

INTRODUCTION

Type 1 diabetes occurs predominantly in young people (diagnosis at 30 years of age or younger) and is usually precipitated by autoimmune destruction of insulin-producing pancreatic beta cells, leading to insulin deficiency and an absolute need for exogenous insulin replacement [1]. Type 2 diabetes is a progressive metabolic disease that is characterized by insulin resistance and eventually failure of functional pancreatic beta cells [2]. The common complications associated with type 2 diabetes mellitus are atherosclerotic cardiovascular disease, heart failure, and chronic kidney disease [3].

The treatment of type 2 diabetes requires multifactorial approach in terms of diet, lifestyle modification and pharmacological treatment to prevent or delay complications and maintain the quality of life. The choice of glucose-lowering agents in type 2 diabetes should be individualized based on comorbidities and risk of adverse effects. Metformin has high efficacy in lowering HbA1c, minimal hypoglycemia risk when used as monotherapy, weight neutrality with the potential for modest weight loss, good safety profile, and low cost. Hence, it has traditionally been recommended as first-line glucose-lowering therapy for the management of type 2 diabetes. On the other hand, sulfonylureas have a high glucose-lowering efficacy and inexpensive [4]. However, due to their glucose-independent stimulation of insulin secretion, they are associated with an increased risk for hypoglycemia.

Further, dipeptidyl peptidase 4 (DPP4) inhibitors are oral medications that inhibit the enzymatic inactivation of endogenous incretin hormones, resulting in glucose-dependent insulin release and a decrease in glucagon secretion [5]. The sodium–glucose cotransporter 2 (SGLT2) inhibitors are oral medications that reduce plasma glucose by enhancing urinary excretion of glucose. Their scope of use has significantly expanded based on cardiovascular and renal outcome studies [4]. These studies have demonstrated a reduction in the risk of composite major adverse cardiovascular events, cardiovascular death, myocardial infarction, hospitalization for heart failure, and all-cause mortality and improvement in renal outcomes in individuals with type 2 diabetes with an established/high risk of CVD with the use of SGLT2 inhibitors.

The combination therapy has several potential advantages, including increased duration of the glycemic effect, simultaneous targeting of the multiple pathophysiological processes and complementary clinical benefits (e.g., on glycemic control, weight and cardiovascular risk profiles) [6]. The multinational VERIFY trial has shown that combination of two glucose lowering drugs at the start of treatment can improve blood glucose levels and delay the need for insulin [7]. So, this study was conducted to gain information about the disease, prevalence, risk factors and recent trends in the management of type 2 diabetes mellitus.

MATERIALS AND METHODS

A cross sectional, questionnaire based survey was carried out among physicians involved in treating diabetes mellitus in the major Indian cities from June 2022 to December 2022.

Questionnaire

The questionnaire booklet named CROWN (Clinical expeRience of Indian Physicians in T2DM subjects With DapaglifloziN) study was sent to the clinicians who were willing to participate in this study. The CROWN study questionnaire was used to obtain information about the prevalence, patient awareness of the disease, its consequences and recent trends in the management of type 2 diabetes. The study was conducted after getting approval from Bangalore Ethics, an Independent Ethics Committee which is recognized by the Indian Regulatory Authority, Drug Controller General of India.

Participants

An invitation was sent to leading clinicians in treating diabetes mellitus in the month of March 2022 for participation in this Indian survey. About 551 doctors from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provide necessary data. Practitioners were requested to complete the questionnaire without discussing with peers. A written informed consent was obtained from each clinician before initiation of the study.

Statistical Analysis

The data were analyzed using descriptive statistics where the categorical variables were presented as percentages to provide a clear understanding of their distribution. The frequency of occurrence and the corresponding percentage were used to represent the distribution of each variable. Microsoft Excel was used to visualize the distribution of the categorical variables, pie, and bar charts.

RESULTS

In this survey, 48% of the clinicians observed newly diagnosed diabetic patients in the age group of 41-50, 39% of them observed in 31-40 groups, 10% of them in 51-65% and only 2% in 20-30 groups. About 44% doctors reported that 5-10 patients per week were newly diagnosed with type 2 diabetes, 29% of them noted 10-20 cases per week and 15% of them observed less than 5 cases per week. Further, it was seen that 43% of the clinicians reported that only 25-50% of their patients were aware about diabetes and its consequences, 32% of them in 10-25% of their patients and 21% of them in 50-75% of the individuals.

It was notable that 34% of the physicians reported a reduction of insulin usage by around 16-20% in their patients with the use of recent advances in oral anti-diabetic drugs like SGLT2 inhibitors and DPP4 inhibitors (Figure 1). 58% of the respondents reported that they have been using DPP4 inhibitors in their clinical practice since last 5-10 years and 23% of them were used more than 10 years (Figure 2). About 66% of the doctors reported cardiovascular events as a major complication and 28% of the doctors reported renal complications in uncontrolled type 2 diabetes patients. Only 3% of the doctors each reported retinopathy and stroke. Also, it was seen that 48% of the 551 clinicians used DPP4 inhibitors as an add on therapy, followed by 30% who reported the use of SGLT2 inhibitors and the remaining 22% who reported the use of sulphonylureas.

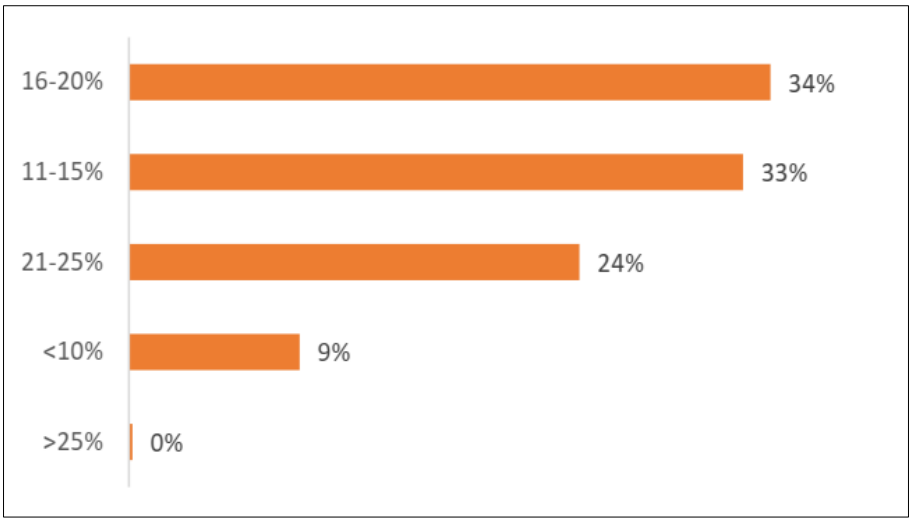

Figure 1: Percentage reduction in usage of insulin due to concomitant use of SGLT2 & DPP4 inhibitors

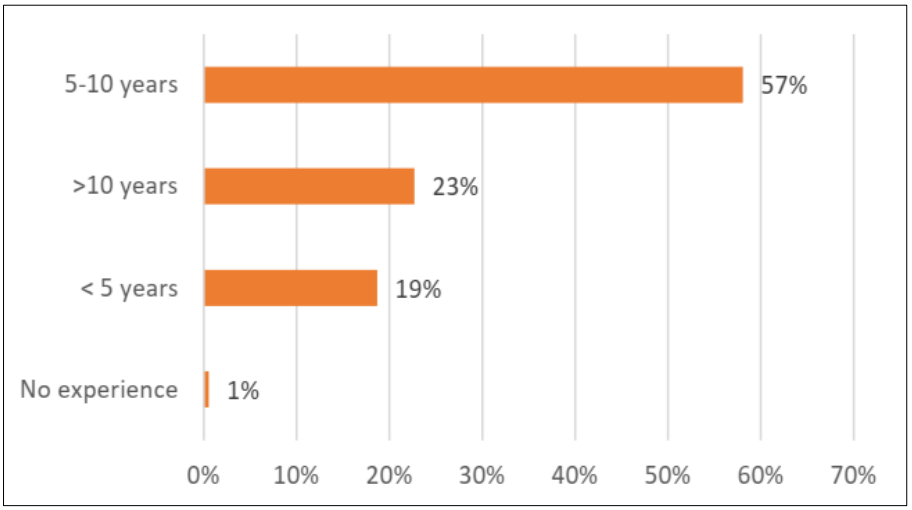

Figure 2: No. of years of experience in prescribing DPP4 inhibitors in their practice

Importantly, it was observed that almost 98% of the clinicians preferred dapagliflozin among the SGLT2 inhibitors in their practice. In addition, half of the participants preferred dapagliflozin as an add-on to metformin monotherapy, 30% of them preferred with DPP4 inhibitors, 17% of them with sulfonylureas and only 3% of them with insulin.

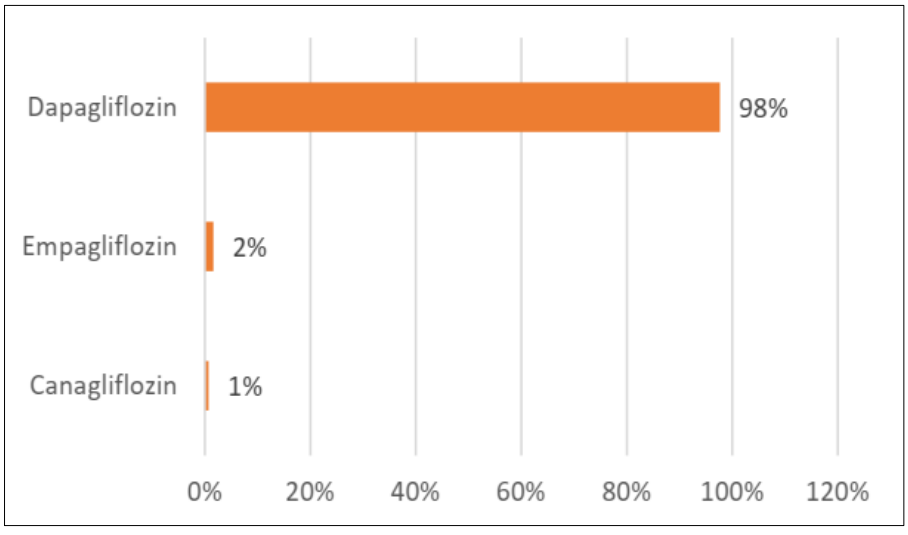

Figure 3: Proportion of commonly prescribed SGLT2 inhibitors

Majority of the respondents (52%) reported initiation of SGLT2 inhibitors after one drug's failure, 34% reported after first line of therapy, and 14% reported after two drug's failure. In that, 92% of the participants reported urinary tract infection as the most common undesirable effect in their patients, with the usage of dapagliflozin, 5% reported necrotizing fasciitis of the perineum (Fournier's Gangrene), and 2% reported ketoacidosis. Over 46% of the participants reported prescribing a fixed dosage of SGLT2 inhibitor + DPP4 inhibitor to 25-50% of their patients, 28% reported more than 50% cases, 25% reported less than 25% cases, and 1% reported 100% cases.

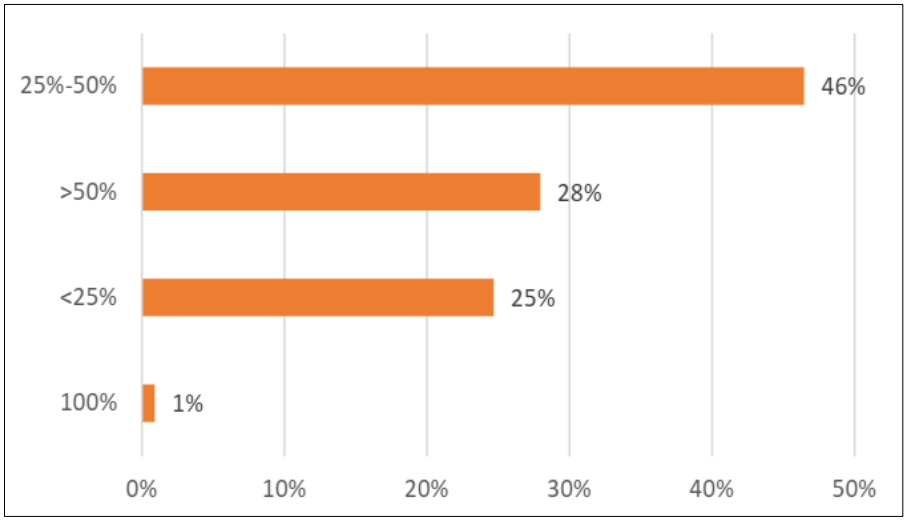

Figure 4: Practitioners prescribing FDC of SGLT2 inhibitors and DPP4 inhibitors

DISCUSSION

In this survey, 34% of the physicians reported a reduction of insulin usage by around 16-20% in their patients with the use of recent advances in oral anti-diabetic drugs like SGLT2 inhibitors and DPP4 inhibitors. A 6-month open-label randomized controlled study comparing a DPP-4 inhibitor with basal insulin in long-term care observed that mean daily blood glucose was similar, with fewer hypoglycemic events with DPP4 inhibitor compared with insulin [8]. In the current study, 58% of the respondents reported that they have been using DDP4 inhibitors in their clinical practice since last 5-10 years. Also, 66% of the doctors reported cardiovascular events as a major complication and 28% of the doctors reported renal complications in uncontrolled type 2 diabetes patients. 46% of the doctors reported prescribing a fixed drug dose combination of SGLT2 inhibitor and DPP4 inhibitor in 25-50% of their patients.

Through this study, it is seen that 98% of the doctors had prescribed oral anti-diabetic drugs (OAD) to 40-80% of their patients for the control of glycaemic index. This implies that a majority of the patients are on OADs. Results from Ashutosh Kakade *et al*., stated that 92.3% patients were on OADs only and 7.7% were on combined OADs and insulin therapy [9]. According to the guidelines proposed by the American Diabetes Association (ADA), metformin is the first line treatment in the management of diabetes. From our survey, it is seen that most physicians practice the same and drugs belonging to other groups such as SGLT2 inhibitors, DPP4 inhibitors, sulphonylureas and others are often used as add on in cases where there is a failure to control the glycaemic index with metformin alone.

From our study, it is seen that 48% of the 551 clinicians used DPP4 inhibitors as an add on, followed by 30% who reported the use of SGLT2 inhibitors and the remaining 22% who reported the use of sulphonylureas. However, in studies conducted by Jamuna Rani *et al*., and Mohammad Haghighatpanah *et al*., it has been observed that sulphonylureas are the most commonly prescribed add on drug to the first line antidiabetic metformin [10, 11]. Majority of the doctors felt that there was a need to add SGLT2 inhibitors to metformin for a better glycaemic control. Of all the commonly used SGLT2 inhibitors, dapagliflozin scored highest since 97% of the doctors who took part in this survey chose Dapagliflozin as their drug of choice among all the SGLT2 inhibitors.

Moreover, 82% of the doctors chose dapagliflozin for treating diabetic patients with either heart failure or other cardiovascular co-morbidities. 47% of physicians have reported that there was a reduction in the rate of cardiovascular death and hospitalization for heart failure. This seems to be a beneficial result as even the analysis done by McGuire *et al*., reveal that SGLT2 inhibitors are excellent in reducing the hospitalization due to heart failure in diabetic patients [12]. In addition, the study done by Lim *et al*., stated that dapagliflozin has a superior take on prevention of hospitalizations related to CV morbidities than empagliflozin [13].

Furthermore, 28% reported that the use of SGLT2 inhibitors showed increased efficacy in early and late stages of T2DM, 14% reported providing effective glycaemic control and reduced body weight. Results from the studies performed by Davies *et al*., are also in line with the results obtained from our survey. The study done by Davies *et al*., revealed that there was a good glycaemic control, reduction in weight and reduction in cardiorenal morbidities on using the SGLT2 inhibitors group of drugs [14].

Since the SGLT2 inhibitors group imparts its action by inhibiting renal reabsorption of glucose, the most commonly encountered adverse effect with the SGLT2 inhibitors group was urinary tract infection. An increased urinary glucose excretion makes the patients susceptible to recurrent urinary tract infection. The survey assessed the incidence of urinary tract infection among the patients and the results revealed that 92% of the clinicians stated that urinary tract infection was frequently seen among their patients. Others also reported side effects such as necrotizing fasciitis of the perineum and ketoacidosis seen among their patients. Studies by Li *et al*., and many others have resulted in similar side effect profiles as inferred from this survey [15, 16].

On analysing the methods practiced to reduce the incidence of severity of UTI among the patients, 33% of the practitioners stated that they reduced the dose of the SGLT2 inhibitors, 30% of the practitioners prescribed antibiotics, 23% of the practitioners advised adequate hydration while the remaining 14% of the practitioners discontinued the therapy with SGLT2 inhibitors. In addition, SGLT2 inhibitors improve glomerular hemodynamic function and are thought to ameliorate other local and systemic mechanisms involved in the pathogenesis of CKD and CVD [17]. About 30% of the clinicians in our survey have prescribed SGLT2 inhibitors for patients who are at >50% risk of developing CKD. Only 40% of the participants revealed prescribing SGLT2 inhibitors to 25-50% of their non-diabetic HF patients. SGLT2 inhibitors have shown good results in reducing the morbidity in patients with heart failure. Studies done by Butler *et al*., stated that SGLT2 inhibitors significantly improve cardiovascular outcomes including cardiovascular and all-cause mortality in patients with HF [18].

Furthermore, 43% of the clinicians reported that they prescribed SGLT2 inhibitors to less than 25% of their non-diabetic CKD patients and 36% reported 25-50%. SGLT2 inhibitors have emerged as a key disease-modifying therapy to prevent the progression of chronic kidney disease (CKD). These agents prevent decline in kidney function through reduction in glomerular hypertension mediated through tubule-glomerular feedback independent of their effect on glycemic control [19]. A combination of a DPP4 inhibitor and SGLT2 inhibitor is being prescribed for a better glycaemic control, for their plethora of pleiotropic effects and for their cardiorenal protective actions. In our study 28% of the clinicians prescribed this combination for more than 50% of their patients.

CONCLUSION

Most of the clinicians use DPP4 Inhibitors and SGLT2 inhibitors as an add on to metformin in patients with a failure to control the glycaemic index. Among the SGLT2 inhibitors, the commonly prescribed one was dapagliflozin. This drug was prescribed not only to control the glycaemic index but also to reduce the hospitalization due to heart failure and other cardiovascular and renal co-morbidities. The clinicians have also stated that they prescribe a combination of SGLT2 inhibitors and DPP4 inhibitors in order to maintain adequate glycaemic index and for the overall benefits of the patient's health. This study helps the healthcare professionals and researchers to make informed decision regarding the prevention and management of type 2 diabetes mellitus.

Acknowledgement: We would like to thank all the clinical practitioners who were participated in this study.

Funding: No funding sources.

Conflict of Interest: None declared.

Ethical Approval: This study was approved by the Independent Ethics Committee.

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