CLINICAL STUDY

Practice Patterns of Usage of Glimepiride and Metformin FDC Along with Other OADs: A New Age Approach to Diabetes Management in Indians

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ABSTRACT

Background: Diabetes is a progressive disease managed by different oral antidiabetic drugs (OADs) with or without glimepiride/metformin. As diabetes continues to be a significant health concern in India, novel therapeutic strategies are essential to effectively control the disease and improve patient outcomes. New drugs like sodium-glucose cotransporter-2 inhibitors (SGLT2i) and dipeptidyl peptidase-4 inhibitors (DPP-4i) have intermediate efficacy. Understanding clinicians' prescription patterns is crucial for optimizing treatment strategies for better long-term type 2 diabetes mellitus (T2DM) control. **Methods**: This was a retrospective, multicenter, observational case-based questionnaire study on T2DM patients undergoing pharmacotherapy. It aimed to collect data on clinical utilization patterns of glimepiride and metformin FDC (fixed-dose combination) with other OADs and comorbidities. The study included responses from 500 health care professionals (HCPs) across India. Statistical analysis was performed using SPSS® Version 23.0 software. Independent *t*-test was used to compare the change in fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and glycated hemoglobin (HbA1c) between two groups and Fisher's exact and Chi-square tests were used to compare categorical variables. P-value <0.05 was considered statistically significant. **Results**: The study analysis included responses from 500 HCPs. It showed that 6,250 patients received glimepiride/metformin FDC. The HbA1c was found to be 8.81% before treatment, which decreased to 7.75% after treatment. Among the 6,250 patients, 1,704 patients also recieved other OADs, where some patients recieved more thn one OADs. DPP4i was prescribed the most (1,064 patients followed by sodium-glucose cotransporter 2 inhibitors (SGLT2i) (573 patients), pioglitazone (229 patients), alpha-glucosidase inhibitor (AGI) (207 patients), insulin (178 patients), and lastly glucagon-like peptide 1 receptor agonist (GLP1RA) being prescribed in 35 patients along with the combination. Hypoglycemia was observed in very few patients (4.49%). Hypertension was the most prevalent (60.5%) comorbidity in the studied patient population. **Conclusion:** Use of glimepiride and metformin FDC along with other OADs offer optimized glycemic control, promote weight loss, and help to reduce complications in patients with T2DM.

Keywords: Type 2 diabetes mellitus, OADs, glimepiride, metformin, glycemic control, HbA1c

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Introduction

Diabetes has emerged as a global epidemic, affecting millions of people worldwide[1]. The incidence of diabetes has been increasing in South-East Asian countries for at least 20 years, according to the International Diabetes Federation (IDF) 10th edition, and current figures have surpassed all prior projections.

According to a recent study by Kumar et al the prevalence of diabetes was 10.5%, 8.8%, and 9.6%, respectively, in the globe, Southeast Asia, and India in 2021, and it will increase to 12.5%, 11.5%, and 10.9%, respectively, by 2045[2].

India, in particular, has witnessed a significant rise in the prevalence of diabetes over the past few decades, making it a major public health concern. Over 77 million people in India are dealing with diabetes. By 2045, researchers project that number will rise to 134 million[3].

Managing diabetes effectively requires a comprehensive approach, as shown in Figure 1.

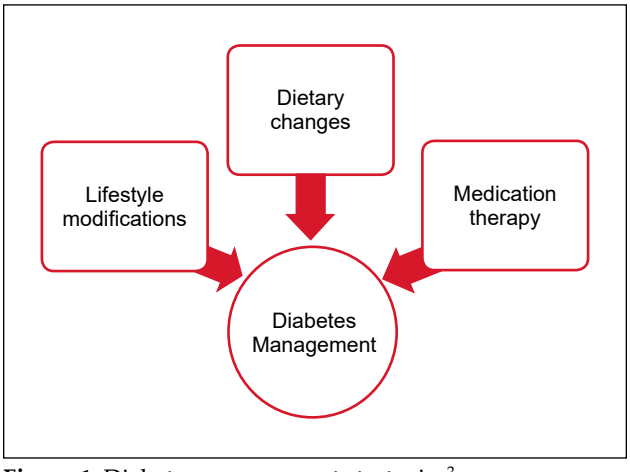

Figure 1. Diabetes management strategies[3].

Among the various treatment options available, oral antidiabetic drugs (OADs) play a crucial role in controlling blood glucose levels and preventing complications. Accordingly, metformin is the recommended first-line diabetes treatment option[4].

The use of modern sulfonylureas (SUs) like glimepiride in type 2 diabetes mellitus (T2DM) management has been advocated by a number of other international organizations, including the World Health Organization (WHO), South Asian Federation of Endocrine Societies (SAFES), IDF, and American Diabetes Association/ European Association[5-8]. The WHO advises using SUs in combination with the first-line therapy among patients who are unable to achieve treatment objectives with first-line oral hypoglycemic medications[9].

Additionally, the modern SUs have significant safety and efficacy profile. A study by Basit et al (2012) have shown that glimepiride is a safer and more affordable option for treating T2DM, as it lowers fasting blood sugar, post-meal glucose, and glycated hemoglobin (HbA1c) levels, without adversely affecting ischemic preconditioning[10]. The evidence of glimepiride's cardiovascular safety from the CAROLINA trial, compared to dipeptidyl peptidase-4 inhibitors (DPP4i), will provide cardiologists with greater confidence to use it in various conditions, including stable coronary artery disease, cerebrovascular disease, and peripheral arterial disease[11]. This article delves into analyzing the usage patterns of one of the most commonly prescribed OADs in India glimepiride and metformin along with other OADs.

Material and Methods

Study Design

The study was a retrospective, multicenter, observational case-based questionnaire survey on T2DM patients undergoing pharmacotherapy. It aimed to collect data on clinical utilization patterns of glimepiride/metformin FDC (fixed-dose combination) with other OADs, demographics, and comorbidities. Independent *t*-test was used to compare the change in fasting plasma glucose (FPG), postprandial plasma glucose (PPG), and HbA1c between two groups and Fisher's exact and Chi-square tests were used to compare categorical variables. All the reported p-values were two-sided and p-values <0.05 were considered to indicate statistical significance. Statistical analysis was performed using SPSS® Version 23.0 software.

Study Population

Patients of both sexes, aged above 18 years, diagnosed with T2DM who received glimepiride/metformin and patients with comorbidities who were prescribed medications. T2DM patients below the age of 18 years and who were on monotherapy for T2DM were excluded from the study.

Data Collection

A case report format (CRF) was developed to determine the pattern of use of different strengths of glimepiride/metformin FDCs with or without other oral hypoglycemic agents in diabetes patients. Vital parameters including body mass index (BMI), hypertension, and other comorbidities, T2DM duration, dosage regimens of different OADs and the laboratory glycemic investigations were also included.

A questionnaire was sent to 500 healthcare professionals in India via an online portal for a descriptive analysis.

Data was collected digitally from clinicians through digitized CRF, clinical characteristics, laboratory findings, and treatment regimens from electronic medical records or doctor's records. The data was independently supervised by two investigators and reviewed by different investigators.

Statistical Analysis

All continuous variables were expressed as mean ± standard deviation (SD) or median with the interquartile range per the data distribution. Categorical variables were expressed as numbers and their respective percentage. Independent *t*-test was used to compare the change in FPG, PPG, and HbA1c between two groups and Fisher's exact and Chi-square tests were used to compare categorical variables. All the reported p-values were two-sided and p-values <0.05 were considered to indicate statistical significance. All data entries and statistical analyses were performed by using SPSS@ Version 23.0 software.

Compliance with Ethics Guidelines

The study was approved by the ethical committee. All procedures adhered to the ethical standards established by the relevant institutional or national research committees. Since the study used an anonymized database and was done retrospectively, patient consent was not needed.

Results

The study analysis included responses from 500 HCPs. It showed that 6,250 patients received glimepiride/metformin FDC. The ages of the patients were between 18 to 90 years and a mean BMI was 27.97 ± 4.29 who received glimepiride/metformin combination. The mean (±SD) duration for which patients were having diabetes was 7.54 ± 3.48 years. The HbA1c was found to be 8.81% before treatment, which decreased to 7.75% after treatment. Among the 6,250 patients, 1,704 patients also received other OADs, where some patients received more than one OADs. Figure 2 shows the trend of OADs in combination with Metformin + Glimepiride.

DPP4i was prescribed the most (1,064 patients) followed by sodium-glucose cotransporter-2 inhibitors (SGLT2i) (573 patients), pioglitazone (229 patients), alpha-glucosidase inhibitor (AGI) (207 patients), insulin (178 patients), and lastly glucagon-like peptide 1 receptor agonist (GLP1RA) being prescribed in 35 patients along with the combination as is depicted in Figure 2.

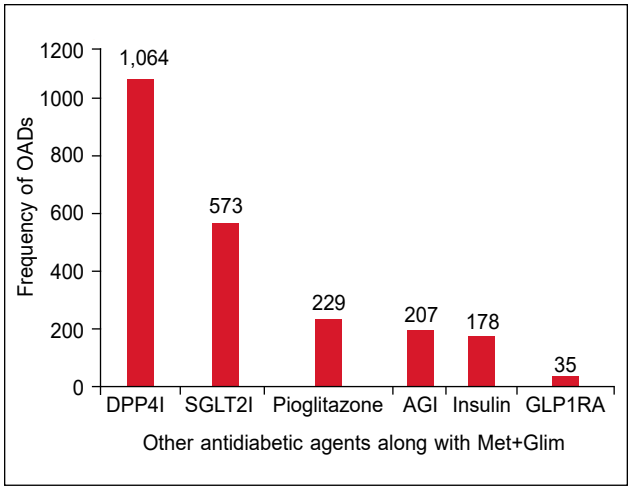

Figure 2. Trend of OADs being prescribed with glimepiride/metformin combination.

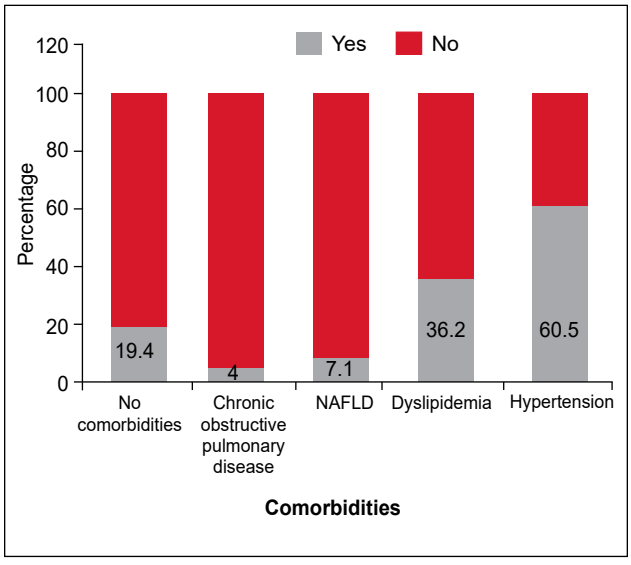

Figure 3. Comorbidities found in the participating diabetic patients.

NAFLD = Nonalcoholic fatty liver disease.

Hypoglycemia was observed in very few patients (4.49%). Hypertension was the most prevalent (60.5%) comorbidity in the studied patient population mostly aged between 18 to 90 years as is observed in Figure 3, followed by dyslipidemia (36.2%) among the patients included.

Discussion

Over half of the populations in India are at risk of having diabetes at some time in their life, which is making it a public health problem. An assessment in

the review article published in 2021 stated that people residing in the cities and metropolitan regions in India are more likely to get diabetes due to lifestyle changes which increases the person's BMI, a risk factor for diabetes. A significant surge is also being observed in rural parts of India[3].

Hence, selection of proper drugs to control the rise becomes essential. Presently, there are approximately 60 medications that have been authorized by the Food and Drug Administration (FDA) as therapeutic choices for the treatment of T2DM[11].

The selection of these drugs is typically affected by the numerous national and international recommendations created by various organizations in an effort to improve the management of diabetes mellitus[12-14].

For many T2DM patients, combination therapy is necessary to maintain blood glucose levels within the desired range and prevent complications from diabetes. Some OADs are advantageous for heart and renal health as well as weight loss[15,16].

Progressive beta-cell loss, a hallmark of T2DM, necessitates the sequential addition of various oral and injectable drugs to provide the best possible glycemic control. As the condition worsens, combination therapy becomes the need of the hour to establish appropriate glycemic control. Presence of comorbid conditions such as dyslipidemia, hypertension, and cardiovascular disease along with polypharmacy which comes with an increased load of pills and dose frequency, adds to the burden of medication[17,18].

In the present study, hypertension was the most prevalent (60.5%) comorbidity in the total studied patient population, followed by dyslipidemia and nonalcoholic fatty liver disease (NAFLD).

It was further seen that among 1,704 patients (some of whom also received more than one OADs along with Metformin + Glimepiride combination), 1217 (71.04%) were hypertensive, 720 (42.22%) had dyslipidemia, 1,164 (68.31%) had lifestyle related risk factors. Hence, the presence of these comorbidities might be one of the causes to add other OADs.

Also studies have shown that one method to improve drug adherence is to use additional OADs along with the existing combination therapy. Drug combinations have been associated with improved compliance and improved glycemic control[17].

The pattern observed in the present study showed that along with the glimepiride/metformin combination, DPP4i was prescribed the most (1,064 patients) followed by SGLT2i (573 patients), pioglitazone (229 patients), AGI (207 patients), insulin (178 patients), and lastly GLP1RA being prescribed in only 35 patients along with the combination as shown.

Dipeptidyl peptidase-4 (DPP-4) is a serine protease that cleaves and inactivates hormones, leading to decreased insulin secretion and disrupted visceral fat metabolism. It also plays a role in regulating postprandial glucose by degrading glucagon-like peptide 1 (GLP-1). DPP4i has been explored as a therapeutic target for the treatment and management of T2DM[19]. Research has demonstrated that DPP4i possess a favorable therapeutic profile, do not increase cardiovascular risk, and are safe and effective for most patients with T2DM[20].

A large retrospective real-world investigation shows that adding a DPP4i to the existing medication improves glucose control in normal diabetic outpatient clinical practice. While DPP4i and gliclazide both increase endogenous insulin secretion, DPP4i has a stronger physiological effect that is meal-dependent and may be better able to enhance beta and alpha cell activity, which would lead to improved glycemic control[21]. DPP4i were found to have no hypoglycemia risks, neutral effect with respect to weight change, atherosclerotic cardiovascular disease (ASCVD) and renal diseases. Also it was found to decrease postprandial triglycerides and blood pressure (BP), hence is beneficial for hypertensive diabetic patients. In the current study, most of the patients taking the combination were also hypertensive and were also given DPP4i. This is in accordance with the fact that DPP4i helps in lowering (BP) and with blood glucose level[22].

Metformin increases insulin sensitivity, while glimepiride increases - cell glucose sensitivity and promotes endogenous insulin production. A complementary mechanism of action between glimepiride and metformin results in a considerable decrease in glycemic indices (FPG, PPG, and HbA1c levels)[10,23].

In India, SUs are second-line medications for T2DM patients who are not obese and also reduce the risk of hypoglycemia. Hence, SUs are preferred in this population[24]. Glimepiride is also a desirable choice for the management of people with long-term diabetes due to its shown cardiovascular safety/neutrality and decreased hypoglycemic episodes[25]. Hence, addition of other OADs like DPP4i along with the glimepiride/metformin seems to be beneficial in T2DM patients having comorbidities such as hypertension, dyslipidemia, etc.

In T2DM patients, strict glycemic management lowers the related comorbidities and raises quality of life[26]. According to the United Kingdom Prospective Diabetes Study (UKPDS) trial, there is a 12% to 43% reduction in the risk of diabetes-related mortality and morbidity for every 1% drop in HbA1c[27,28].

Glimepiride increases cell sensitivity to glucose and promotes endogenous insulin production, whereas metformin increases sensitivity to insulin. Glycemic markers (FPG, PPG, and HbA1c levels) are significantly decreased when glimepiride and metformin are used in combination due to their complementary mechanisms of action.

When compared to older-generation SUs, glimepiride offers a number of benefits: weight-neutral effects, lack of cardiovascular risk, and fewer hypoglycemia episodes. It also has extrapancreatic effects, which are superior, enhanced insulin secretion[22]. Glimepiride + Metformin show synergistic effects by reducing hypoglycemia, weight gain, and cardiovascular risks, good glycemic control and improved safety profile[23,29-31].

Prasanna Kumar et al also reported similar observations in a trial which showed that the combination had a good to outstanding effectiveness and tolerability in the majority of patients (97.3% and 96.6%)[32].

Another prospective research found that diabetic individuals on glimepiride experienced fewer hypoglycemia episodes than those taking glibenclamide[33].

Glimepiride's documented cardiovascular safety/neutrality and reduced hypoglycemia episodes make it an attractive alternative for the management of persons with long-standing diabetes[25]. SUs are affordable and are also effective alternatives to other more recent antidiabetic drugs[31].

Combination drugs in diabetes treatment are cost-effective as they reduce the need for multiple medications, simplify dosing, and improve patient adherence, ultimately lowering overall health care costs. Hence, the combinations are preferred in developing countries like India[34]. This study showed that among 6,250 patients in the age between 18 to 90 years and a mean BMI of 27.97 ± 4.29 received glimepiride/metformin combination.

The mean (±SD) duration for which patients were having diabetes was 7.54 ± 3.48 years. The HbA1c was found to be 8.81 ± 1.25 before treatment, which decreased to 7.75 ± 3.62 after treatment. The mean FPG values before treatment was 190.46 ± 53.20 which reduced to 139.50 ± 39.51 mg/dL after treatment, while the mean PPG values before treatment was 274.62 ± 32.11, which decreased to 165.22 ± 45.63 mg/dL after treatment.

Among the 6,250 patients, 1,704 patients also received other OADs, 758 achieved HbA1c <7. Moreover, 228 patients achieved target FPG values, i.e., FPG values <100 and 95 achieved target PPG values, i.e., values <125.

In the current study, a significant decrease in the HbA1c, FPG, and PPG was observed, which is in similar lines with the findings by Hassan and Abd-Allah (2015), Surendra Kumar (2021), Shrivastava et al (2023)[23,30,35].

A variety of antidiabetic medications are now used as monotherapy or in combination for treating T2DM. Several studies have shown that in various Afro-Asian nations, including India, modern SUs alone or in combination with metformin are the OADs prescribed most often as they achieved better HbA1c, FPG, and PPG when used along with different OADs[36,37].

Conclusion

Prevalence of diabetes is increasing in India. Glimepiride/Metformin FDC can be used with various other OADs for better management of diabetes among patients with additional comorbidities. The study shows that DPP4i was the most common OAD being prescribed along with glimepiride/metformin combination.

This new age approach offers valuable insights into the multifaceted management of diabetes, highlighting the importance of individualized treatment strategies for Indian patients. The study would help HCPs to understand and optimize diabetes management in a better manner, which in turn would enable patients to lead healthier and more productive lives.

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Conflicts of Interest

Dr Aushili M, Dr Ashish Prasad, Dr Abhijit Pednekar are employees of USV Private Limited, Mumbai, Maharashtra, India.

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