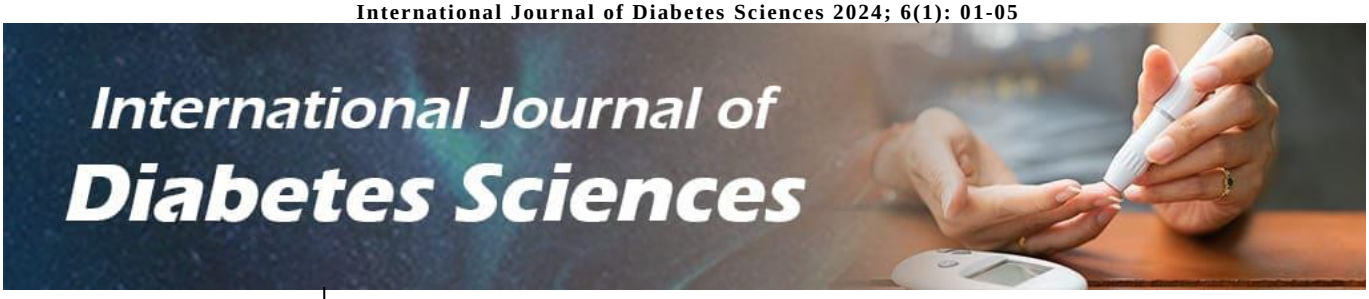

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Expert opinion on glimepiride, pioglitazone, and metformin fixed-dose combination in Type 2 Diabetes Mellitus patients: The results of One Pride study

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Abstract
Objective: The present "One Pride study" questionnaire-based survey aims to assess professional opinions on the use of glimepiride + metformin + pioglitazone (GMP) fixed-dose combination (FDC) for the efficient management of type 2 diabetes mellitus (T2DM).
Methods: A cross-sectional study was carried out to get opinions on the usage of GMP FDC from specialists across India. Twenty questions in the survey aimed to elicit thoughts from specialists on whether they would advise T2DM patients to use the GMP FDC.
Results: The majority (60.3%) of the 941 participants reported that GMP was their preferred FDC therapy for type T2DM. After receiving GMP treatment, about 42% reported a drop in fasting blood glucose of 31 to 50 mg/dl. In addition to achieving ideal glycemic control, 45.86% of the responders stated that the GMP therapy helped lower low-density lipoprotein (LDL) levels. High-density lipoprotein (HDL) levels increased while triglycerides (TG) levels decreased, according to 33.01% and 19.75% of the respondents. The common side effects reported by the experts were weight gain, gastrointestinal disturbances, hypoglycemia, pedal edema/overall bloating, bone marrow edema (BME) pain, edema, fluid retention, headache/dizziness, and swelling of feet.
Conclusion: According to expert opinion, using FDC to treat T2DM may help in achieving ideal glycemic control, lowering LDL cholesterol levels, controlling weight, and lowering fasting insulin levels. Experts notably advise GMP combination treatment as a successful strategy for controlling glucose levels in T2DM patients and also for lowering the risk of cardiovascular problems. However, more investigation is required to assess the security, efficiency, and acceptability of different combinations and dose schedules of triple treatment in diabetic patients.

Keywords: Type 2 Diabetes Mellitus, Glimepiride, Metformin, Pioglitazone, Oral anti-diabetic drug, Glycemic control

Abbreviations: T2DM: Type 2 diabetes mellitus; GMP: Glimepiride + Metformin + Pioglitazone; FDC: fixed-dose combination; LDL: Low-density lipoprotein; HDL: High-density lipoprotein; TG: Triglycerides; BME: Bone marrow edema; HbA1c: Glycosylated haemoglobin; PPBG: Post-prandial blood glucose; FBG: Fasting blood glucose; AEs: Adverse events; BMI: Body mass index.

Introduction

As per the reports of the International Diabetes Federation, the prevalence of T2DM is rapidly increasing worldwide. In 2021, there were approximately 537 million individuals aged 20-79 with diabetes globally. This number is projected to reach 643 million by 2030 and 783 million by 2045 [1]. India has emerged as the diabetes capital of the world with an estimated 77 million Indian adults living with T2DM and more than 25 million individuals in prediabetes state [2]. The disease poses a significant economic burden on individuals, families, and the healthcare system due to the exorbitant demand for diabetes-related services. Considering the progressive nature of T2DM, strict glycemic control plays a crucial role in managing the condition effectively [3]. The FDC of multiple antidiabetic medications, such as GMP is preferred over monotherapy due to several potential benefits. Improved glycemic control, simplified treatment regimen, convenience, patient compliance, cost-effectiveness, and prescribing simplicity are some of the key benefits conferred by this FDC.

The combination therapy aims to improve glycemic control by targeting multiple mechanisms of action and each component plays a specific role in managing blood glucose levels. Pioglitazone increases insulin sensitivity in peripheral tissues, glimepiride boosts pancreatic insulin secretion, and metformin lowers hepatic glucose synthesis while boosting insulin sensitivity [4]. A study by Meshram *et al*. involving 101 Indian subjects demonstrated that the triple drug combination effectively achieved the recommended goals set by the American Diabetes Association for fasting blood glucose levels of 140 mg/dL or lower and glycosylated hemoglobin (HbA1c) levels by ≤8%. After 8 weeks, the average fasting blood glucose level reduced by 41% and the average HbA1c level by 26%. Furthermore, the triple drug combination led to significant reductions in TG levels, LDL levels, and total cholesterol levels [5].

Understanding the prescription practice of diabetes medications is pivotal to improving medication adherence, enhancing self-management behaviors, preventing medication errors, achieving optimal glycemic control, empowering decision-making, and addressing health disparities. The present questionnaire-based survey, titled 'One Pride study', is intended to understand the expert opinion on the use of GMP FDC for the effective management of T2DM.

Materials and Methods

We carried out a cross sectional, multiple-response questionnaire based survey among clinicians experienced in treating T2DM patients in the major Indian cities from June 2022 to December 2022.

Questionnaire

The questionnaire booklet titled One Pride study was sent to the physicians who were interested to participate. The One Pride study questionnaire consisted of 20 questions seeking experts' opinions on whether they would recommend the GMP FDC to patients with T2DM. The questionnaire inquired about the use of the FDC in newly diagnosed T2DM patients, the use of triple treatment (OAD), the prescription of the GMP combination in different age groups, and the potential adverse effects of this FDC on patients. The study was conducted after receiving 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 leading clinicians in managing T2DM patients in the month of March 2022 for participation in this Indian survey. About 941 doctors from major cities of all Indian states representing the geographical distribution shared their willingness to participate and provided necessary data. The participants were requested to complete the questionnaire without discussing with their peers. A written informed consent was obtained from each practitioner's prior initiation of the study.

Statistical methods

Descriptive statistical analysis was conducted, and the distribution of each variable was represented by the frequency of occurrence and its corresponding percentage. All tables were generated using Excel 2019. Pie charts and bar charts were created using Excel version 2013 (16.0.13901.20400).

Results

The study included a total of 941 participants, with the majority from Karnataka (19.5%), followed by Tamil Nadu (9.88%). West Bengal and West Bengal (Sumanta) each accounted for 8.40% of the total participants. Chennai, Delhi, Kerala, Odisha, and Telangana had participation rates of 5% or higher.

Among the total of 941 participants, the majority (60.3%) reported GMP as the preferred FDC treatment for type T2DM. This was followed by 16.0% of participants prescribing glimepiride + metformin + SGLT2 inhibitors, 10.8% prescribing glimepiride + metformin + voglibose, and 9.3% prescribing glimepiride + metformin + DPP4 inhibitors. All respondents stated that these treatment options were their preferred choices when prescribing OAD medications to T2DM patients with HbA1c >9%. Around 1.8% of the respondents prescribed additional therapies, such as SGLT2 inhibitors + metformin + voglibose, and considered combination therapy based on individual patient needs. They also mentioned the possibility of adding insulin if necessary (Figure 1).

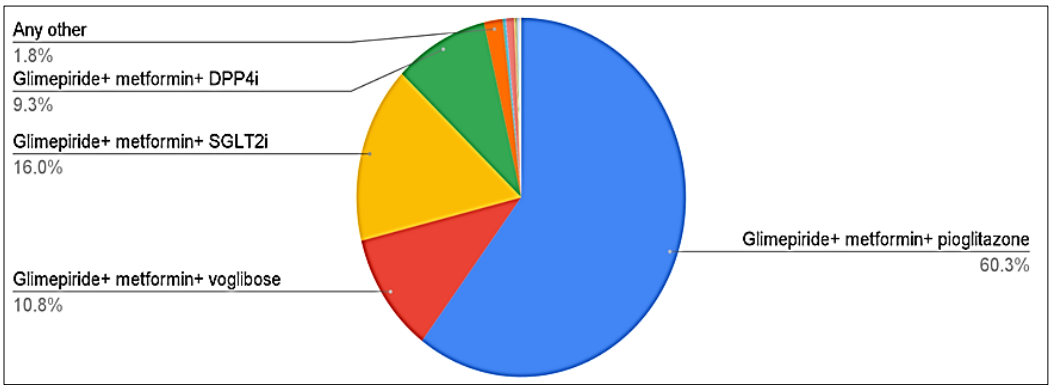

Figure 1: Representation of the treatment choice in T2DM patients with HbA1c >9%

All the respondents reported prescribing GMP combination therapy to cases with high insulin resistance and HbA1c levels, as well as to individuals who were hesitant to receive insulin. Among the respondents, 22.80% prescribed this combination therapy exclusively to cases with high insulin resistance, while 16.72% and 13.23% of the respondents prescribed it to cases with high HbA1c levels and individuals who were reluctant to take insulin, respectively (Figure 2).

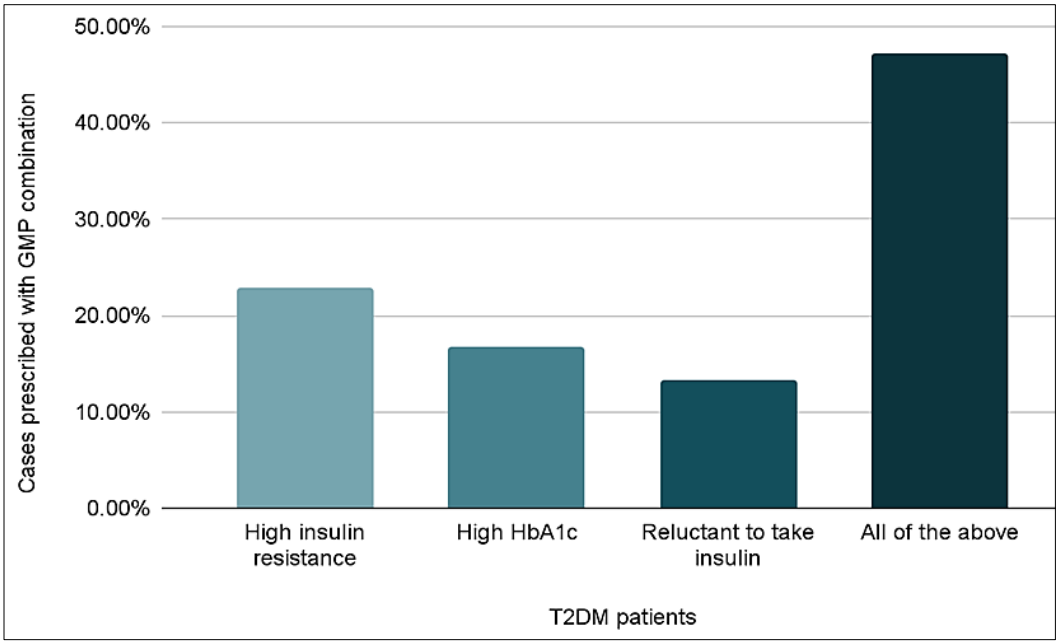

Figure 2: Representation of T2DM patients prescribed with GMP combination therapy

Approximately 76.91% of the 931 respondents agreed that FDC requirements would be higher in certain geographic areas, while 23.10% of the respondents disagreed. Furthermore, among 738 of the respondents, 38.92% of the respondents reported that T2DM patients residing in rural areas would require more FDCs, and 36.54% and 24.54% expressed the same for semi-urban and urban areas.

Out of the total of 926 respondents, 42% reported fasting blood glucose reduction of 31 to 50 mg/dl following GMP therapy. About 23.65% and 22.46% of the participants reported corresponding fasting blood glucose reductions of 51 to 70 mg/dl and up to 30 mg/dl. Additionally, 11.88% of the respondents reported reductions of more than 70 mg/dl. Nearly 45.42% of the participants reported that 60 to 80% of the patients achieved a glycemic target of <7% HbA1c following GMP combination therapy. Additionally, 37.24% of the respondents reported that the target was reached by 30 to 60% of the patients, while 11.19% reported success in more than 80% of their patients.

Apart from optimal glycemic control, 45.86% of the respondents reported that the GMP treatment contributed to the reduction of LDL levels. Reduction of TG levels and increase in high-density lipoprotein (HDL) levels were reported by 33.01% and 19.75% of the respondents) respectively. Other reported benefits of the treatment included weight loss, decreased fasting insulin, and improvements in fatty liver and fat distribution.

Out of 623 participants, 39.32% of respondents reported that 10-30% of patients experienced weight gain. Around 55.27% of the respondents reported the occurrence of a gastrointestinal disturbance in 10-30% of the subjects, while 41.05% reported its incidence as <10%. Hypoglycemia episodes were reported by 64.02% and 32.64% of the respondents for <10% and 10-30% of their patients, respectively. Approximately 4-17% of the respondents reported experiencing all of the above-cited side effects (weight gain, gastrointestinal disturbances, and hypoglycemia), including pedal edema/overall bloating, BME pain, edema, fluid retention, headache/dizziness, and swelling of feet.

Discussion

The current study is one of its kind to gather real-life data on the use of GMP FDC in routine practice for the management of T2DM. The study also highlights the popularity of FDC treatment among healthcare professionals for managing T2DM. It also sheds light on the specific combinations of medications prescribed in different scenarios, particularly when targeting patients with high HbA1c levels.

The current study revealed that approximately 60% of the respondents expressed a preference for using GMP FDC treatment in the management of T2DM patients. Among the participants, 16% expressed a preference for the prescription of glimepiride, metformin, and SGLT2 inhibitors, while approximately 10% each recommended combinations of glimepiride, metformin, and voglibose, as well as glimepiride, metformin, and DPP4 inhibitors. Furthermore, when treating T2DM patients with HbA1c levels >9%, all respondents unanimously reported that these treatment alternatives were their preferred choices as OAD medication.

Most medical experts believe that a triple-drug combination has the potential to enhance glucose control and delay or prevent microvascular and cardiovascular complications associated with T2DM [6]. By combining glimepiride, metformin, and either SGLT2 inhibitors, DPP4 inhibitors, or voglibose, it is expected that patients can achieve better glycemic control and potentially experience a reduction in long-term complications related to T2DM. The use of FDCs offers a convenient approach to simplify treatment regimens and improve patient adherence, which is crucial for optimizing outcomes in T2DM management. A randomized control trial by Umpierrez *et al.* observed that in patients with inadequate glycemic control on metformin monotherapy, the addition of either glimepiride or pioglitazone yielded comparable overall improvements in glycemic control. However, glimepiride was associated with faster achievement of glycemic control, lower levels of total and LDL cholesterol, and reduced short-term healthcare costs than pioglitazone [7]. Several other studies have also shown that the addition of glimepiride and

thiazolidinediones improves treatment effectiveness in patients with T2DM who do not achieve adequate glycemic control with metformin mono-therapy [8, 9].

Approximately 45% of the current study participants indicated that 60 to 80% of their patients achieved a glycemic target of <7% HbA1c following GMP combination therapy, while 11% reported success in more than 80% of their patients. In addition to optimizing glycemic control, 46% of the respondents reported that GMP treatment reduced LDL levels as well. According to the respondents, 33% of them reported reduced triglyceride levels and 19.75% had reported increased HDL levels in their patients. Additionally, GMP therapy was associated with improvements in weight management, fatty liver, and fat distribution. These multifaceted benefits further reinforce the value of GMP FDCs in the comprehensive management of T2DM.

An 8-week trial by Kaku *et al*. noted that a higher proportion of patients in the pioglitazone plus metformin group achieved HbA1c <6.5% (38.6% vs. 8.1%; *P* <0.0001). Furthermore, patients receiving the combination therapy experienced a significantly greater decrease in fasting blood glucose levels compared to those on metformin alone (-20.5 vs. 1.9 mg/dl; *P* <0.0001) [10]. The combination therapy was also associated with significantly increased levels of HDL-cholesterol, total cholesterol, and adiponectin. Furthermore, patients on combination therapy exhibited significantly decreased levels of fasting insulin, free fatty acids, and homeostasis model assessment insulin resistance. An Indian-based trial conducted by Panicker *et al*. involving 373 subjects reported that the use of insulin sensitizers such as pioglitazone in combination with metformin showed promising results in inducing and maintaining long-term glycemic control in individuals with T2DM, referred to as 'pharmacological remission' [11].

Around 42% of the 926 current study respondents reported a decrease in fasting blood sugar levels ranging from 31 to 50 mg/dl following the use of GMP therapy. Additionally, 11.88% of the respondents reported a reduction in blood sugar levels by more than 70 mg/dl. The combination of pioglitazone and glimepiride in fixed-dose form has been shown to improve glycemic and metabolic control in patients with T2DM by promoting increased patient compliance [12]. Upon comparison of the metabolic effects of the drugs, Yamanouchi *et al*. reported that pioglitazone, metformin, and glimepiride are equally effective in reducing blood glucose in patients with newly diagnosed T2DM. However, their specific characteristics such as the rapid action on blood glucose levels of glimepiride and the favorable action on fasting plasma glucose and free fatty acids of pioglitazone, warrant consideration when choosing an appropriate agent [13].

The present study has reported weight gain, gastrointestinal disturbances, and hypoglycemia episodes, as the major side effects of GMP therapy. Weight gain has been identified as a significant side effect associated with the use of FDCs in the treatment of T2DM [14]. In another study involving 3705 patients, it was observed that hypertension was the most prevalent co-occurring ailment (64.7%), followed by weight reduction in 33.2% of the patients and weight gain in 66.8% of the patients. Hypoglycemia incidents were reported by 432 out of 3705 patients [15]. These findings emphasize the importance of carefully monitoring and managing the potential side effects associated with FDC therapy.

International and national recommendations advocate the use of an FDC consisting of two or more anti-diabetic medications to achieve improved and sustained glycemic control with minimal risk of side effects such as hypoglycemia and weight gain [16, 17]. The present study provides compelling evidence that the GMP combination therapy offers enhanced glycemic management by effectively reducing HbA1c levels and fasting plasma glucose levels. The use of FDC plays a crucial role in achieving optimal glycemic goals in the management of T2DM. To make well-informed recommendations, primary care doctors should adopt a multi-step strategy in this field, considering the individual needs and characteristics of their patients [18].

Although several studies have explored FDCs involving different combinations of medications, none have specifically focused on the prescription practice of the GMP FDC. The present study findings may serve as a guide to healthcare professionals in making evidence-based decisions regarding the prescription of GMP FDC to patients with T2DM. The survey findings address an important knowledge gap and have the potential to contribute significantly to the understanding of the clinical use of GMP FDC as a treatment option for T2DM. It also emphasizes the need for comprehensive evaluation and investigation of various combination therapies to enhance the overall management and outcomes for individuals with T2DM.

The current study has certain limitations. Firstly, the sample size was small, which may impact the generalizability of the findings. Secondly, relying on expert opinions introduces the possibility of bias influencing the results.

Conclusion

The consensus among experts has shown that the use of FDC for managing T2DM can potentially contribute to achieving optimal glycemic control, reducing LDL cholesterol levels, managing weight, and decreasing fasting insulin levels. GMP combination therapy is specifically recommended by experts as an effective approach for regulating glucose levels in T2DM patients and also for reducing the risk of cardiovascular complications. However, further research is necessary to evaluate the safety, effectiveness, and tolerability of various combinations and dosage regimens of triple therapy in individuals with diabetes.

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