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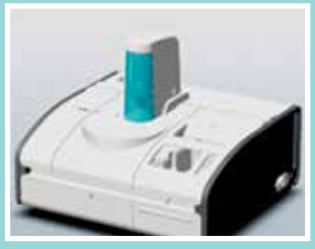

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Evidence from Experience: Unity in Diversity

ABSTRACT

Diabetes in India presents unique challenges, which merit bespoke solutions. The early onset and rapid progression of diabetes, along with late presentation to the healthcare system, call for more proactive management strategies. At the same time, persons living with diabetes ask for convenient, uncomplicated treatment regimens, which offer comprehensive control with minimal dose frequency. The original research published in this issue highlights the relevance of fixed-dose combinations (FDCs) of sulfonylurea and metformin, as well as fixed-ratio combinations (FRCs) of rapid-acting and long-acting insulin analogs, in diabetes care. In this editorial, we highlight the similar preferences of oral and insulin medication, and explore the rationale behind this. We hope that this insight will encourage further discussion and research on ethnocentric pharmacotherapy in diabetology.

Keywords: Co-formulation insulin, diabetes, FDC, glimepiride, India, insulin, IDegAsp, type 2 diabetes

INTRODUCTION

India is a large country, united in its diversity. Type 2 diabetes is also a diverse syndrome, united not only in terminology, but in many other ways as well. Does the motto "unity in diversity" hold true for Indian diabetes care? We do see this in our epidemiology; similar trends are noticed across the country, and the entire nation seems to be marching towards an increased prevalence of diabetes.[1] We note unity in terms of the quality of care and control: diabetes targets are accomplished in only a minority of patients in every state.[2] Underlying this reality is the healthcare-seeking behavior and dietary preferences that are common to most of our fellow citizens. The baseline HbA1c is usually high at diagnosis[2] and patients report their preference for a high-carbohydrate diet, in all regions of the country.[3] Yet another facet of healthcare-accepting behavior is the preference for minimal doses, of both oral and injectable drugs.[4]

QUESTIONS AND QUERIES

Are physicians united in diversity? Do they preferentially choose the same therapeutic options for persons living with type 2 diabetes? Are these preferences exhibited across various patient phenotypes, are they concordant between the oral and insulin therapeutic landscape, and can they be explained on the basis of current/contemporary knowledge of diabetes etiopathogenesis and natural history? This editorial explores subtle insights that come to mind while analyzing the results of the original research reported in this issue of the Asian Journal of Diabetology (AJD).

THE CHALLENGE

Indian diabetes care can be quite challenging. Earlier onset and rapid progression of disease, coupled with delayed presentation and erratic follow up of patients, makes it difficult for the treating physician to craft a therapeutic plan, which balances efficacy with safety. Heavy burdens, however, create strong shoulders, and this is what happens in our diabetes care ecosystem. Our physician-researchers, cognizant of the complaints, concerns and the clinical condition of their patients, are able to use evidence-based modern drugs to achieve optimal glucose control in a safe and smart manner.

THE EVIDENCE

Most Indian patients present with a high baseline HbA1c, which cannot be controlled by monotherapy.[2] Hence, a fixed-dose combination (FDC) of oral drugs, or a fixed-ratio combination (FRC) of dual-action insulin is usually required for glycemic management. This approach is supported by contemporary treatment guidelines.[5] The choice of oral glucose-lowering drugs is based upon cardiovascular status, concerns about body weight, risk of hypoglycemia and cost.[5]

In this issue of AJD, Rao et al report the utility of glimepiride/metformin combination in young adults,[6] while Ray et al report that it is a preferred choice in persons with

atherosclerotic cardiovascular disease (ASCVD)/high risk of ASCVD as well.[7] Kurmur et al find that different strengths of glimepiride/metformin FDCs are commonly prescribed in combination with insulin in patients with type 2 diabetes with favorable efficacy and safety profile.[8]

This issue also features a real-world study on the use of dual action insulin like insulin degludec/insulin aspart (IDegAsp) fixed ratio coformulation. Chatterjee et al show that in insulin-naïve Indian patients with type 2 diabetes inadequately controlled with oral antidiabetic drugs alone, initiating insulin therapy with IDegAsp was superior to insulin glargine (IGlar U100) in terms of glycemic control and also in managing postprandial plasma glucose excursions.[9]

THE PREFERENCE

Sulfonylurea and metformin combinations address insulin deficiency and resistance, both of which contribute to the pathogenesis of diabetes in Indian adults. FDC preparations provide the added advantage of economical, error-free, easy-to-use drug administration.[10]

These FDCs can be used along with virtually every non-insulin glucose-lowering drug, except repaglinide, and with certain insulins such as basal insulin.

A similar experience is noted in the insulin space in India. Dual action insulin, also termed as premixed or co-formulation insulin, has been found to be an effective, and efficient, way of achieving glucose control. Insulin preparation such as biphasic insulin, biphasic aspart, lispromix and IDegAsp offer both prandial and basal coverage, while minimizing the number of injections needed.[11]

THE EXPLANATION

The preferred choice of drugs, both oral and injectable, in Indian persons living with type 2 diabetes, bears uncanny resemblance. FDCs are preferred over oral monotherapy and FRCs over basal insulin. This seems to be a response to the complex pathogenesis of diabetes, which involves both insulin secretory defect and insulin resistance. It addresses the commonly encountered clinical presentation, which includes both fasting and postprandial hyperglycemia, and may be associated with symptoms. It is mindful of the carbohydrate-based Indian diet, as well as the expressed desire of our patients to achieve glucose control as swiftly as possible, in a safe and well-tolerated manner. The choice of therapy respects the Law of Therapeutic Parsimony,[4] which enjoins us to manage diabetes with as few doses of drugs as possible.

SUMMARY

This issue of the AJD explores the evidence related to experiences of Indian diabetes care. Taken together, the studies highlight the consistency and concordance of physician's choices in both oral and injectable drug segments. We emphasize this similarity, and suggest possible reasons for this. Clarification of this facet of diabetes pharmacotherapy will help us understand our response to the etiopathophysiologic complexity of type 2 diabetes and allow us to improve it further.

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ORIGINAL ARTICLE

Insulin Initiation with Insulin Degludec/Insulin Aspart versus Insulin Glargine in Oral Antidiabetic Drugs Failure Patients with Type 2 Diabetes Mellitus: A Real-World Study from India

SANJAY CHATTERJEE*, SOUMYABRATA ROY CHAUDHURI†, ANIRBAN MAJUMDER†, DEBMALYA SANYAL†

ABSTRACT

Context: Oral antidiabetic drug (OAD) failure is an indication for starting insulin therapy, but there is still a dilemma as to whether basal insulin or a premixed/co-formulation analog should be the choice. **Aim**: To compare the safety and efficacy of once daily (OD) insulin degludec/insulin aspart (IDegAsp) to OD insulin glargine (IGlar U100) in insulin-naïve Indian subjects with type 2 diabetes mellitus (T2DM), inadequately controlled with OADs alone. **Setting and design**: Retrospective study. **Methods and material**: Data was retrieved from the author's clinic database of OAD failure patients (18-80 years), who were started either with (IGlar U100, n = 120) or IDegAsp (n = 89) OD over and above the standard of care. Data of fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and glycated hemoglobin (HbA1c) from baseline and at last follow-up visits were collected. **Statistical analysis used**: Baseline characteristics and change in study parameters during the follow-up period were computed between two groups (IGlar U100 vs. IDegAsp) by unpaired *t*-test and paired *t*-test, respectively. ANCOVA test was used to compute percentage reduction in body weight, body mass index (BMI), FPG, PPG and HbA1c in between two groups (IGlar U100 vs. IDegAsp). **Results**: IDegAsp caused a significantly greater reduction in FPG, PPG and HbA1c as compared to the IGlar U100 arm. There was no significant difference in the proportion of patients with hypoglycemia between IDegAsp and IGlar U100 groups (p = 0.208). No episodes of severe hypoglycemia were reported. **Conclusion**: Comparison of IDegAsp and IGlar U100 OD in T2DM patients indicated that both were relatively safe but the former controlled FPG and PPG levels more effectively.

Keywords: Oral antidiabetic agent, insulin, hypoglycemia, type 2 diabetes mellitus, India

Currently, 573 million people are living with diabetes globally. There is a worldwide increase in the prevalence and incidence of diabetes which is predicted to rise to 643 million by 2030. In India, the number of adults with diabetes in 2021 was 74.2 million which is expected to exceed 124 million by 2045.[1] Several national and international guidelines on the treatment of type 2 diabetes mellitus (T2DM) exist.[2-5] As per all the national and international guidelines, oral antidiabetic drug (OAD) failure is an indication for starting insulin therapy. It can be defined as a clinical situation where glycated hemoglobin (HbA1c) remains above goal, despite concurrent use of an optimum dose of three or more glucose-lowering drugs of different classes, one of which should be metformin and the second, preferably a sulfonylurea, provided adequate diet and exercise have been followed, and comorbid conditions causing hyperglycemia have been ruled out.[6] Nevertheless, there is still a dilemma as to whether basal insulin or a premixed/co-formulation analog should be the choice for initiation.

Insulin treatment is administered as an injection of basal insulin or a combination of bolus and basal insulins. Insulin degludec/insulin aspart (IDegAsp) is a soluble combination of insulin degludec (IDeg), an ultra-long-acting basal insulin and the rapid-acting insulin analog, insulin aspart (IAsp). Within the

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IDegAsp formulation and after subcutaneous injection, independent pharmacokinetic/pharmacodynamic characteristics of the components are maintained.[7] IDeg has a flat and stable glucose-lowering effect that results in a much longer duration of action (>42 h), and four times lower pharmacodynamic variability than insulin glargine (IGlar U100) under steady-state conditions.[8-10] This in turn results in a lower risk of hypoglycemia, particularly nocturnal hypoglycemia with IDeg, a distinct clinical advantage over other basal insulin.[11,12] In T2DM, IDegAsp once daily (OD) has been analyzed as initiation as well as intensification strategy. IDegAsp can be initiated in either OD or twice daily (BID) doses based on the clinical situation, as monotherapy or together with metformin. T2DM patients switching from OD basal or premix insulin therapy can be converted unit-to-unit to IDegAsp OD at an equivalent previous total daily insulin dose.[13,14] IDegAsp has been shown to provide significant reductions in fasting plasma glucose (FPG), the total daily dose of insulin, and rate of overall and nocturnal hypoglycemia as compared to biphasic insulin.[15]

To suit Indian reality of diabetes management (such as high carbohydrate diet), guidelines and recommendations need to be adapted.[16,17] Thus, consensus on initiation and intensification of premix insulin in the management of T2DM recommends premix insulin/co-formulation for effective and accessible glycemic control (predominantly postprandial hyperglycemia).[18] This real-world study aimed at comparing the safety and efficacy of IDegAsp OD to that of IGlar U100 OD in insulin-naïve Indian subjects with T2DM insufficiently controlled with oral antidiabetic medicines alone.

SUBJECTS AND METHODS

Data was retrieved from the author's clinic database of OAD failure patients (18-80 years) who were started on basal insulin (IGlar U100, n = 120) or IDegAsp (n = 89) OD over and above the standard of care. The data of FPG, postprandial plasma glucose (PPG) and HbA1c from baseline and at last follow-up visit was collected for analysis.

Key eligibility criteria for study consisted of the following:

Inclusion Criteria

- Indian insulin naïve adults with T2DM.
- Age 18 to 80 years.
- On stable optimal dose of 3 OADs for last 90 days.
- HbA1c <11%.

Exclusion Criteria

- Type 1, gestational diabetes mellitus (GDM) and other types of diabetes.
- Pregnancy and lactation.
- Requiring insulin as rescue medication due to intercurrent illness in last 3 months.
- Incomplete dataset and irregular intake of history of insulin.
- Faulty injection technique.

All patients visiting the author's outdoor clinic from 1st January 2019 to 30th October 2019 were assessed for the type of diabetes therapy. Patients who had been on basal insulin (IGlar U100) or IDegAsp, OD for 35 weeks or more were included in the study. Informed consent was obtained from all subjects. Details were collected regarding basic demographics, dosage, frequency of insulin, body weight, blood pressure and glycemic control. Indications for the use of IGlar U100 and IDegAsp were recorded. Data is expressed using descriptive statistics as mean ± SEM (standard error of the mean), wherever applicable. Data was analyzed using SPSS/Microsoft Excel software. Baseline characteristics and changes in study parameters during the follow-up period were compared between two groups (IGlar U100 vs. IDegAsp) by unpaired *t*-test and paired *t*-test, respectively. Analysis of covariance (ANCOVA) test was used to compare the percentage change in body weight, body mass index (BMI), FPG, PPG and HbA1c between two groups (IGlar U100 vs. IDegAsp). Data at baseline, 35.56 ± 25.97 weeks (IGlar U100 cohort), and 28.53 ± 19.63 weeks (IDegAsp cohort) was used for analysis.

Assessment

Subjects were treated with either IDegAsp or IGlar U100 OD, using stratification (by previous OAD treatment). The IDegAsp dose was administered subcutaneously just before the largest meal of the day and IGlar U100 (Lantus®, SoloSTAR®, Sanofi-Aventis, Frankfurt, Germany) was administered according to the approved labeling (either before breakfast or at bedtime).

RESULTS

The baseline demographics and clinical parameters were found to be comparable, except for body weight that was nonsignificantly higher in the IGlar U100 arm and hence required a higher insulin dose. The mean (±SD) duration of follow-up was 35.56 ± 25.97 weeks in IGlar U100 cohort and 28.53 ± 19.63 weeks in IDegAsp

cohort and this difference was nonsignificant (p = 0.104). The glycemic triad, i.e., FPG, PPG and HbA1c was significantly reduced from baseline in both the arms (Table 1). However, IDegAsp caused statistically significant greater reduction in FPG, PPG and HbA1c as compared to the IGlar U100 arm. Three patients of IGlar U100 complained of injection site burning but no such adverse events were reported in the IDegAsp arm. There were overall 18 episodes of hypoglycemia in the IGlar U100 group and 10 episodes in the IDegAsp group. Though the proportion of patients with hypoglycemia was higher in IGlar U100 group as compared to IDegAsp group, the difference failed to reach any statistical significance (p = 0.208; Chi-square test). Severe hypoglycemia episodes were not reported.

Eighty-nine subjects (53 men and 36 women; mean age 59.49 ± 3.31 years) received IDegAsp and, 120 subjects (71 men and 49 women; mean age 61.88 ± 10.87 years) who received IGlar U100 treatment had completed the duration of 26 weeks or more. Fall in HbA1c from baseline to follow-up visit was 9.61 ± 0.78% to 8.56 ± 0.18% in the IGlar U100 cohort, and from 9.61 ± 2.12% to 8.02 ± 1.02% in the IDegAsp cohort. Mean percentage reduction in the IDegAsp cohort was found to be -16.55 ± 4.07 and was statistically significant (p = 0.044) compared -9.88 ± 2.22 in the IGlar U100 cohort.

FPG decreased from 230.69 ± 7.49 mg/dL to 154.78 ± 7.59 mg/dL (IGlar U100 cohort), from 236.08 ± 86.31 to 134.31 ± 51.40 (IDegAsp cohort) and was found statistically significant (p < 0.001). Mean percentage reduction was -33.04 ± 8.61 (IGlar U100 cohort) and -34.63 ± 9.12 (IDegAsp cohort) with p-value 0.041.

Mean percentage reduction in PPG was -20.34 ± 2.89 (IGlar U100 cohort) and -41.53 ± 4.76 (IDegAsp cohort) with p-value 0.036. PPG decreased from 295.18 ± 11.75 mg/dL to 236.37 ± 10.58 mg/dL (IGlar U100 cohort) and from 309.06 ± 106.76 to 180.76 ± 55.09 (IDegAsp cohort) and was found statistically significant (p < 0.001). Mean insulin dose/kg body weight at the end of 26 weeks was significantly lower for patients treated with IDegAsp (0.23 ± 0.22) than IGlar U100 (0.42 ± 0.57), (p = 0.010).

Table 1. Baseline Characteristics of the Patients

	IGlar U100 (n = 120)	IDegAsp (n = 89)	P (*t*-test)
Male, n (%)	71 (59.17)	53 (59.55)	0.629
Female, n (%)	49 (40.83)	36 (40.45)	
Age (years), Mean ± SEM	61.88 ± 10.87	59.49 ± 3.31	0.816
Body weight (kg), Mean ± SEM	69.65 ± 2.13	68.51 ± 11.88	0.716
SBP (mmHg), Mean ± SEM	132.22 ± 2.21	130.65 ± 2.28	0.487
DBP (mmHg), Mean ± SEM	80.56 ± 1.31	78.97 ± 1.73	0.943
BMI (kg/m^2), Mean ± SEM	26.78 ± 3.22	26.97 ± 2.19	0.865
FPG (mg/dL), Mean ± SEM	230.69 ± 7.49	236.08 ± 86.31	0.206
PPG (mg/dL), Mean ± SEM	295.18 ± 11.75	309.06 ± 106.76	0.578
HbA1c (%), Mean ± SEM	9.61 ± 0.78	9.61 ± 2.12	0.385
Insulin dose (IU), Mean ± SEM	13.44 ± 0.41	10.23 ± 1.41	0.001
Insulin dose/kg body wt. (IU), Mean ± SEM	0.20 ± 0.18	0.14 ± 0.09	0.032
LDL cholesterol (mg/dL), Mean ± SEM	90.01 ± 3.99	81.31 ± 4.86	0.039
Serum creatinine (mg/dL), Mean ± SEM	0.95 ± 0.03	1.01 ± 0.33	0.701

SEM = Standard error mean; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; BMI = Body mass index; FPG = Fasting plasma glucose; PPG = Postprandial plasma glucose; HbA1c = Glycated hemoglobin; LDL = Low-density lipoproteins.

P < 0.05 considered as statistically significant, p computed by unpaired *t*-test.

DISCUSSION

In this Indian real-world evidence study of 26 weeks, IDegAsp administered OD significantly improved HbA1c levels as compared to IGlar U100 OD. While this analysis is retrospective, not controlled, and is limited by the fact that dropouts were not studied, it does add value to existing literature. It must be noted that this study was performed in a nonreimbursed environment, where patients have to pay from their pocket for insulin and other supplies.

A multicenter, prospective, noninterventional, preference study was conducted with T2DM patients (n = 505) in India, with biphasic insulin aspart 30/70 (BIAsp 30). After 12 weeks of treatment, 96.4% of patients were willing to pay for BIAsp 30. Significantly improved mean treatment and device satisfaction was reported from baseline as well ($p < 0.0001$).[19]

As IDegAsp comprises rapid-acting insulin aspart and ultra-long-acting IDeg, it allows control over both FPG and PPG levels. IDegAsp provides advantages in dose titration, dose timing flexibility, treatment intensification (from OD to BID dose adjustments), lower injection burden, easy switching and lower hypoglycemia risk. IDegAsp and other antihyperglycemic drugs can be co-administered; however, sulfonylureas need to be stopped or their dose reduced. On the other hand, dose of IDegAsp may need to be lowered upon the addition of glucagon-like peptide-1 receptor agonists or sodium-glucose co-transporter-2 inhibitors.[13,14] In a 12-week follow-up study with treatment-naïve, recently diagnosed T2DM Indian patients (n = 41), Chaudhuri et al observed a significant improvement in FPG, PPG and HbA1c over the study period with 85.4% of patients receiving OD IDegAsp (10 units) + metformin extended-release (1 g/day).[20] Only 2 patients were reported for symptomatic hypoglycemia and none for severe or nocturnal hypoglycemia. Weight changes were nonsignificant. Conclusively, IDegAsp (OD or BID) was safe and effective for treatment-naive Indian patients.

In a 16-week long exploratory study, it was found that IDegAsp was able to achieve target HbA1c <7.0%, without confirmed hypoglycemia in 67% of subjects (who were poorly controlled on metformin). The daily dose requirement of IDegAsp was 0.57 ± 0.23 U/kg and was 13% lower than that of BIAsp 30. In this study, significantly lower FPG and lower rate of confirmed hypoglycemia were noted with IDegAsp.[21] Another 26-week long Asian study observed a lower dose requirement of IDegAsp OD (0.79 U/kg), as compared to BIAsp 30, in controlling HbA1c, with lower FPG and similar (low) risk of severe hypoglycemia.[22]

Effective glycemic control was achieved including achievement of target HbA1c levels (8.02 ± 1.02%) with IDegAsp, after 26 weeks of treatment, with a percentage reduction -16.55 ± 4.07 in the IDegAsp cohort compared to -9.88 ± 2.22 in the IGlar U100 cohort ($p = 0.044$) (Table 2). Superior reduction in HbA1c was seen with OD IDegAsp as compared to OD IGlar U100 in a 26 weeks randomized controlled trial wherein patients in the OD IDegAsp arm took it before the major meal.[23] In this study, participants on IDegAsp received relatively lower mean total insulin dose compared with those on IGlar U100. Patients receiving IDegAsp were able to reduce their FPG levels (134.31 ± 51.40) to a greater extent than with IGlar U100 (154.78 ± 7.59) $p < 0.001$, while receiving lower insulin dose (Table 2), suggesting that the glucose-lowering effects of IDeg are preserved in IDegAsp. A nonsignificant increase in mean body weight was observed in patients at 26 weeks associated with IDegAsp. IDegAsp provided significant control as compared to IGlar U100 in reducing the PPG increment. Monnier et al[24] had reported that reduction of PPG excursions has profound effects on long-term glycemic control once FPG has reached the target. The results of this real-world study support this observation as we find a larger reduction in HbA1c with IDegAsp while, the reduction in FPG was similar in both treatment groups after 26 weeks (Table 3).

Both treatments had similar safety profiles. Findings demonstrate that IDegAsp results in a lower rate of hypoglycemia compared with IGlar U100 when using this threshold in the Indian population.[23] The BOOST study data also supports this finding. As hypoglycemia is of particular concern in the elderly, the results of this post hoc analysis are reassuring. The low rates of hypoglycemia are suggest that there is no need for special precautions when using IDegAsp in the elderly.[13] A different approach was selected by Monnier and co-authors[24] to estimate the relative contribution of FPG and PPG to the overall glycemia. It was stated that PPG plays a major role in patients suffering from mild or moderate hyperglycemia. In Asian T2DM patients, PPG at 4 and 24 hours after meals was a predominant contributor to excess hyperglycemia in well-controlled patients and was equally important as FPG or PPG in moderately to poorly controlled patients with mean HbA1c up to 10%.[25] The data on the Indian population from this study indicates that PPG strongly correlates with HbA1c or contributes significantly to overall glycemic control. Hence, PPG monitoring will be more

Table 2. Change in Study Parameters During the Follow-up Period

	IGlar U100 Cohort (n = 120)			IDegAsp Cohort (n = 89)		
	Baseline, Mean ± SEM	Follow-up Mean ± SEM	P	Baseline, Mean ± SEM	Follow-up Mean ± SEM	P
Body weight (kg)	69.65 ± 2.13	69.58 ± 2.13	0.714	68.51 ± 11.88	69.04 ± 1.19	0.873
BMI (kg/m^2)	26.78 ± 3.22	27.05 ± 0.69	0.830	26.97 ± 2.19	27.19 ± 3.42	0.812
SBP (mmHg)	132.22 ± 2.21	130.61 ± 1.59	0.736	130.65 ± 2.28	130.44 ± 1.64	0.907
DBP (mmHg)	80.56 ± 1.31	81.36 ± 1.07	0.782	78.97 ± 1.73	77.21 ± 1.71	0.901
FPG (mg/dL)	230.69 ± 7.49	154.78 ± 7.59	<0.001	236.08 ± 86.31	134.31 ± 51.40	<0.001
PPG (mg/dL)	295.18 ± 11.75	236.37 ± 10.58	<0.001	309.06 ± 106.76	180.76 ± 55.09	<0.001
HbA1c (%)	9.61 ± 0.78	8.56 ± 0.18	<0.001	9.61 ± 2.12	8.02 ± 1.02	<0.001
Serum creatinine (mg/dL)	0.95 ± 0.03	0.99 ± 0.03	0.901	1.01 ± 0.33	1.03 ± 0.39	0.897
Insulin dose (IU)	13.44 ± 0.41	24.1 ± 1.45	<0.001	10.23 ± 1.41	16.31± 3.78	0.768
Insulin dose/kg body wt. (IU), Mean ± SEM	0.20 ± 0.18	0.42 ± 0.57	<0.001	0.14 ± 0.09	0.23 ± 0.22	0.010

SEM = Standard error mean; SBP = Systolic blood pressure; DBP = Diastolic blood pressure; BMI = Body mass index; FPG = Fasting plasma glucose; PPG = Postprandial plasma glucose; HbA1c = Glycated hemoglobin.

P < 0.05 considered as statistically significant, p computed by paired *t*-test.

Table 3. Percentage Reduction in Study Variables

	IGlar U100	IDegAsp	P (ANCOVA)
Percent change in body weight, Mean ± SEM	-0.11 ± 0.02	0.72 ± 0.66	0.102
Percent change in BMI, Mean ± SEM	-0.93 ± 0.08	0.85 ± 0.52	0.712
Percent change in FPG, Mean ± SEM	-33.04 ± 8.61	-34.63 ± 9.12*	0.041
Percent change in PPG, Mean ± SEM	-20.34 ± 2.89	-41.53 ± 4.76*	0.036
Percent change in HbA1c, Mean ± SEM	-9.88 ± 2.22	-16.55 ± 4.07*	0.044

SEM = Standard error mean; BMI = Body mass index; FPG = Fasting plasma glucose; PPG = Postprandial plasma glucose; HbA1c = Glycated hemoglobin.

P < 0.05 considered as statistically significant, p computed by ANCOVA test adjusted for baseline values.

conducive for optimal glycemic control and prevent long-term diabetes complications than FPG alone in the absence of HbA1c, especially in developing countries.

The STARCH study on the Indian population showed that T2DM patients from across India consume higher carbohydrates (CHO) in their diet (such as rice, idli and so on), more than the dietary recommendations.[14,25] Around 64.1 ± 8.3% (95% confidence interval [CI] 63.27-64.93) of total calories came from total CHO in the T2DM group. This reflects that CHO consumption by Indian T2DM patients is higher (Δ4.1% above the upper limit of 60%) than that recommended by the guidelines and within the recommended limits as per the WHO expert consensus. In addition to dietary and lifestyle modifications, multiple therapeutic strategies like insulin may benefit T2DM patients. This approach may have a leading role in an Indian setting where the role of α-glucosidase inhibitors (AGIs) is more significant because of CHO-rich meal, as seen in this study.[14] The choice of insulin for initiation has been a matter of debate, with evidence slightly being in favor of basal insulin as recommended by various western guidelines. Nonetheless, insulin initiation was considered at HbA1c levels as high as 8.5 or 9%, where the contribution of FPG was found to be substantially higher in the western population. On the contrary, a study done by Wang et al has conclusively revealed contribution of PPG at all quintiles of HbA1c in the South-East Asian population.[25] While premixed analogs were a part of the International Diabetes Federation (IDF) guidelines to initiate insulin,

studies revealed greater reduction of HbA1c at the cost of increased hypoglycemia. Availability of IDegAsp with data of reduced overall and nocturnal hypoglycemia versus premixed analogs as well as IGlar U100 made us ponder about its utility as a choice of once daily insulin in OAD failure subjects. IDegAsp demonstrated greater reduction in FPG, PPG and HbA1c as compared to IGlar U100. On the safety front, no statistically significant difference in hypoglycemia was noted between the two arms.

CONCLUSION

In conclusion, IDegAsp OD was significantly better as compared to IGlar U100 in improving glycemic control and in controlling PPG excursions without compromising FPG control or safety in Indian patients. IDegAsp OD provides predictable and efficacious FPG and PPG control in insulin-naïve patients with T2DM in a single injection while significantly reducing the risk of nocturnal-confirmed hypoglycemia compared with IGlar U100 in the Indian population. In the context of high CHO utilization in India, or patients with dominant postprandial hyperglycemia, premix insulin/co-formulation can offer effective and convenient glycemic control.

Key Messages

IDegAsp OD superiorly improves glycemic control and PPG excursions without compromising FPG control than IGlar U100. IDegAsp provides effective FPG and PPG control along with significant risk reduction of nocturnal-confirmed hypoglycemia. In a high carbohydrate consumption setting or predominant postprandial hyperglycemia, premix insulin/co-formulation can offer effective and convenient glycemic control.

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OBSERVATIONAL STUDY

Usage Pattern of Glimepiride/Metformin Fixed-dose Combination in Type 2 Diabetes Patients with CVD or at Risk of CVD: An Experience in Indian Setting

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ABSTRACT

Background: Diabetes is associated with almost twofold increased risk of cardiovascular diseases (CVD). The present case-based questionnaire survey evaluated the treatment pattern and clinical experience of healthcare professionals in prescribing glimepiride/metformin fixed-dose combination (FDC) to type 2 diabetes mellitus (T2DM) patients with CVD or those patients who are at risk of CVD in the Indian settings. **Material and methods:** A retrospective, multicenter, observational, case-based questionnaire survey was conducted in Indian healthcare centers using medical records of patients having T2DM, with CVD or are at risk of CVD, who were prescribed any strength of glimepiride/metformin FDC. Data was collected from the patients' medical records and was analyzed using statistical tests. **Results:** A total of 680 patients with T2DM with CVD or at risk of CVD were included in this study. Mean duration of diabetes in the patients was 5.7 ± 4.8 years. About 68.5% patients had hypertension, 47.9% had dyslipidemia, 25.4% had coronary artery disease (CAD), 3.6% had transient ischemic attack (TIA), 4.8% had peripheral arterial disease (PAD) and 2.9% had heart failure. Around 18.1% patients had CVD after diabetes was diagnosed, while 81.9% presented with cardiovascular (CV) issues at the time of diabetes diagnosis. All patients received glimepiride/metformin FDC as first-line therapy. About 68.2% patients on glimepiride/metformin FDC had blood pressure within optimal limits. A large proportion of patients had improvement in glycemic parameters. Weight change was noted in 18.4% of the patients overall. Of these, 59.2% had reduction in weight. There were no major adverse events and treatment efficacy and tolerability were reported as good to excellent for 94.6% and 92.9% patients, respectively. **Conclusion:** This case-based questionnaire survey demonstrates the usage pattern of various strengths of glimepiride/metformin FDC and the clinicians' practice approach regarding early initiation of this combination in Indian patients with diabetes who have or are at risk of CVD.

Keywords: Type 2 diabetes, CVD, glimepiride/metformin combination, combination therapy

Diabetes and raised levels of blood glucose, even below the threshold for diabetes diagnosis, are linked with almost twofold increased risk of cardiovascular diseases (CVD). It has been reported that the prevalence of CVD is around 32% and that of coronary artery disease (CAD) is about 21% among adults living with diabetes in high- and middle-income countries.[1]

The most common forms of CVD tied to diabetes include coronary heart disease, cerebrovascular disease, peripheral artery disease (PAD) and congestive heart failure.[1] Diabetes, and even lesser degree of dysglycemia, are associated with adverse cardiovascular (CV) outcomes.[2]

Across the spectrum of fasting plasma glucose (FPG), glycated hemoglobin (HbA1c) or 2-hour glucose test results, each standard deviation (SD) is tied to a 6% to 20% increased risk of CV events.[1] Diabetes tends to increase the risk of CVD by several mechanisms, such as insulin resistance, inflammation, endothelial dysfunction and the adverse effects of glucose on microvasculature. Raised blood glucose levels are also

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linked with hypertension, dyslipidemia and obesity. Smoking and low levels of physical activity also contribute to increased CVD risk.[1]

Metformin is a well-established first-line treatment of type 2 diabetes mellitus (T2DM) and is effective both as monotherapy and in combination with other hypoglycemic agents. Recent data from CV and renal outcomes trials have shown additional protection from complications for some high-risk patients with other hypoglycemic medications. So, use of newer antihyperglycemic drugs with CV benefits can be considered in high-risk patients.[3] The 10-year follow-up of the United Kingdom Prospective Diabetes Study (UKPDS) noted persistent benefit after metformin therapy in overweight T2DM patients, with significant risk reductions persisting for any diabetes-related end point, myocardial infarction (MI) and death from any cause over the long-term.[4]

Modern sulfonylureas (SUs), like glimepiride, are CV-neutral. They can maintain myocardial ischemic preconditioning with lesser CV side effects in comparison with conventional SUs. Additionally, these SUs do not seem to be associated with all-cause or CV mortality, or with an increased risk of MI or stroke. Thus, they are cardiac-friendly and can be safely used in diabetes patients with CV risk, MI or stroke.[5] An International expert group advocates that on account of their safety, efficacy as well as low-cost, modern SUs could be the drugs of choice for the treatment of diabetes. The group endorses the use of newer SUs like glimepiride on account of their CV safety. The International Diabetes Federation also says that SUs have neutral effects on major CV events. Glimepiride, in particular, has been found to be associated with reduced mortality in diabetes patients with CAD, compared with other SUs.[5]

Experts are also of the opinion that because modern SUs have been used as comparators in other cardiovascular outcome trials (CVOTs), CVOTs with SUs are not needed.[6] For instance, the CAROLINA trial compared linagliptin, a dipeptidyl peptidase-4 (DPP-4) inhibitor, with glimepiride in terms of major adverse CV outcomes in diabetes patients and noted the drugs to exert a similar effect with regard to a risk of a composite CV outcome.[7]

The CV-neutral profile of metformin and modern SUs in diabetes patients has opened new avenues for the management of patients with diabetes and CVD. There is a need for physician opinion on the use of glimepiride/metformin FDC in diabetes patients with CVD. A case-based questionnaire survey was thus designed to evaluate the demography, treatment pattern including duration and various dosages of glimepiride/metformin FDC in T2DM patients with CVD or at risk of CVD.

MATERIAL AND METHODS

Study Design

This was a retrospective, multicenter, observational, case-based questionnaire survey. It was conducted with 86 healthcare professionals (HCPs) across different centers in India between July 2020 and May 2021. The study protocol was designed in accordance with the principles of the Declaration of Helsinki.

Study Population

Patients of both sexes, aged above 18 years, who received a glimepiride/metformin FDC in any strength, for the treatment of T2DM were recruited in the study. Patients with existing CVD comorbidities or at risk of CVD were included in the study.

Data Collection

A case report format was developed to evaluate the clinical utilization pattern of different strengths of glimepiride/metformin FDC in addition to other oral hypoglycemic agents (OHAs) in diabetes patients. The questionnaire was sent to 86 HCPs across India via an online portal. Link to the portal was shared through e-mail. Questions regarding demographic characteristics, such as age, sex, body mass index (BMI) and medical history; presence of CVD; duration of diabetes; biochemical measures, including FPG, postprandial plasma glucose (PPG) and HbA1c levels; comorbidities; antidiabetic drugs taken; antidiabetic drug up-titrations and down-titrations; weight changes; hypoglycemic episodes and other adverse events during treatment, were included in the questionnaire. An online portal was developed where the HCPs were required to fill in the information. A descriptive analysis was performed with the data provided on the portal.

Statistical Analysis

All continuous variables are expressed as mean ± SD or median with interquartile range as per the distribution of data. Categorical variables are expressed as number and their respective percentage. Differences in binary and ordinal variables between two independent groups were analyzed by the exact Chi-square test. All the

reported p-values are two-sided and p-values <0.05 are considered to indicate statistical significance. All data entries and statistical analyses were performed by using SPSS® Version 23.0 software.

RESULTS

A total of 680 patients with T2DM with CVD or at risk of CVD were included in this retrospective observational questionnaire-based analysis. The mean (±SD) age of patients was 49.2 (±12.9) years (range 19-84 years). Patient demographics are summarized in Table 1.

Mean duration of diabetes in the patients was 5.7 ± 4.8 years (range 0.0-25.5 years). A vast majority of patients had diabetes duration of 1 to 5 years (n = 407), followed by 6 to 10 years (n = 164), 11 to 15 years (n = 46), <1 year (n = 29), 16 to 20 years (n = 22) and >20 years (n = 12).

A total of 466 (68.5%) patients had hypertension, 326 (47.9%) had dyslipidemia, 173 (25.4%) had CAD, 25 (3.6%) had transient ischemic attack (TIA), 33 (4.8%) had PAD and 20 (2.9%) had heart failure (Table 2). A total of 123 (18.1%) patients had CVD after diabetes was diagnosed, while 557 (81.9%) presented with CV issues at the time of diabetes diagnosis.

All patients included in the study received glimepiride/metformin FDC as first-line therapy. The most commonly prescribed regimen was glimepiride 0.5 mg/metformin 500 mg (31.8%) (Table 3). A majority of the patients (n = 407) received glimepiride/metformin FDC therapy early during the course of the disease, i.e., a total of 407 patients with diabetes duration of 1 to 5 years were prescribed combination therapy.

Table 1. Patient Demographics

Variable	Mean ± SD/n (%)
Age (years)	49.2 ± 12.9
Weight (kg)	73.2 ± 10.4
BMI (kg/m^2)	27.7 ± 3.9
Gender	Male - 446 (65.6)
	Female - 231 (34)
	Other - 3 (0.4)

SD = Standard deviation; BMI = Body mass index.

Table 2. Comorbidities with T2DM

Comorbidities	Patients N (%)
Hypertension	466 (68.5)
Dyslipidemia	326 (47.9)
CAD	173 (25.4)
TIA	25 (3.6)
PAD	33 (4.8)
Heart failure	20 (2.9)

T2DM = Type 2 diabetes mellitus; CAD = Coronary artery disease; TIA = Transient ischemic attack; PAD = Peripheral artery disease.

Table 3. Different Strengths of Glimepiride/Metformin FDC Prescribed to Study Participants

Glimepiride/Metformin FDC regimen	Patients N (%)
Glimepiride 0.5 mg/Metformin 1000 mg	14 (2.1)
Glimepiride 1 mg/Metformin 1000 mg	44 (6.5)
Glimepiride 2 mg/Metformin 1000 mg	53 (7.8)
Glimepiride 3 mg/Metformin 1000 mg	10 (1.5)
Glimepiride 4 mg/Metformin 1000 mg	7 (1)
Glimepiride 0.5 mg/Metformin 500 mg	216 (31.8)
Glimepiride 1 mg/Metformin 500 mg	175 (25.7)
Glimepiride 2 mg/Metformin 500 mg	119 (17.5)
Glimepiride 1 mg/Metformin 850 mg	4 (0.6)
Glimepiride 2 mg/Metformin 850 mg	15 (2.2)
Glimepiride 3 mg/Metformin 850 mg	23 (3.4)
Total	**680 (100)**

Dose titration was done in 277 patients. Up-titration was done in 239 patients (35.1%) while down-titration was done in 38 patients (5.6%). In all, 392 (57.6%) patients received other OHAs along with glimepiride/metformin FDC. These included sodium-glucose cotransporter-2 (SGLT2) inhibitors (n = 123 [18.1%]), DPP-4 inhibitors (n = 241 [35.4%]), alpha-glucosidase inhibitors (AGIs) (n = 71 [10.4%]), thiazolidinediones (n = 18 [2.6%]) and glucagon-like peptide-1 (GLP-1) agonists (n = 3 [0.4%]). Around 7.9% patients also received insulin therapy. Very few patients experienced hypoglycemia (n = 36 [5.3%]).

Majority of the patients on glimepiride/metformin FDC therapy had blood pressure (BP) within optimal limits (n = 464 [68.2%]). Weight change was evident in 125 patients (18.4%) overall. Majority of these patients (n = 74 [59.2%]) had reduction in weight. Mean HbA1c at study initiation was 8.3% ± 1.3% and decreased to 7.2% ± 3.1% after treatment with glimepiride/metformin FDC therapy. Mean FPG prior to treatment was 174.1 ± 46.4 mg/dL and declined to 124.9 ± 28.9 mg/dL after treatment. Likewise, mean PPG before and after

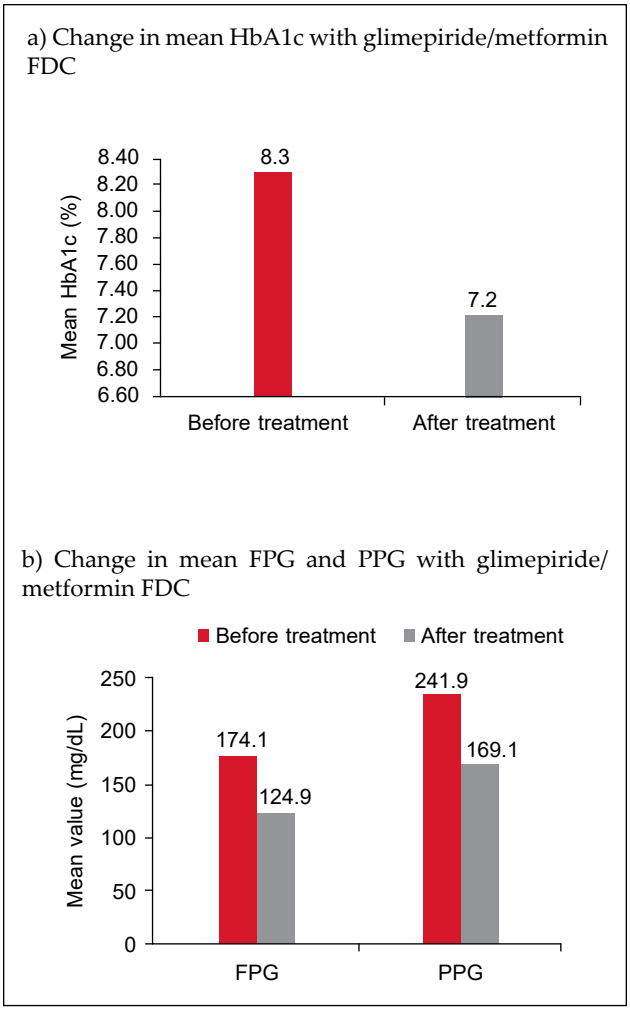

Figure 1. Changes in glycemic parameters after glimepiride/ metformin therapy.

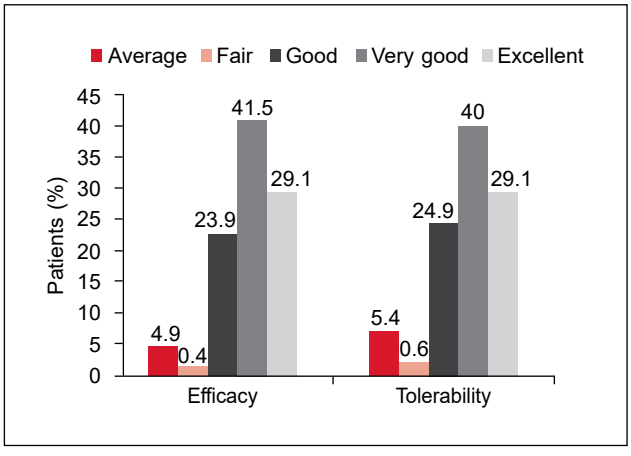

Figure 2. Treatment efficacy and tolerability rating in study patients.

treatment was 241.9 ± 56.7 mg/dL and 169.1 ± 34.7 mg/dL, respectively. Changes in the three glycemic parameters are depicted in Figure 1 a and b.

No major adverse events were noted during the study duration. Minor adverse events included flatulence, heartburn, nausea, occasional dyspepsia, reduced appetite and occasional diarrhea.

Physician evaluation of efficacy and tolerability were reported as good to excellent for 94.6% and 92.9% patients, respectively (Fig. 2).

DISCUSSION

India, with the second highest diabetes population in the world, faces several challenges in the management of this chronic disease. The high prevalence of comorbid conditions makes it tough for both the patient and the healthcare practitioner to appropriately manage the condition.[8]

The likelihood of macrovascular complications increases with hyperglycemia severity. While the available antidiabetic agents are effective for the management of hyperglycemia, most patients with T2DM are at a considerable risk for CVD.[9]

The present study explored the usage of glimepiride/ metformin FDC in patients with T2DM who had CVD or were at risk of developing CVD. This case-based questionnaire survey also assessed the approach of HCPs across India regarding early use of glimepiride/ metformin FDC in these patients.

About 18.1% patients in our study were reported to have developed CVD after diabetes was diagnosed, while 81.9% had CV issues at the time of diabetes diagnosis. Hypertension was the most common comorbidity in the study participants. This is in line with other studies conducted in Indian patients. A study by Pati and Schellevis also noted hypertension (62%) to be the most common comorbid condition in diabetes patients.[8] In a real-world study by Sahay et al, 42.3% patients had hypertension.[10] Similar results were noted by Prasanna Kumar et al.[11]

Other common comorbidities in our study included dyslipidemia (47.9%) and CAD (25.4%). Similar findings have been noted in other studies conducted in Indian T2DM patients, with other common comorbidities being dyslipidemia, CAD and neuropathy.[10,11] One of the studies also noted retinopathy, nephropathy, peripheral vascular disease and diabetic foot as common comorbidities.[12] These studies present a picture of the varied comorbid conditions seen in T2DM patients in India.

The co-existence of diabetes and comorbidities like hypertension can heighten the odds of micro- and

macrovascular complications.[13] Early combination therapy with glimepiride and metformin carries the advantage of a legacy effect, by means of early glycemic control and averting a negative glycemic memory tied to micro- and macrovascular complications.[10]

All patients included in this study received glimepiride/metformin FDC as first-line therapy. Besides, a large number of the patients received glimepiride/metformin FDC therapy soon after diagnosis (duration 1-5 years). This is in accordance with the recommendations of the American Diabetes Association (ADA), which recommends that early combination therapy has to be considered in some patients right at treatment initiation in order to delay treatment failure. In patients with HbA1c ≥1.5% above the target, dual combination therapy is needed.[14] While the usual practice is to follow stepwise addition of antidiabetic medications to metformin to maintain A1c target, evidence now favors initial combination therapy in order to attain glycemic goals early.[15]

The CV risks associated with antidiabetic drugs have long been debated, especially those for SUs. However, there is ample data pointing to the CV-neutral effects of metformin and modern SUs now. Use of metformin is associated with a significant reduction in CV events and decrease in BP.[16] It is associated with lower all-cause mortality, lower CV mortality and lower rates of MI and stroke. It also has potential favorable effects on some CV risk factors, such as plasma triglycerides, low-density lipoprotein (LDL), very low-density lipoprotein (VLDL) and high-density lipoprotein (HDL) levels.[16] Metformin is also effective in reducing biomarkers of inflammation and endothelial dysfunction in T2DM patients and is tied to reduced CV risk, both with regard to mortality and incidence in patients with diabetes.[17,18]

The modern SU, glimepiride, is also associated with decreased CV risk, compared with other SUs.[16] Modern SUs may not be linked to the unfavorable effects seen with conventional SUs. Glimepiride use is associated with decreased mortality rates in diabetes patients with CAD when compared with glyburide and may be preferred in patients with underlying CAD.[19] Based on recent reports from trials like ADVANCE, TOSCA.IT and CAROLINA, there seems to be no difference in CV risk between SUs and OHAs, like pioglitazone or linagliptin.[20] In a recent comparison from the CAROLINA and CARMELINA trials, the investigators emphasized that the CV safety of glimepiride is re-assuring.[21] An international clinical expert group also suggests that modern SUs are safe for use in T2DM patients with CV risk, MI or stroke.[5] Glimepiride also has anti-atherosclerotic effect.[22] The ADA and the Research Society for Study of Diabetes in India (RSSDI) also suggest that modern SUs, such as glimepiride, have a neutral CV risk profile.[10]

Combination therapy with metformin and SUs has also been reported to be as safe as metformin monotherapy in terms of CV mortality and all-cause mortality.[23] Ioacara et al noted a beneficial effect on all-cause mortality for SUs added to initial metformin monotherapy and also when metformin was added to initial SU monotherapy among T2DM patients.[24] Metformin and glimepiride combination has also been associated with significant reduction in total cholesterol, triglyceride, LDL cholesterol and VLDL cholesterol levels, compared to metformin combined with sitagliptin or voglibose.[25] These effects validate the use of a combination of glimepiride and metformin in T2DM patients who have CVD or are at risk of CVD, as seen in our study.

The use of this combination has become increasingly common in India. A recent real-world study in the Indian setting showed that glimepiride/metformin FDCs were commonly used in T2DM patients with comorbidities and diabetes complications. The authors concluded that glimepiride/metformin FDCs are appropriate for both early and long-standing diabetes.[10] This is in line with our study, where all patients, across various age groups and diabetes duration, received glimepiride/metformin FDC as first-line therapy.

Around 7.9% patients in our study received insulin therapy along with glimepiride/metformin FDC treatment. Glimepiride/metformin combination therapy plus insulin has been reported to result in significant improvement in overall glycemic control.[26] Prasanna Kumar and colleagues also corroborated the beneficial effects of glimepiride/metformin combination with insulin on glycemic control.[11] Only 5.3% of the patients experienced hypoglycemia. Similar results were observed in a study by Unnikrishnan et al, where only 5.8% patients on glimepiride/metformin FDC therapy had a hypoglycemic event.[12]

Majority of the patients on glimepiride/metformin FDC therapy had BP within optimal limits (68.2%). Derosa and Sibilla have shown that antidiabetic medications might have a small, though significant, impact on BP in patients with T2DM.[27] While metformin has beneficial effects on several CV risk factors and decreases cardiac events in overweight individuals with T2DM, newer SUs, such as glimepiride, are considered CV safe as they are more selective.[27] Around 18.4% patients in this study had a change in weight and out of these patients,

59.2% had reduction in weight. Previous studies have; however, shown that combination therapy with glimepiride and metformin was associated with increase in weight.[28] Improvements in glycemic parameters were noted in this study with the use of different strengths of glimepiride/metformin FDCs. A study by Pareek et al also showed that glimepiride/metformin combination led to improvement in metabolic control as determined by changes in HbA1c, FPG and PPG.[29] Prasanna Kumar and colleagues also noted a significant reduction in HbA1c in patients treated with glimepiride/metformin combination along with insulin.[11] The efficacy and tolerability were reported to be good to excellent for 92.79% and 92.2% of patients, respectively. The real-world study by Prasanna Kumar et al also noted similar findings with good to excellent tolerability irrespective of disease duration.[11]

This study includes data on key parameters such as HbA1c, FPG and PPG as well as on efficacy and tolerability with glimepiride/metformin FDC, which are valuable to interpret the effects of this combination in T2DM patients having CVD or at risk of developing CVD. The limitation of this study is its retrospective nature. There is a need to further validate these findings in large-scale prospective observational studies to understand the efficacy and safety of glimepiride/metformin FDCs in this patient population in the Indian setting.

CONCLUSION

This case-based questionnaire survey of the usage of glimepiride/metformin FDC in the Indian setting shows that various strengths of glimepiride/metformin FDCs are commonly prescribed in patients with T2DM who have CVD or have a risk of developing CVD, as a first-line therapy, with or without other OHAs. There was a significant improvement in glycemic parameters with weight loss and fewer hypoglycemia episodes with this combination, with the BP being within optimal limits for a majority of patients. It can be concluded that early initiation of this combination is widely prescribed to diabetes patients with CVD or those patients who are at risk of CVD.

Authorship

All authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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Conflict of Interest

There are no conflicts of interest to declare.

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■■■■

OBSERVATIONAL STUDY

Usage of Glimepiride/Metformin Fixed-dose Combination with Insulin in Management of Type 2 Diabetes Mellitus: An Indian Experience

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ABSTRACT

Background: Type 2 diabetes mellitus (T2DM) poses a major public health burden. The present case-based questionnaire survey evaluated the treatment pattern and clinical experience of healthcare professionals (HCPs) in prescribing glimepiride/metformin fixed-dose combination (FDC) with insulin, with or without other oral hypoglycemic agents (OHAs), to patients with T2DM in the Indian setting. **Material and methods:** A retrospective, multicenter, observational, case-based questionnaire survey was conducted at several healthcare centers in India with the help of medical records of patients having T2DM, who were prescribed different strengths of glimepiride/metformin FDC. Data was collected from the patients' medical records and were analyzed using statistical tests. **Results:** A total of 1,013 patients with T2DM were included in this study. The mean (± standard deviation [SD]) age of patients was 53.5 ± 13.9 years. Mean duration of diabetes was 6.3 ± 4.8 years. About 70.1% of the patients received glimepiride/metformin FDC as first-line therapy and 29.9% received it as second-line therapy. Around 66.3% of the patients in first-line glimepiride/metformin FDC group received insulin once a day, and the proportion increased to 86.8% of the patients in second-line therapy group. Other OHAs were used in 754 (74.4%) patients. About 18.2% (n = 185) patients reported change in weight, with a slightly larger number of patients having reduction in weight. There was considerable reduction in HbA1c, FPG and PPG in patients receiving glimepiride/metformin FDC with insulin, irrespective of OHA use. Efficacy and tolerability were reported as good to excellent for 96.2% and 94.8% patients, respectively. **Conclusion:** This case-based questionnaire survey shows the usage pattern of various strengths of glimepiride/metformin FDC with insulin and the HCPs' practice approach regarding early initiation of this combination in Indian patients with T2DM.

Keywords: Type 2 diabetes mellitus, glimepiride/metformin combination, combination therapy, insulin

The global public health crisis of type 2 diabetes mellitus (T2DM) has already attained the status of a pandemic, and has seen a shift from the developed world to the developing nations of Asia, Africa and Latin America.[1] India has the second largest number of adults with diabetes globally, and is expected to retain the spot even in 2045.[2]

Type 2 diabetes is a metabolic disorder which occurs as a result of either deficient insulin secretion, pancreatic β-cell damage or insulin resistance. The noninsulin pharmacological management of type 2 diabetes involves several different drug classes, including biguanides, insulin secretagogues (sulfonylureas [SUs] and mitiglinides), insulin sensitizers (peroxisome proliferator-activated receptor [PPAR] agonists), alpha-glucosidase inhibitors (AGIs), incretin mimetics (glucagon-like peptide 1 [GLP-1] agonists and dipeptidyl peptidase-4 [DPP-4] inhibitors), amylin antagonists and sodium-glucose cotransporter-2 (SGLT2) inhibitors.[3]

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Metformin, a biguanide, is the choice of initial pharmacologic agent for the treatment of type 2 diabetes. Biguanides diminish intestinal glucose absorption and limit hepatic glucose production as well as output as they decrease gluconeogenesis and stimulate glycolysis. This drug class does not cause hypoglycemia or lead to weight gain, has antihypertriglyceridemic effect and can reduce the risk of cardiovascular (CV) events.[3,4]

Considering the progressive nature of T2DM, it may not be possible to maintain the glycemic targets with monotherapy beyond a few years. Combination therapy becomes necessary in order to achieve glycemic control and delay β-cell deterioration. While it is recommended to follow stepwise addition of drugs to metformin, initial combination therapy may also be considered to quickly attain glycemic goals in some patients.[3,4]

Sulfonylureas are the agents which have a large body of evidence, experience and outcome data to support their role in managing patients with diabetes. The World Health Organization (WHO) recommends using an SU as second-line treatment in patients who fail to achieve glycemic control with metformin alone or have contraindications to metformin therapy, especially in resource-limited settings where a large number of patients have to pay for their treatment out of their own pocket.[5] Modern SUs, such as glimepiride, have an established safety and efficacy profile in T2DM patients. SUs can safely be used in combination with all classes of oral hypoglycemic agents (OHAs), except glinides.[6]

Additionally, modern SUs are cardio-safe. The CV safety of SUs was established by the CAROLINA trial, the first cardiovascular outcome trial (CVOT) that compared glimepiride with DPP-4 inhibitor linagliptin and reported no difference in CV risk between the groups.[7] The risk of hypoglycemia is also reduced with the use of modern SUs, such as glimepiride, and they have weight neutral effects, when compared with conventional SUs.[6] SUs can therefore be used across the diabetes continuum right from an early stage as monotherapy added to lifestyle measures, as dual or triple therapy, or as add-on to basal insulin.[8]

Oral antidiabetic drugs (OADs) sometimes fail, or are inadequate, to achieve the target glycemic control and maintain it. This OAD failure or inadequacy necessitates the use of insulin therapy.[9] The rationale for insulin and OAD combination can be appreciated after understanding the pathophysiology of T2DM and the action of the oral agents. Patients with T2DM are insulin-deficient as well as insulin-resistant, thus requiring high doses of exogenous insulin. Secondly, peripheral insulin delivery results in hyperinsulinemia, which eventually contributes to late complications. SUs act by stimulating insulin release into the portal vein and have a role in enhancing peripheral insulin action. Meanwhile, metformin enhances glucose metabolism and insulin sensitivity and decreases the amount of insulin required.[10] OADs alone may not be able to achieve and maintain glycemic control on account of a deterioration in β-cell function. Hence, the need for exogenous insulin. Combination therapy with OADs and insulin can yield excellent glycemic control, reduce insulin dosages and certain combinations can even check the weight gain seen with insulin therapy.[11]

Sustained glycemic control may not be achieved in many patients with insulin combination with non-SU drugs.[12] A combination of insulin and SU has rather been reported to be more effective than insulin alone in the treatment of diabetes patients with better glucose profiles and reduced insulin requirement.[10] For instance, addition of glimepiride to insulin treatment has been shown to result in greater improvement in glycemic control with a significantly smaller daily insulin dose.[12] Use of glimepiride/metformin combination plus insulin has also been reported to yield greater reduction in blood glucose levels than glimepiride plus insulin.[13] In a study by Prasanna Kumar et al, glimepiride/metformin combination with insulin led to reduction in glycated hemoglobin (HbA1c) in T2DM patients with a mean change of 1.33%.[14]

Considering the benefits of glimepiride and metformin in combination with exogenous insulin in the management of T2DM, there is a need for physician opinion on glimepiride/metformin FDC along with insulin amongst Indian T2DM patients.

A case-based questionnaire survey was conducted to evaluate the demography, treatment pattern, including duration and various dosages of glimepiride/metformin FDC used with insulin in the management of T2DM.

MATERIAL AND METHODS

Study Design

This was a retrospective, multicenter, observational, case-based questionnaire survey. It was conducted with 147 healthcare professionals (HCPs) across different centers in India from July 2020 through May 2021. The study protocol was designed in accordance with the principles of the Declaration of Helsinki.

Study Population

Patients of both sexes, aged above 18 years, diagnosed with T2DM who received a glimepiride/metformin FDC in any strength along with insulin were recruited in the study.

Data Collection

A case report format was developed to determine the pattern of use of different strengths of glimepiride/metformin FDCs with insulin with or without other OHAs in diabetes patients. The questionnaire was sent to 147 HCPs across India via an online portal. Questions regarding demographic characteristics, such as age, sex, body mass index (BMI) and medical history; duration of diabetes; comorbidities; biochemical measures, such as fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and HbA1c levels; antidiabetic drugs used; antidiabetic drug up-titrations and down-titrations; weight change; hypoglycemic episodes and other adverse events during treatment, were included in the questionnaire. An online portal was developed where the HCPs filled in the information. A descriptive analysis was performed with the data provided on the portal.

Statistical Analysis

Descriptive statistical analyses, including mean and standard deviation (SD) for continuous variables and count and percentage for categorical variables, have been performed. Fisher's exact test was used for two categorical variables with two categories. For categorical variables with more than two categories, Chi-square test was used. All the reported p-values are two-sided and p-values <0.05 is considered to indicate statistical significance. All data entries and statistical analyses were performed using SPSS® Version 23.0 software.

RESULTS

A total of 1,013 patients with T2DM were included in this retrospective observational questionnaire-based analysis (612 male and 401 female). The mean (±SD) age of patients was 53.5 ± 13.9 years. Table 1 summarizes the distribution of patients according to age. The distribution of patients in different age groups based on duration of diabetes is shown in Table 2.

A total of 121 patients (11.9%) were in the normal BMI category (18.5-22.9 kg/m^2), 147 (14.5%) were overweight (23-24.9 kg/m^2) and 745 (73.5%) were obese (≥25 kg/m^2). Mean duration of diabetes was 6.3 ± 4.8 years. About 45.1% of patients had diabetes duration of 1 to 5 years

Table 1. Distribution of Patients According to Age

Age group	No. of patients	Percentage (%)
18-25	31	3.1
26-45	258	25.5
46-59	372	36.7
60-75	299	29.5
>75	53	5.2
Total	**1,013**	**100.0**

Table 2. Distribution of Patients in Different Age Groups Based on Duration of Diabetes

Age group (years)	Newly diagnosed	Diabetes duration (years)				
		1-5	6-10	11-15	16-20	Over 20
18-25	22 (53.7)	5 (1.1)	4 (1.2)	0 (0)	0 (0)	0 (0)
26-45	6 (14.6)	173 (37.9)	71 (21.2)	8 (6.3)	0 (0)	0 (0)
46-59	6 (14.6)	128 (28)	175 (52.2)	50 (39.4)	11 (26.2)	2 (18.2)
60-75	5 (12.2)	116 (25.4)	80 (23.9)	65 (51.2)	26 (61.9)	7 (63.6)
>75	2 (4.9)	35 (7.7)	5 (1.5)	4 (3.1)	5 (11.9)	2 (18.2)
Total	**41**	**457**	**335**	**127**	**42**	**11**

The values are described as n (%).

(n = 457), followed by 6 to 10 years (33.1%, n = 335). The least number of patients had diabetes duration of >20 years (n = 11).

About 70.1% of the patients received glimepiride/metformin FDC as first-line therapy and 29.9% received it as second-line therapy.

The most commonly prescribed glimepiride/metformin FDC regimen was glimepiride 0.5 mg + metformin 500 mg. Table 3 summarizes the dosage regimens used in study participants.

Dose titration was done in only 160 (15.1%) patients. Out of these, up-titration was done in 84 patients and down-titration was done in 61 patients (data was not available for some patients).

Around 66.3% of the patients in first-line glimepiride/metformin therapy group received insulin once a day. This increased to 86.8% of the patients in second-line

Table 3. Different Strengths of Glimepiride/Metformin FDC Prescribed to Study Participants

Glimepiride/Metformin FDC regimen	No. of patients	Percentage (%)
Glimepiride 0.5 mg + Metformin 1000 mg	8	0.8
Glimepiride 1 mg + Metformin 1000 mg	66	6.5
Glimepiride 2 mg + Metformin 1000 mg	83	8.2
Glimepiride 3 mg + Metformin 1000 mg	25	2.5
Glimepiride 4 mg + Metformin 1000 mg	38	3.8
Glimepiride 0.5 mg + Metformin 500 mg	299	29.5
Glimepiride 1 mg + Metformin 500 mg	189	18.7
Glimepiride 2 mg + Metformin 500 mg	203	20.0
Glimepiride 1 mg + Metformin 850 mg	29	2.9
Glimepiride 2 mg + Metformin 850 mg	28	2.8
Glimepiride 3 mg + Metformin 850 mg	45	4.4
Total	**1,013**	**100.0**

Table 4. Insulin Dosage Regimen Used in Patients on Glimepiride/Metformin FDC Therapy

Insulin	Glimepiride/Metformin FDC therapy	
	First-line therapy	Second-line therapy
BD	239 (33.7)	40 (13.2)
OD	471 (66.3)	263 (86.8)
Total	**710 (70)**	**303 (29.9)**

The values are described as n (%).

BD: Twice a day; OD: Once a day.

therapy group (Table 4). Overall, 754 (74.4%) patients also received another OHA. Among these patients, 295 (39.1%) received SGLT2 inhibitors, 89 (11.8%) received thiazolidinediones, 449 (59.5%) received DPP-4 inhibitors, 115 (15.2%) received AGIs and 10 (1.3%) received GLP-1 agonists.

Hypoglycemia at 6 months was noted in 34.5% patients. There were no other major adverse events. About 18.2% (n = 185) patients reported change in weight, with a slightly larger number of patients (n = 96) having reduction in weight.

A total of 624 (61.6%), 502 (49.6%) and 490 (48.3%) patients had a reduction in HbA1c, FPG and PPG. Mean HbA1c values decreased after treatment with glimepiride/metformin FDC plus insulin from

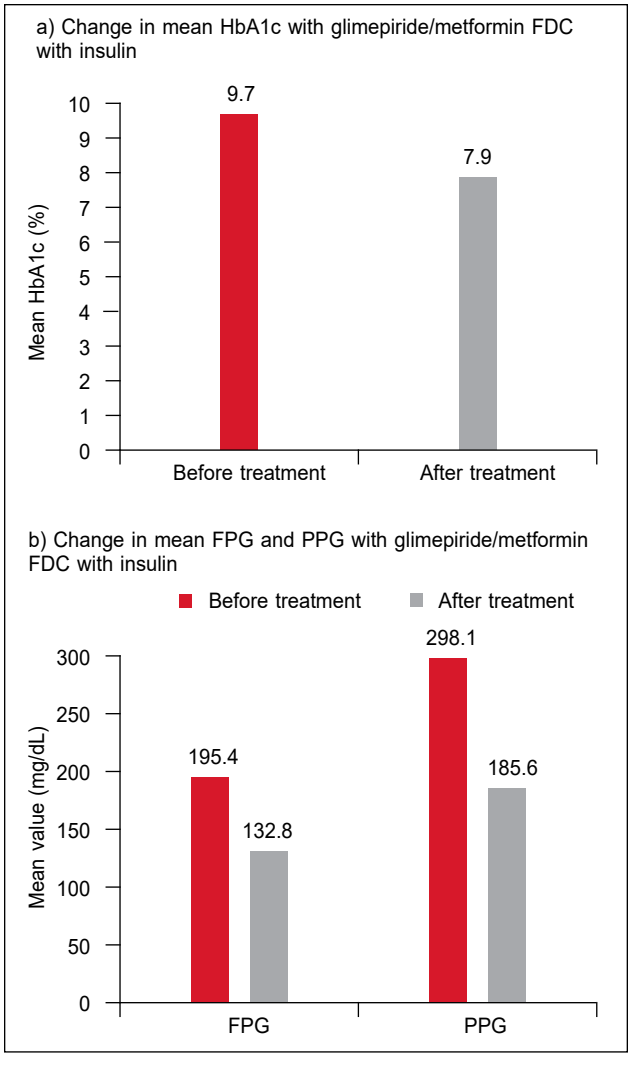

Figure 1. Mean change in glycemic parameters after treatment with glimepiride/metformin FDC with insulin.

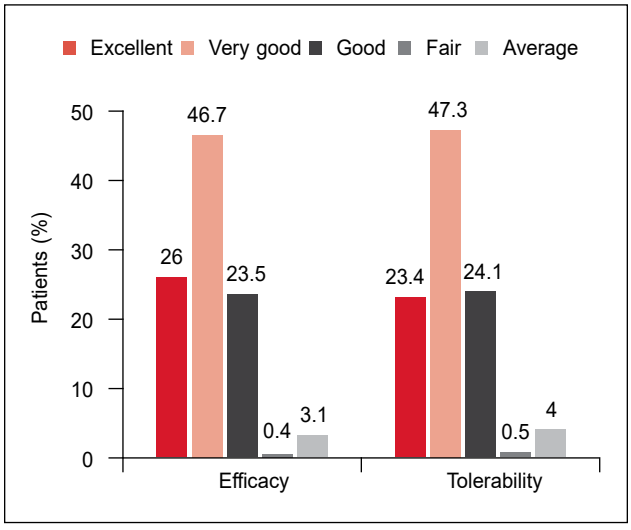

Figure 2. Treatment efficacy and tolerability rating in study patients.

9.7% ± 1.3% to 7.9% ± 4.2%. Mean FPG and PPG were also reduced post-treatment from 195.4 ± 42.8 mg/dL to 132.8 ± 34.3 mg/dL and from 298.1 ± 59.5 mg/dL to 185.6 ± 39.3 mg/dL, respectively (Fig. 1 a and b). The percentage reduction in HbA1c, FPG and PPG was 18.55%, 32.04% and 37.74%, respectively.

Physician evaluation of efficacy and tolerability were reported as good to excellent for 96.2% and 94.8% patients, respectively (Fig. 2).

DISCUSSION

The present case-based questionnaire survey evaluated the usage of glimepiride/metformin FDC with insulin, with or without other OHAs, in patients with T2DM. It looked at the approach of HCPs across India regarding the use of glimepiride/metformin FDC along with insulin in people with diabetes.

Around 36.7% of the patients were in the 46 to 59 years age group. In this particular age group, more than half of the patients (52.2%, n = 175) had a diabetes duration of 6 to 10 years. A vast majority of patients (70.1%) received glimepiride/metformin FDC as first-line therapy. This is in line with the American Diabetes Association (ADA) recommendation that early combination therapy may be needed in some patients to delay treatment failure.[4] The conventional stepwise approach may result in a delay in achieving the glycemic goals. Moreover, the up-titration of monotherapy may be associated with untoward effects. Thus, early combination therapy seems to be a judicious approach where submaximal doses of the antidiabetic agents can be combined to yield better glycemic control with minimal side effects.[15]

Glimepiride/metformin combination is a time-tested treatment regimen in T2DM management. This combination has been reported to be more effective than metformin up-titration to achieve glycemic control in patients uncontrolled on metformin low-dose monotherapy.[16] Moreover, within the SU class, glimepiride has been found to be a better alternative to other SUs, in combination with metformin. A study by González-Ortiz and colleagues found glimepiride/metformin combination to be more effective compared to glibenclamide/metformin combination to attain glycemic control and was associated with less hypoglycemic events.[17] In the Indian setting as well, this is a widely used OAD combination.[18] Fixed-dose combinations of glimepiride and metformin are extensively used in India, considering their availability in a wide range of strengths, and this is associated with an ease of titration as well.[19] An added advantage in the Indian setting is that this combination is a cost-effective treatment approach.[18] Sahay and colleagues, in their real-world study in T2DM patients, noted that glimepiride/metformin FDCs are commonly used in those with comorbidities and diabetes complications. The investigators stated that these combinations are well suited for both early and long-term diabetes.[18] Unnikrishnan et al noted in a case-based questionnaire survey that glimepiride/metformin FDC has potential benefits in patients with T2DM, regardless of age, duration of diabetes, BMI, diabetes complications, as well as the use of concomitant medications, like insulin.[19] A study conducted in Nepal also noted glimepiride/metformin low-dose combination (glimepiride 0.5 mg/metformin 500 mg) to be effective in T2DM patients, across an age range of 23 to 85 years, for glycemic control. There was an average 26% reduction in FPG and PPG in the patients.[20]

These results were replicated in our study, where the benefits of glimepiride/metformin FDC were evident in T2DM patients across age groups, BMI categories, diabetes duration and use of other OHAs. Use of glimepiride/metformin FDC with insulin has also been reported to be efficacious in attaining glycemic control. Yu et al reported that glimepiride/metformin FDC along with insulin is associated with reduction in blood glucose levels in T2DM patients and is a relatively safe option.[13] Park and colleagues also noted in their study that use of glimepiride/metformin with insulin was associated with significantly greater improvement in glycemic control vs. treatment with insulin and glimepiride or insulin and metformin.[21]

In an Indian study, glimepiride/metformin FDC usage with insulin was shown not to increase the risk of hypoglycemia and weight gain. The study showed that different strengths of glimepiride/metformin FDCs are used with insulin in diabetes patients, without any increased risk of adverse events.[19] Our study had similar findings where a higher number of patients receiving glimepiride/metformin FDC with insulin reported weight reduction and there were no increased risk of adverse events.

A real-world study by Prasanna Kumar et al, conducted in India, noted good HbA1c lowering with glimepiride/metformin combination with insulin and the most frequently used glimepiride/metformin regimen in this study was glimepiride 2 mg/metformin 500 mg.[14] In our study as well, there was considerable reduction in HbA1c, FPG and PPG levels in patients receiving glimepiride/metformin FDC with insulin, with the

most frequently used regimen being glimepiride 0.5 mg/metformin 500 mg. Physician evaluation of efficacy and tolerability were reported as good to excellent for 96.2% and 94.8% patients, respectively. This is similar to the results of the study by Prasanna Kumar et al, where physician global evaluation of efficacy and tolerability revealed that a vast majority of patients were on good to excellent (97.3% and 96.6%).[14]

This study has presented data on key glycemic parameters such as HbA1c, FPG and PPG and demonstrated the efficacy and tolerability of glimepiride/metformin FDC with insulin, with or without other OHA use, in T2DM patients. These results provide valuable insights into the effects of this regimen in these patients.

However, the retrospective nature of this study is one of its limitations. Additionally, the glycemic control achieved in this study could not be correlated with different glimepiride/metformin FDCs prescribed since patients also received other OADs. Furthermore, it could not be determined as to which individual therapeutic agent led to adverse events, if any, because combination therapy was given. The results should be further validated in large-scale prospective studies in order to assess the efficacy and safety of glimepiride and metformin combination with insulin in Indian patients with type 2 diabetes.

CONCLUSION

This case-based questionnaire survey of the usage of glimepiride/metformin FDC with insulin, with or without other OHAs, in the Indian setting revealed that different strengths of glimepiride/metformin FDCs are commonly prescribed along with insulin in T2DM patients. Majority of the patients received once daily insulin dose with glimepiride/metformin FDC. A large proportion of patients attained reduction in key glycemic parameters with this regimen.

Glimepiride/metformin FDC with insulin is commonly used in diabetes patients in India and this treatment approach has a favorable efficacy and tolerability profile.

Authorship

All authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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Conflict of Interest

There are no conflicts of interest to declare.

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OBSERVATIONAL STUDY

Usage of Glimepiride/Metformin Fixed-dose Combination in Young Individuals with Type 2 Diabetes: The Indian Experience

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ABSTRACT

Background: The prevalence of diabetes has been rising among the younger population and is a cause for concern. The present case-based questionnaire survey evaluated the treatment pattern and clinical experience of healthcare professionals (HCPs) in prescribing glimepiride/metformin fixed-dose combination (FDC) to young diabetes patients (up to 40 years of age) in the Indian setting. **Material and methods:** A retrospective, multicenter, observational, questionnaire-based survey was conducted in Indian healthcare centers using medical records of patients having type 2 diabetes mellitus (T2DM), who were prescribed different strengths of glimepiride/metformin FDCs. Data was collected from the patients' medical records and were analyzed using statistical tests. **Results:** A total of 2,715 patients aged between 18 and 40 years were included in the study. Mean diabetes duration among the young patients was 2.76 ± 1.97 years. Among the young T2DM patients, 83.2% patients received glimepiride/metformin FDC as first-line therapy, and 16.8% received it as second-line therapy. Hypoglycemia at 6 months was noted in only 2.47% of the young patients. Mean glycated hemoglobin (HbA1c) before and after treatment was 8.7% ± 3.4% and 7.3% ± 3.9%, respectively. Mean fasting plasma glucose (FPG) was 171.8 ± 80.1 mg/dL in patients prior to treatment initiation and came down to 122.8 ± 41.8 mg/dL after treatment with glimepiride/metformin FDC. Mean postprandial plasma glucose (PPG) prior to combination therapy use was 248.7 ± 64.0 mg/dL and dropped to 177.2 ± 39.9 mg/dL after treatment. Good to excellent efficacy and tolerability were reported for 86% and 86.6% patients, respectively. **Conclusion:** This case-based questionnaire survey demonstrates the usage pattern of various strengths of glimepiride/metformin FDCs and the HCPs' practice approach regarding the use of this combination in young T2DM patients in the Indian setting. The combination is commonly prescribed to young diabetes patients in India and is associated with beneficial effects on glycemic parameters.

Keywords: Type 2 diabetes, young adults, glimepiride/metformin combination, combination therapy

The prevalence of diabetes has been rising among the younger population and is a cause for concern as development of diabetes at a young age is linked with longer exposure to high blood glucose levels and an increased risk for complications during the lifetime. It also impacts the patient's work and quality of life during the productive years.[1] Indian data have shown a prevalence of type 2 diabetes mellitus (T2DM) between 1.1% and 4.7% among patients aged 30 years or below. There has been an increasing trend particularly over the past 10 years.[2]

Further, evidence has been strengthening that onset of T2DM at a young age is tied to a more aggressive disease phenotype.[1] Insulin deficiency has been identified as the major factor accountable for T2DM in young Indians, unlike their European counterparts in whom obesity and insulin resistance are the key drivers.[3] Considering the fact that a rising number of young adults are being diagnosed with diabetes, the recommendations for screening have undergone

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revision. The United States Preventive Services Task Force (USPSTF) recommended lowering the age of screening in the United States from 40 to 35 years. However, it recommends screening at an earlier age in people belonging to groups with a higher prevalence, with special emphasis on screening Asian Americans at lower age as well as body mass index (BMI). It is thus suggested that screening should be initiated at age 25 years for nonpregnant adults in India and must focus overweight and obese individuals and people with a positive family history.[2]

Considering this, the treatment of young-onset T2DM must target a reduction of complications. The available data hints at the fact that tight glycemic control reduces the risk of microvascular complications.[4] Metformin, one of the most extensively prescribed agents for T2DM management, is recommended for use in individuals aged above 10 years. Therapy starts at ages 10 to 16 years with 500 mg/day, and the dosage can be increased to 500 mg every 1 to 2 weeks, until a maximum dose of 2000 mg.[4]

Glimepiride is a sulfonylurea (SU) which has been reported to be tied to a low rate of hypoglycemia in adults. Besides affecting the pancreatic β-cell function, the agent also works by improving tissue sensitivity to insulin, with a favorable safety and efficacy profile.[5] Interestingly, glimepiride has been shown to be as effective as metformin in reducing glycated hemoglobin (HbA1c) in young T2DM patients.[5] A SU, glimepiride in particular, is the preferred drug to be used in combination with metformin in patients with diabetes.[6,7] Adding a SU to metformin is preferred as the combination targets insulin resistance as well as insulin deficiency. Moreover, in resource-limited settings like India, SUs are cheaper than several other oral hypoglycemic drug classes, and effective as well.[7]

A study by Devarajan et al compared the safety and efficacy of glimepiride and sitagliptin in combination with metformin in T2DM patients and revealed that glimepiride/metformin combination led to significant reduction in glycemic parameters in comparison with sitagliptin/metformin combination.[8]

A case-based questionnaire survey conducted in Indian T2DM patients noted that different strengths of glimepiride/metformin fixed-dose combinations (FDCs) are safely prescribed in the young and the elderly population.[9] A post-marketing surveillance study conducted in Nepal also showed beneficial effects of glimepiride/metformin FDC in young adults with T2DM, with improvements in glycemic parameters after 3 months of treatment.[10]

Glimepiride/metformin combination can also be used along with insulin therapy. In a study, the commonly prescribed oral antidiabetic drug combinations to be used as add-on with insulin glargine in patients with uncontrolled T2DM were assessed.

The result showed that the combination therapy of metformin and glimepiride with insulin significantly improved overall glycemic control, in comparison with other combinations.[11] A real-world study conducted in India also noted good HbA1c reduction with glimepiride/metformin combination with insulin, and good to excellent efficacy and tolerability in patients across different age groups, including the young adults.[12]

Their proven efficacy, safety profile, pleiotropic benefits and low-cost, make SUs the preferred choice for treatment of diabetes in South Asians, and among SUs, modern agents like glimepiride are the preferred agents.[13]

A combination of glimepiride and metformin is commonly used in clinical practice for the management of diabetes in the Indian T2DM patients.[14] There is a need for physician opinion on glimepiride/metformin combination amongst young T2DM patients in the Indian setting. A case-based questionnaire survey was, therefore, designed to evaluate the demography, treatment pattern including duration and various dosages of glimepiride/metformin FDCs in the management of T2DM in young patients.

MATERIAL AND METHODS

Study Design

This was a retrospective, multicenter, observational, questionnaire-based survey. It was conducted with 372 healthcare professionals (HCPs) across different centers in India between July 2020 and May 2021. The study protocol was designed in accordance with the principles of the Declaration of Helsinki.

Study Population

Patients of both sexes, aged between 18 and 40 years, diagnosed with T2DM who received a glimepiride/metformin FDC in any strength were recruited in the study.

Data Collection

A case report format was developed to determine the pattern of use of different strengths of glimepiride

and metformin combination with or without other oral hypoglycemic agents (OHAs) in young diabetes patients. The questionnaire was sent to 372 HCPs across India through an online portal. Link to the portal was shared through e-mail. Questions regarding demographic characteristics, such as age, sex, BMI, medical history, education, occupation, area of stay and economic class; duration of diabetes; comorbidities; prevention program initiated; biochemical measures, such as fasting plasma glucose (FPG), postprandial plasma glucose (PPG) and HbA1c levels; antidiabetic drugs used; antidiabetic drug up-titrations and down-titrations; weight change; hypoglycemic episodes and other adverse events during treatment, were included in the questionnaire. The HCPs filled in the information on the online portal. A descriptive analysis was performed with the data provided on the portal.

Statistical Analysis

Descriptive statistical analyses, including mean and standard deviation (SD) for continuous variables and count and percentage for categorical variables, was performed. Chi-square test/Fisher's exact test was used to compare two 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.

RESULTS

A total of 2,715 T2DM patients aged ≤40 years receiving different strengths of glimepiride/metformin FDC were included in this retrospective observational questionnaire-based analysis.

The mean (± SD) age of patients was 34.7 ± 5.5 years. Mean duration of diabetes was 2.76 ± 1.97 years. A majority of patients had diabetes duration of 0 to 5 years. Mean BMI of the study participants was 28.12 ± 4.47 kg/m^2. Table 1 summarizes the association of age with duration of diabetes.

According to the level of education, 41.3% patients were graduate, 27.3% had studied till or below 10th standard, 21.2% had studied till 12th standard and 10.2% had a postgraduate degree. Around 9.9% of the patients were unemployed, 19.9% worked in private service and 7.2% worked in government service, among other occupations. Based on the area of stay, 16.8% of the patients were from rural areas, 21.2% were from semi-urban areas, 27.6% were from urban areas and 34.5% were from metropolitans.

Table 1. Patients in Different Age Groups Based on Diabetes Duration

Age group (years)	Diabetes duration (years)			
	0-5	6-10	11-15	>15
18-20	100 (3.94)	5 (3.01)	1 (12.5)	0 (0)
21-25	120 (4.73)	3 (1.81)	0 (0)	0 (0)
26-30	302 (11.9)	16 (9.64)	2 (25)	0 (0)
31-35	582 (22.94)	30 (18.07)	1 (12.5)	0 (0)
36-40	1433 (56.48)	112 67.47)	4 (50)	4 (100)

The values are mentioned as no. of patients (%).

Table 2. Demographics of the Patients Included in the Study

Variable	Number of patients (%)
Education	
≤10th standard	741 (27.3)
12th standard	576 (21.2)
Graduate	1,122 (41.3)
Postgraduate	276 (10.2)
Occupation	
Government service	196 (7.2)
Manual laborer	140 (5.2)
Private service	539 (19.9)
Professional	292 (10.8)
Self-employed	393 (14.5)
Semi-skilled	849 (31.3)
Unemployed	270 (9.9)
Any other	36 (1.3)
Area of stay	
Rural	456 (16.8)
Semi-Urban	575 (21.2)
Urban	748 (27.6)
Metropolitan	936 (34.5)
Economic class	
Poor	101 (3.7)
Lower-middle	693 (25.5)
Upper-middle	933 (34.4)
Higher-middle	387 (14.3)
Rich/elite	601 (22.1)

Table 3. Different Glimepiride + Metformin Dosage Regimens Used in Young Participants

Glimepiride/Metformin FDC regimen	Number of patients (%)
Glimepiride 0.5 mg/Metformin 500 mg	905 (33.3)
Glimepiride 1 mg/Metformin 500 mg	685 (25.2)
Glimepiride 2 mg/Metformin 500 mg	638 (23.5)
Glimepiride 1 mg/Metformin 850 mg	83 (3.1)
Glimepiride 2 mg/Metformin 850 mg	67 (2.5)
Glimepiride 3 mg/Metformin 850 mg	53 (1.9)
Glimepiride 0.5 mg/Metformin 1000 mg	59 (2.2)
Glimepiride 1 mg/Metformin 1000 mg	93 (3.4)
Glimepiride 2 mg/Metformin 1000 mg	114 (4.2)
Glimepiride 3 mg/Metformin 1000 mg	10 (0.4)
Glimepiride 4 mg/Metformin 1000 mg	8 (0.3)

Majority of the patients belonged to the upper-middle, higher-middle and the rich/elite economic class (70.7%). Table 2 summarizes the patient demographics in terms of education, occupation, area of stay and economic class.

In this study, we could see that most patients belonged to the urban and metropolitan areas and the upper-middle, higher-middle and rich economic class.

Diabetes knowledge was average in 14.4% patients, fair in 2.6%, good in 45.5%, very good in 26.6% and excellent in 9.8% (result was not available for 1.1% of the patients).

A total of 2,258 patients (83.2%) received glimepiride/metformin FDC as first-line therapy, and 457 patients (16.8%) received it as second-line therapy. The most commonly prescribed glimepiride/metformin regimen was glimepiride 0.5 mg + metformin 500 mg (33.3%). Table 3 summarizes the dosage regimens used in the study participants.

Overall, 1097 (40.4%) patients also received another OHA with glimepiride/metformin FDC. About 153 patients (5.6%) received insulin along with glimepiride/metformin therapy, and 576 patients (21.2%) received concomitant medications, such as antihypertensives, antiplatelets, statins, calcium, methylcobalamin, etc. In the young T2DM patients, up-titration of glimepiride/metformin FDC was done in 32.5% and down-titration was done in 8.7%. Hypoglycemia at 6 months was evident in 2.5% patients. There were no other major adverse events.

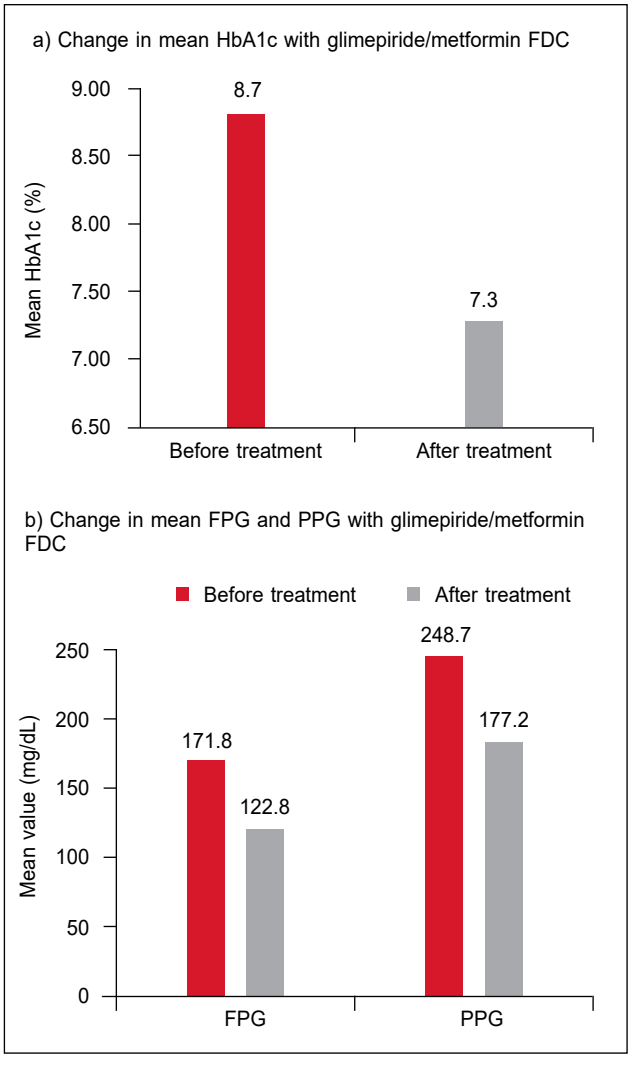

Figure 1. Changes in glycemic parameters after glimepiride/metformin FDC therapy.

Figure 2. Treatment efficacy and tolerability rating in study patients.

Mean HbA1c before treatment initiation was 8.7% ± 3.4% and decreased to 7.3% ± 3.9% after treatment with glimepiride/metformin FDC therapy. Mean FPG before initiating glimepiride/metformin FDC was 171.8 ± 80.1 mg/dL and came down to 122.8 ± 41.8 mg/dL after treatment. Mean PPG prior to combination therapy use was 248.7 ± 64.0 mg/dL and dropped to 177.2 ± 39.9 mg/dL after treatment. Changes in the glycemic parameters are depicted in Figure 1 a and b. Physician evaluation of efficacy and tolerability were reported as good to excellent in 86% and 86.6% patients, respectively (Fig. 2).

DISCUSSION

Diabetes usually affects individuals above the age of 50 years in high-income countries, while in middle-income countries, the prevalence appears to be higher in young individuals. The young population in India is at a high risk for diabetes.[15] Therefore, early aggressive treatment is needed in this population.[16]

The present case-based questionnaire survey explored the usage of glimepiride/metformin FDC in young patients with T2DM. This study assessed the approach of HCPs across India regarding the use of this combination in young patients with T2DM. A total of 2,715 patients were aged between 18 and 40 years were included in the study.

Although the trends are changing, diabetes is still more prevalent in urban areas. In this study also, somewhat similar findings were noted as only 16.8% of the patients were from rural areas. A recent study conducted in India among young adults (aged <35 years) noted that based on the Indian diabetes risk score (IDRS), the urban young population has a higher risk of diabetes compared to its rural counterparts.[15]

About 70.8% of the patients in this study belonged to the upper-middle, higher-middle and the rich/elite economic class. An increased prevalence of diabetes mellitus was noted in the higher social class in the Chennai Urban Rural Epidemiology Study (CURES-116) also.[17]

Around 83.2% of the young patients in the study received glimepiride/metformin FDC as first-line therapy, while 16.8% received it as second-line therapy. The combination of glimepiride and metformin is extensively used for controlling blood glucose levels on account of the ability of this combination to offset insulin secretion disorder as well as insulin resistance.[14] Considering the fact that Asians develop diabetes at a relatively younger age compared to their Western counterparts, and at a lower BMI too, it has been suggested that the pathophysiological differences between Asians and Caucasians should be taken into account and only metformin should not be considered as the primary drug. In fact, all possible medications should be considered based on patient characteristics.[18]

There is ample real-world evidence to show that glimepiride/metformin combination is widely prescribed in T2DM patients.[14] Metformin, a biguanide, acts by suppressing the basal hepatic glucose uptake and enhancing insulin-mediated glucose uptake in peripheral muscles. It does not stimulate insulin secretion. Therefore, its use is not tied to episodes of hypoglycemia. Hence, it is widely used in children and adolescents with diabetes. Likewise, the modern SU glimepiride is also tied to a low hypoglycemia rate in adults. The drug has an impact on pancreatic β-cell function.[5]

Like adult T2DM patients, children and adolescents or the young patients also develop diabetes due to insulin resistance and pancreatic β-cell secretory failure. The proven efficacy of OHAs in adults and the similar mode of disease development in the younger patients and in adults points to the fact that these agents will show similar efficacy in the younger patient population.[5]

Glimepiride and metformin combinations can be effectively used for both early and long-standing diabetes.[14] It is noteworthy that within the class of SUs, glimepiride appears to be a better agent, compared to other SUs, used in combination with metformin. A study has reported glimepiride/metformin combination to be more effective than glibenclamide/metformin combination to attain glycemic control.[19] Moreover, early combination therapy with glimepiride and metformin is associated with the benefit of legacy effect on account of early glycemic control while evading a negative glycemic memory linked with micro- and macrovascular complications.[18]

In addition, modern SUs, such as glimepiride, have a cardiovascular-neutral profile. The CAROLINA trial found glimepiride to be at par with the dipeptidyl peptidase-4 (DPP-4) inhibitor linagliptin in terms of a risk of a composite cardiovascular outcome in T2DM patients with a high cardiovascular risk.[20] Meanwhile, metformin has protective effects on several organs, especially the insulin-targeted tissues, including liver, muscles and adipose tissues. It also protects T2DM patients against cardiovascular diseases.[21] Therefore, a combination of glimepiride and metformin seems to be a suitable therapeutic approach for young T2DM patients.

There have been quite a few studies which have corroborated the extensive use of this potent combination in diabetes patients with favorable outcomes, both in elderly and in young patients. A recent case-based questionnaire survey conducted by Unnikrishnan et al evaluated the clinical utilization pattern of different strengths of glimepiride/metformin FDCs in patients with T2DM. The investigators concluded that various strengths of glimepiride/metformin FDCs are effective in diabetes patients, regardless of their age, diabetes duration, BMI, complications and use of concomitant medications.[9] A post-marketing surveillance study conducted in Nepal showed the beneficial effects of the combination, particularly in the young patients. Among young T2DM patients (<40 years of age) receiving a glimepiride/metformin FDC (0.5 mg glimepiride + 500 mg metformin) noted an average reduction of 25% in FPG and a reduction of 43% in PPG after 3 months of therapy.[10]

Dose up-titration was done in 32.5% of the patients and down-titration was done in 8.7% of them in this study. Combinations of OHAs have helped clinicians a lot on account of the ease of up- and down-titration associated with their use.[14]

Like the study conducted in young T2DM patients in Nepal which evaluated the effect of glimepiride 0.5 mg + metformin 500 mg and noted potential benefits of the regimen,[10] in the present study also, the most commonly prescribed glimepiride/metformin regimen in the young patients was glimepiride 0.5 mg + metformin 500 mg. Around 33.3% of the patients received this regimen.

Additionally, similar to other studies conducted with glimepiride/metformin combination,[10] the present study also noted the beneficial effects of this combination in terms of glycemic parameters. There was a reduction in the key glycemic parameters after glimepiride/metformin FDC therapy.

Hypoglycemia at 6 months was noted in only 2.5% of the patients. This is even lesser than that seen in the study by Unnikrishnan et al, where 5.8% patients on glimepiride/metformin FDC therapy had hypoglycemia.[9] In a real-world study, which evaluated the use of glimepiride/metformin combination along with insulin in diabetes patients, hypoglycemic events were noted in 6.1% of the patients.[12] A limitation of this study is its retrospective nature. The strengths of the study include the information gathered on key glycemic parameters like HbA1c, FPG and PPG in young patients, which can be of great help in further evaluating the effects of this combination in young T2DM patients. The findings of this retrospective study should be further validated in large-scale prospective observational studies in order to achieve a better understanding of the efficacy and safety of glimepiride and metformin combination in this patient population in the Indian scenario.

CONCLUSION

This case-based questionnaire survey of the usage of glimepiride/metformin FDC in the Indian setting shows that multiple strengths of glimepiride/metformin FDCs are prescribed in young patients with T2DM. There was a significant improvement in glycemic parameters and fewer hypoglycemia episodes with this combination these patients. It can be concluded that glimepiride/metformin FDC is extensively prescribed to diabetes patients, even in the younger population, and is associated with beneficial effects on glycemic parameters. It would be appropriate to state that glimepiride/metformin FDC is suitable for the young as well as the elderly.

Authorship

All authors take responsibility for the integrity of the work as a whole, and have given their approval for this version to be published.

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Conflict of interest

There are no conflicts of interest to declare.

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CLINICAL STUDY

A Pan-India, Knowledge, Attitudes and Practices (KAP) Study of Healthcare Practitioners in India Regarding Immunomodulatory Role of Vitamin D Supplementation in COVID-19

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ABSTRACT

Introduction: Vitamin D has immunomodulatory effects and vitamin D deficiency has been associated with autoimmune responses and increased risk of infections. Vitamin D-mediated antimicrobial and anti-inflammatory responses play an effective role in the prevention of various respiratory tract infections including coronavirus disease 2019 (COVID-19). **Aims and objective:** To evaluate the therapeutic role of vitamin D via immunomodulation in COVID-19 through a Knowledge, Attitudes and Practices (KAP) study of pan India healthcare practitioners (HCPs) to arrive at a common consensus statement regarding dosage and duration of vitamin D for immune-modulatory function. **Methods:** A pan-India, online, questionnaire-based, KAP survey was conducted on vitamin D and its role in immunomodulation in COVID-19 from April 2021 to January 2022 followed by polling obtained from HCPs through round table meetings (RTMs). **Results:** Approximately 64% of HCPs considered the use of vitamin D in COVID-19 patients for various reasons including prevention of illness, reduced ICU stay, reduction in morbidity and mortality along with decrease in the levels of inflammatory markers in COVID-19 patients. For the dosage regime, 47% of HCPs preferred vitamin D 60,000 IU weekly while 45% of HCPs preferred both 60,000 IU weekly and 2,000 IU daily dose for boosting immune system in their patients. **Conclusion:** The panel agreed that vitamin D levels of 40 ng/mL and above appear to confer better immune-protective response to several infections including COVID-19.

Keywords: Vitamin D, COVID-19, healthcare practitioners, immunomodulation

Vitamin D, also referred to as the "sunshine vitamin" plays a major role in calcium absorption and bone mineralization.[1] It has immunomodulatory effects and vitamin D deficiency has been associated with autoimmune responses and increased risk of infections.[1,2] The beneficial effects of vitamin D are realized primarily based on its role in innate antimicrobial immune response pathways.[3] Vitamin D-mediated antimicrobial and anti-inflammatory responses play an effective role in the prevention of various respiratory tract infections (RTIs).[4] In recent times, there is a surge of evidence regarding the role of vitamin D in cardiometabolic outcomes.[5] Serum 25-hydroxyvitamin D [25(OH)D] levels are inversely correlated with upper RTIs.[6]

Despite this awareness, vitamin D deficiency is highly prevalent among the population of India. Irrespective of the age group or existence of prevailing health conditions, the prevalence of vitamin D deficiency ranges from 40% to 99%, with most studies reporting a prevalence of 80-90%.[7] During the ongoing COVID pandemic, when there were no immunizations available, there was an urgent need to keep the population healthy and devoid of major deficiencies

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that could have implications on immunity. Even when vaccines are available, it is necessary to continue to build immunity and to reduce the deficiencies that could adversely affect immunity.

Vitamin D plays a vital role in regulation of cytokine storm due to immunomodulatory function. Invasion of viral or other respiratory pathogens activates innate immune response resulting in increased local production of 1,25-dihydroxyvitamin D [1,25(OH)2D].[8] Downstream events involving CYP27B1 and vitamin D receptors either constitutively expressed by airway epithelia or inductively expressed by pulmonary alveolar macrophages, lead to viral neutralization and clearance of viral load. The positive effects of vitamin D supplementation in COVID-19 infections include faster viral clearance, immunomodulation, reduced severity and mortality of the disease.[9] Also, the recommendations for dosages and duration for use of vitamin D by different bodies vary and there is a lack of consensus statement for use of vitamin D for immune-protection.

Hence, this study was designed with the objective to achieve a common consensus statement on the therapeutic role of vitamin D for immunomodulation in COVID-19 via Knowledge, Attitudes and Practices (KAP) study of the healthcare practitioners (HCPs).

METHODS

A pan-India, online, questionnaire-based survey was conducted on vitamin D and its role in immunomodulation in COVID-19 from April 2021 to January 2022, based on an initial discussion with an expert panel of endocrinologists from across the country, to evaluate the awareness of HCPs in India regarding the role of vitamin D supplementation in COVID-19. The questionnaire-based survey was conducted online through email. After the online survey of HCPs, 26 virtual regional round table meetings (RTMs) were conducted in various locations across India. The survey questionnaires were again rolled in the virtual RTMs and online polling was conducted to gather the opinions of the HCPs.

RESULTS

A total of 2,338 HCPs participated in the study, which included Consultant Physicians, Diabetologist, Endocrinologists and Cardiologists.

HCPs response to the prevailing population-centric view of vitamin D deficiency was variable. About 30% of HCPs were of the opinion that 60-80% of the patients have vitamin D deficiency while according to 32% of HCPs, 40-60% of the patients have vitamin D deficiency (Fig. 1A).

About 37% of the HCPs responded to a vitamin D level of 30-40 ng/mL as appropriate for maintaining good immunity, while 34% of HCPs were of the opinion that >40 ng/mL was the appropriate level (Fig. 1B).

Almost 64% of HCPs considered the use of vitamin D in COVID-19 patients for various reasons including prevention of illness, reduced ICU stay, reduction in morbidity and mortality along with decrease in the levels of inflammatory markers (Fig. 2A). About 54% of the HCPs said that they would consider prescribing 2,000 IU daily dose of vitamin D in elderly patients (>60 years) and those with atherosclerotic cardiovascular disease (ASCVD), diabetes, hypertension, chronic respiratory diseases and chronic liver diseases (Fig. 2B). With regard to questions pertaining to vitamin D supplementation in COVID-19 affected individuals, 52% of the HCPs preferred not to test for vitamin D levels before prescribing it (Fig. 3A). Approximately 58% of HCPs prescribed vitamin D for viral respiratory infections, while 22% of HCPs prescribed vitamin D in post-COVID-19 convalescent patients (Fig. 3B).

Regarding dosage regime, 47% of HCPs preferred vitamin D 60,000 IU weekly, while 45% preferred both vitamin D 60,000 IU weekly and 2,000 IU daily for boosting the immune system in their patients (Fig. 4A).

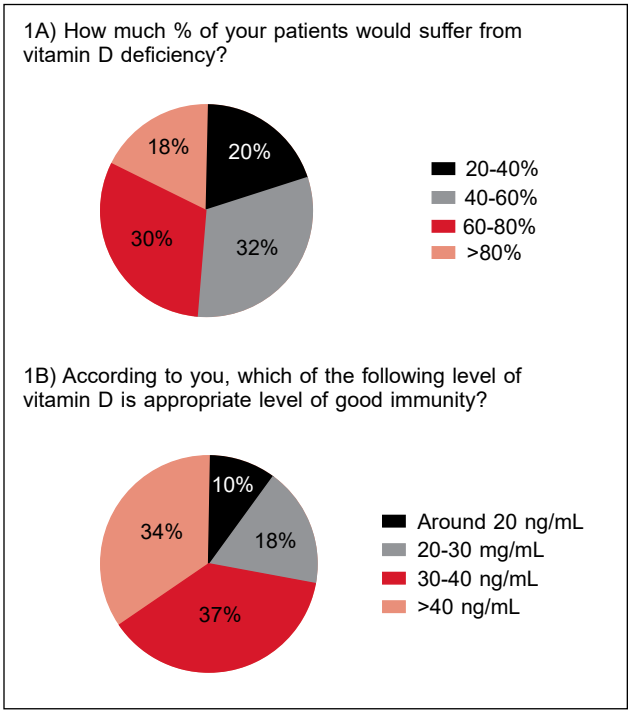

Figure 1. Response to knowledge-based questions on vitamin D deficiency.

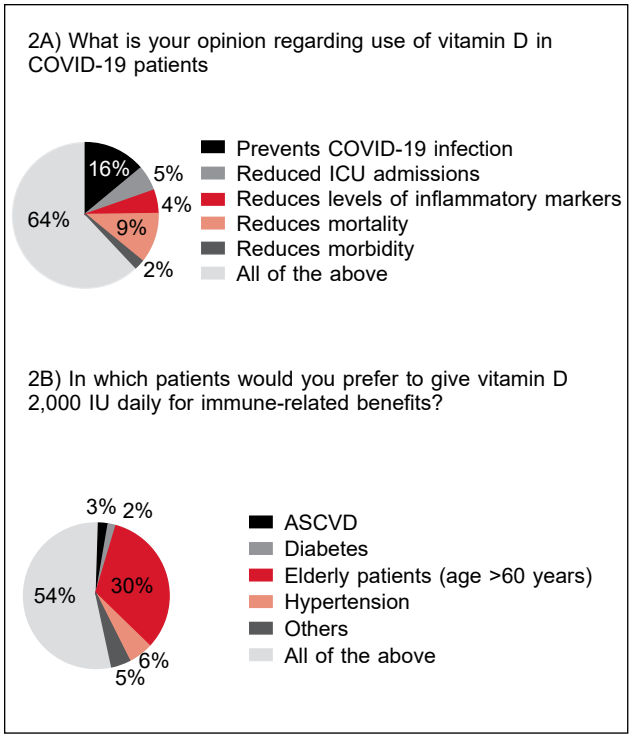

Figure 2. Attitude-based questions on vitamin D supplementation in patients with prevailing conditions.

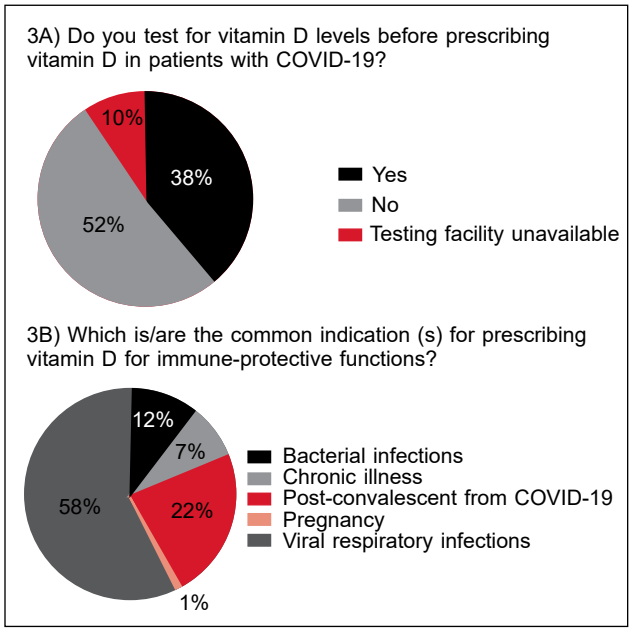

Figure 3. Common vitamin D prescribing practices.

Seventy-two percent of HCPs prescribed vitamin D for 8 to 12 weeks, while 15% of HCPs considered giving vitamin D for over a period of 6 months to 1 year (Fig. 4B).

Regarding loading dose of vitamin D in COVID-19, vitamin D 60,000 IU daily for 5 to 7 days was the preferred dose of 45% of HCPs, while 39% HCPs preferred a weekly regime of 60,000 IU of vitamin D (Fig. 4C). Sixty-four percent of HCPs prescribed vitamin D 60,000 IU weekly for 2 to 6 months as maintenance dose in COVID-19 patients, while 36% of HCPs switched to 2,000 IU daily for 3 to 6 months as maintenance dose (Fig. 4D).

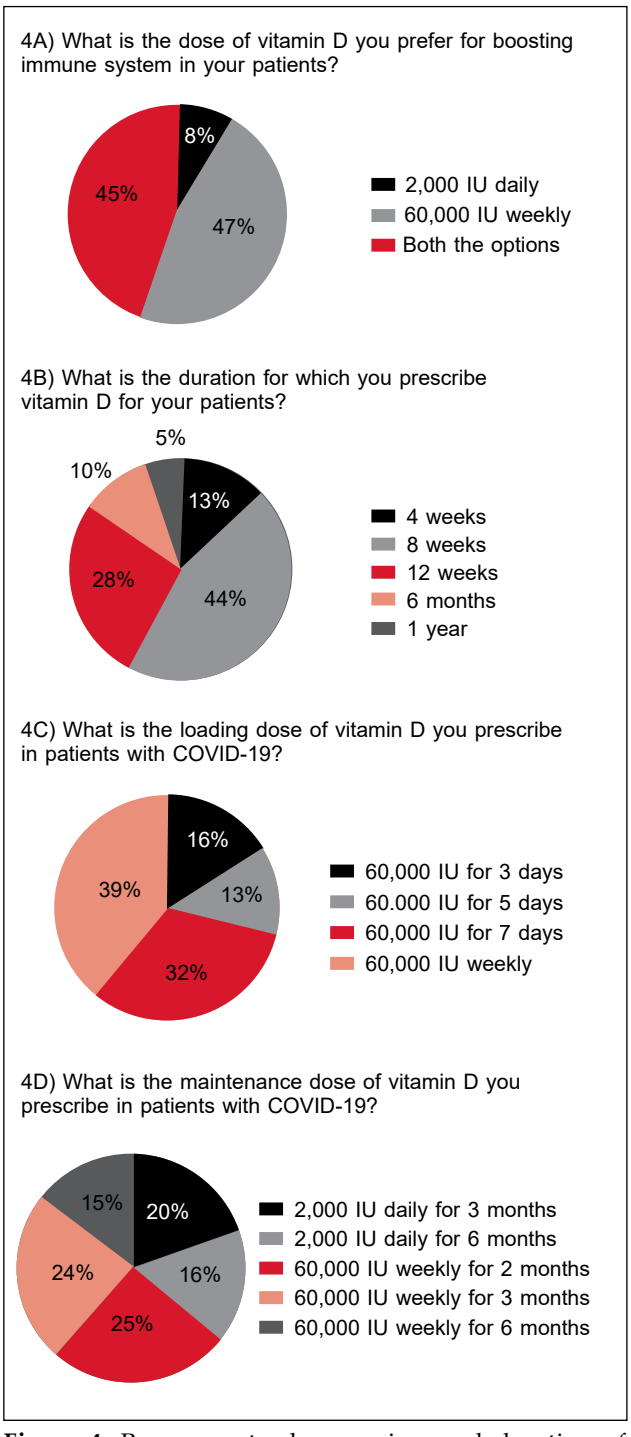

Figure 4. Responses to dose, regime and duration of prescribing vitamin D supplements.

DISCUSSION

The results obtained from the survey and polling from RTMs indicate that there is a high awareness among the HCPs about the prevalence of vitamin D deficiency and supplementation of vitamin D for boosting immunity. But responses with regard to dosage regime, loading and maintenance dosages of vitamin D in COVID-19 were variable.

Despite the increasing awareness of the role of vitamin D in bone health, cardiovascular metabolism and immunity, a significant proportion of Indian population is vitamin D deficient. It is highly pertinent for HCPs to recognize the need for vitamin D supplementation and to ensure its use inadequate doses (loading and maintenance dose) for the recommended duration. This need is much more enhanced in the current COVID-19 pandemic times where strategies that help boost immunity and reduce morbidity and mortality with minimal side effects are much warranted.

Individuals with low vitamin D levels (<30 ng/mL) seem to be more prone for upper RTIs.[7] Opinion regarding the cut-off level was divided in our survey. While 38% of HCPs were of the opinion that vitamin D level of 30-40 ng/mL was sufficient for maintaining a good immunity, 34% opined that levels >40 ng/mL were adequate. Most of the HCPs (52%) in our survey favored supplementing vitamin D in patients with COVID-19 without prior checking vitamin D levels. This could have been due to the poorly defined reference estimates, variations among standard tests[10] or lack of testing facilities.

Currently, there is no consensus on the dose of vitamin D to be used for either prevention or treatment of COVID-19. Instead, what most experts recommend is vitamin D supplementation for which several strategies have been proposed.

Rastogi et al evaluated the positive effects of vitamin D supplementation in asymptomatic and mildly symptomatic COVID-19 patients. Participants were randomized to receive daily 60,000 IU of cholecalciferol for 7 days with therapeutic target 25(OH)D >50 ng/mL (intervention group) or placebo (control group). It was found that daily cholecalciferol 60,000 IU supplementation was useful for achieving vitamin D level >50 ng/mL in 75% of patients by 14th day. Therapeutic high-dose cholecalciferol led to severe acute respiratory coronavirus 2 (SARS-CoV-2) RNA negative in additional 41.7% participants ($p < 0.001$) and was useful for SARS-CoV2 RNA clearance.[11]

In another study by Harinarayan et al, administration of 60,000 IU of vitamin D3 once a week with daily 1,000 IU (along with calcium 1 g/day) for 8 weeks was done to attain a vitamin D level of 30 ng/mL in deficient patients. After 2 months, about one-fourth of the patients attained vitamin D sufficiency. With continued dosage of 60,000 IU of vitamin D3 every 2 weeks with 1,000 IU daily (along with calcium 1 g/day), 46% of the patients attained vitamin D sufficiency by the 5th month.[12] In an open-label, randomized, prospective study of 10 weeks effect of oral high-dose vitamin D regimens (60,000 IU weekly) and daily low-dose of vitamin D regimen of 1,000 IU were evaluated in vitamin D deficient patients (serum levels <30 ng/mL). The study concluded that high-dose vitamin D (60,000 IU weekly) regimen rapidly normalized 25(OH)D levels and ensure symptomatic relief earlier than daily dosing of 1,000 IU vitamin D for same duration.[13] The various dosage regimens and duration of vitamin D used in these studies indicate the need for a common consensus statement for the HCPs.

CONCLUSION

Overall, majority of HCPs surveyed acknowledged the prevalence of vitamin D deficiency in general population and also recognized the immune boosting potential of vitamin D, especially in COVID-19-infected individuals. The results of the online survey and RTMs suggest that vitamin D may have potential role in decreasing morbidity, mortality and ICU admission in COVID-19 patients through regulation of cytokine storm via immunomodulatory actions. Maintenance of optimal vitamin D levels (≥40 ng/mL) appears to confer better immune-protective response to several infections including COVID-19. Most of the HCPs recommended vitamin D supplementation of 60,000 IU/week for 2 to 6 months and 2,000 IU/day for 3 to 6 months in vitamin D-deficient patients for optimal response to therapy in COVID-19 patients. The immunomodulatory function of vitamin D should be further explored considering the increased awareness and use of vitamin D for immune protection from this KAP study.

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मधुमेह का भंवर

बढती जानकारी, बढती सूचनाएं अन गनत शोध, सभाएं.
इस उपलब्धि पर हम फूले नहीं समाते
एक दूजे की पीठ थपथपाते हम है अघाते!

हर तीसरे वर्ष IDF के आंकड़े
आइना हमें दिखाते हमारे ज्ञान को मुंह है चढाते!

खडा सामने यक्ष प्रश्न कैसे करे मधुमेह से बचाव
सारे ज्ञान को धता बता सुरसा मुख सामान
बढ़ा रहा यह अपना फैलाव!

कहाँ रहे हम चूक कहाँ हो रही भूल
अनियंत्रित खल रहे मधुमेह के ज़हरीले फूल!

जो करना है मधुमेह से बचाव बच्चो से करे लगाव
करे लक्ष्य उनको मधुमेह में आ जाएगा ठहराव!

बीता बचपन आई जवानी साथ लए
दूषत जीवन शैली की नादानी
पेट हुआ मटका लगा मधुमेह का झटका
प्रस्फूटित हुआ मधुमेह का अंकुर
छाप लया पूरा खेत अब पछताए होत क्या
जब च ड़या चुग गयी खेत!

डा आलोक कुमार गुप्ता १२.१०.२०

HUMOR

WHAT IF I HAVE A BATH?

Mum: If you wash your face, Sammy, you can have one slice of chocolate cake. But if you wash your neck, too, you can have two slices.

Sammy: What if I have a bath?

DREAM OF A NECKLACE

After she woke up, a woman told her husband, "I just dreamed that you gave me a pearl necklace for our anniversary. What do you think it means?"

"You'll know tonight." he said.

That evening, the man came home with a small package and gave it to his wife.

Delighted, she opened it to find a book entitled, "The Meaning of Dreams."

ABSENT-MINDED PROFESSOR

One of the world's greatest scientists was also recognized as the original absent-minded professor. One day, on board a train, he was unable to find his ticket. The conductor said, "Take it easy. You'll find it."

When the conductor returned, the professor still couldn't find the ticket. The conductor, recognizing the famous scientist, said, "I'm sure you bought a ticket. Forget about it."

"You're very kind," the professor said, "but I must find it, otherwise I won't know where to get off."

DAUGHTER IN COLLEGE

Did you hear about the Banker who was recently arrested for embezzling $100,000 to pay for his daughter's college education?

As the Policeman, who also had a daughter in college, was leading him away in handcuffs, he said to the Banker, "I have just one question for you. Where were you going to get the rest of the money?"

Dr. Good and Dr. Bad

SITUATION: A pregnant lady who had diabetic ketoacidosis presented with complaints of nausea and vomiting.

LESSON: Hyperglycemia and acidosis can be improved with aggressive insulin therapy and resuscitation during pregnancy.

J Neonatal Perinatal Med. 2017;10(1):17-23.

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