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Original Article

Internal Medicine Section

Assessment of Clinical Experience of Triple Drug Fixed-dose Combination of Glimepiride, Metformin and Voglibose in the Management of Type 2 Diabetes Mellitus: A Retrospective Study

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ABSTRACT

Introduction: Poor adherence of patients to the polypharmacy approach is a crucial challenge in the management of Type 2 Diabetes Mellitus (T2DM) and use of triple Fixed-Dose Combination (FDC) of metformin, glimepiride, and voglibose is effective in achieving glycaemic control and would aid in improved drug adherence.

Aim: To analyse clinical profile and treatment patterns of FDC of glimepiride, metformin, and voglibose with or without other antidiabetic therapy in patients with T2DM.

Materials and Methods: A retrospective, observational, multi-centric study conducted during August 2019 to March 2020. Included patients of either sex, ≥18 years of age with T2DM and who had received treatment with FDC of glimepiride, metformin, and voglibose of varying strengths with or without other antidiabetic therapy. Data extracted from medical records included demographic characteristics, duration of disease, co-morbidities, concomitant medications and dosage pattern. Data were analysed using Chi-square test and Mann-Whitney U test.

Results: A total of 2650 patients with T2DM were included, of which 1689 (63.7%) were males. The mean (standard deviation {SD}) age was 54.2 (11.4) years. The average Body Mass Index (BMI) was 27.2 (4.3) kg/m^2 and hypertension 1656 (62.5%) and dyslipidaemia 1109 (41.9%) were the most common co-morbidities. Dipeptidyl peptidase-4 inhibitors 908 (34.3%) and antihypertensives 1601 (60.4%) were the most common concomitant diabetic and non diabetic medications received, respectively. Glimepiride (2 mg)+metformin (500 mg)+voglibose (0.2 mg) FDC twice-a-day 878 (33.1%) was a common triple FDC. A total of 2449 (92.4%) patients were compliant and 2585 (97.9%) achieved glycaemic goal with triple FDC treatment. During the therapy, the majority of patients had decreased weight 1106 (67.2%). The mean Haemoglobin A1c (HbA1c) levels significantly decreased post-treatment (mean change 1.45%; p-value <0.001). Family history of diabetes mellitus, obesity, sedentary lifestyle were the most common risk factors and smoking being prevalent in males.

Conclusion: Overall results demonstrate that triple FDC of glimepiride, metformin, and voglibose was effective in reducing HbA1c and weight and was well tolerated. Also, it improves compliance in Indian patients with T2DM.

Keywords: Antidiabetic, Glycated haemoglobin, Poor glycaemic control

INTRODUCTION

Optimal glycaemic control is at the mainstay of management approach for Type 2 Diabetes Mellitus (T2DM) as it is a gradually advancing phenomenon involving progressive β-cell failure. It is also known that regulations in Postprandial Glucose (PPG) often precede changes in Fasting Plasma Glucose (FPG) in the development of T2DM. Even though, FPG levels cause dominant changes in HbA1c levels in poorly controlled patients with T2DM, the contribution of PPG in glycaemic control increases as HbA1c levels improve. Thus, it is of great importance to manage the levels of PPG as well as FPG in achieving adequate glycaemic control [1].

Administration of oral and/or injectable medicines in the form of combination therapy is the most commonly used treatment approach for achieving a long-term goal of target blood glucose levels and glycated haemoglobin (HbA1c) levels [2,3]. A common approach of concurrent administration with multiple medications to achieve good glycaemic control contributes to the increased pill burden and dosing frequency ultimately impacting patient's compliance with the treatment. Nevertheless, poor adherence of patients to the polypharmacy approach for the long-term is a crucial challenge in the management of T2DM [4-6].

In the last few decades, the complexity of the drug regimen on the medication compliance has gained substantial attention in the medical field. One of the key reasons for patients' non adherence to the medications is the difficulty to continue taking multiple drugs at different times on a daily basis for long-term; however, evidence indicates the use of FDCs as one of the methods that would improve drug adherence [7-10]. A previous Indian study provided substantial evidence in the support of the use of FDC of Oral Antidiabetic Drugs (OAD) in more than 50% of study patients with T2DM [11].

One of the common triple FDC is a combination of sulfonylurea, metformin, and voglibose {an α-glucosidase inhibitor (AGI)}. Sulfonylurea cause insulin release from the beta cell of the pancreas, while metformin improves insulin sensitivity at the muscle and liver, whereas, voglibose reduces postprandial blood glucose. Voglibose helps in glucose absorption when used alone or in combination with other antidiabetic drugs. The general principles of recommended care in the Research Society for Study of Diabetes in India (RSSDI) guidelines also mention the use of triple therapy as a patient-centric approach, if the glycaemic targets are not achieved with two agents [12]. RSSDI recommends AGIs as one of the oral agents to be started as triple therapy.

Various randomised clinical trials and real world studies have revealed voglibose as an effective and well tolerated OAD with cardiovascular benefits that significantly reduced HbA1c and blood glucose levels in patients with T2DM [13-15]. The triple-drug combination of metformin, glimepiride, and voglibose has been shown to be effective in the control of glycaemic pentad in Indian patients. This triple FDC demonstrated efficacy in controlling both fasting and PPG levels and thereby, regulating HbA1c and glycaemic variations [16,17]. Substantial evidence in support of efficacy and safety of this combination in the management of T2DM was provided in a relevant study [18].

Meanwhile, there are no adequate nationwide real word data analysis in the Indian population on the use of FDC of sulfonylurea, metformin, and voglibose, in varying doses. Therefore, the present study was conducted to assess real-world clinical profile and treatment patterns of FDC of glimepiride, metformin, and voglibose with or without other antidiabetic therapy in T2DM prescribed by the primary care physicians, diabetologists and endocrinologists.

MATERIALS AND METHODS

This was a retrospective, observational, non randomised, non comparative and multi-centric study conducted during August 2019 to March 2020. The study included patients' data extracted from health facility records of total 111 clinical sites in India. The study was conducted in accordance with the ethical principles that are consistent with the Declaration of Helsinki, International Conference on Harmonisation-Good clinical practices (ICH-GCPs) and the applicable legislation on non-interventional studies. The study protocol approval was obtained from the Independent Ethics Committee (IEC) prior to the commencement of the study {CLINICOM IEC: 01567/01.08.2019 and ACEAS IEC: USV/REALTRIO/05 (26 Aug 2019; 13 Nov 2019; 12 Dec 2019; 17 Jan 2020)}.

Inclusion criteria: Patients of either sex, above 18 years of age with T2DM and who had received treatment with FDC of glimepiride, metformin sustained release (SR) and voglibose of any strength with or without other antidiabetic therapy in T2DM were included in the study.

Exclusion criteria: Patients who had incomplete data or any condition that according to the discretion of the investigator indicated that the patient is not suitable for the study were excluded.

Data Collection

The data of all patients were extracted from their medical records authenticated by physicians during routine care at hospitals/clinics and entered into paper-based Case Report Forms (CRF). Each CRF at the investigation sites were given a unique identifying number and data entry were done for the CRFs received from the sites using a customised data entry platform with an inbuilt data matching system. Collected data included demographic characteristics, duration of disease and treatment, co-morbidities, concomitant medications and dosage pattern. The physician evaluation of efficacy and tolerability was based on a physician's perception about the efficacy and tolerability of triple FDC used in the study for each patient. It was graded on the scales of fair, average, good, very good and excellent.

According to the Standards of Medical Care in Diabetes by the American Diabetes Association (ADA) 2020 the optimal glycaemic control in non pregnant adults was defined as HbA1c <7%; while uncontrolled diabetes was defined as HbA1c ≥7%; Fasting Blood Glucose (FBG) >130 mg/dL; and PPG ≥200 mg/dL [19].

Body Mass Index (BMI) classification according to the consensus statement for diagnosis of obesity, abdominal obesity, and the metabolic syndrome for Asian Indians is underweight: <18.5 kg/m^2, normal: 18.5 to <25 kg/m^2, overweight: 25 to <30 kg/m^2, obese: ≥30 kg/m^2 [20].

STATISTICAL ANALYSIS

Data were analysed using Statistical Package for the Social Sciences (SPSS) software, version 23.0. Qualitative data were presented as numbers and percentages, while quantitative data were presented as mean {Standard Deviation (SD)} or median {Interquartile Range (IQR)}, depending on the normal or skewed distribution of data. The normal distribution of quantitative data was assessed by the Shapiro-Wilk test. A comparison of qualitative and quantitative variables between the groups was done using the Chi-square test and Mann-Whitney U test, respectively. The p-value<0.05 was considered statistically significant.

RESULTS

Out of 2700 patients screened, a total of 2650 patients with T2DM were included in this retrospective analysis. The mean (SD) age of patients was 54.2 (11.4) years and more than half of the study population were in the age group of >40 to ≤60 years 1530 (57.7%). The proportion of male patients1689 (63.7%) was higher than female patients 961 (36.3%). The average BMI of the study population was 27.2 (4.3) kg/m^2 [Table/Fig-1].

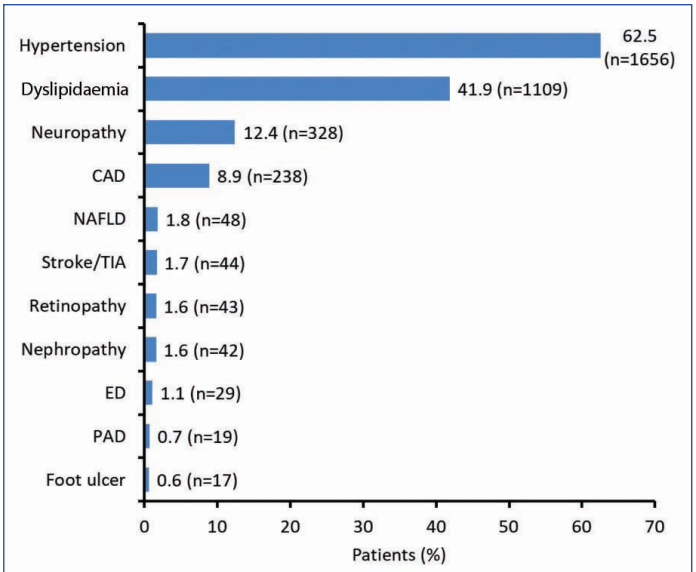
It was observed that, a large proportion of patients 878 (33.1%) received the dose of glimepiride (2 mg) +metformin (500 mg) +voglibose (0.2 mg) followed by glimepiride (2 mg)+metformin (500 mg)+voglibose (0.3 mg), (n=472, 17.8%). Other concominant diabetic medications include glimepiride (1 mg)+metformin (500 mg)+voglibose (0.2 mg) and glimepiride (2 mg)+metformin (500 mg)+voglibose (0.2 mg); glimepiride (1 mg)+metformin (500 mg)+voglibose (0.2 mg) and glimepiride (2 mg)+metformin (500 mg)+voglibose (0.3 mg); glimepiride (1 mg)+metformin (500 mg)+voglibose (0.2 mg) and glimepiride (2 mg)+metformin (1000 mg)+voglibose (0.2 mg); glimepiride (2 mg)+metformin (500 mg)+voglibose (0.2 mg) and glimepiride (2 mg)+metformin (500 mg)+voglibose (0.3 mg); glimepiride (2 mg)+metformin (500 mg)+voglibose (0.2 mg) and glimepiride (2 mg)+metformin (1000 mg)+voglibose (0.2 mg); glimepiride (1 mg)+metformin (500 mg)+voglibose (0.3 mg) and glimepiride (2 mg)+metformin (500 mg)+voglibose (0.3 mg); glimepiride (1 mg)+metformin (500 mg)+voglibose (0.3 mg) and glimepiride (2 mg)+metformin (1000 mg)+voglibose (0.2 mg); glimepiride (2 mg)+metformin (500 mg)+voglibose (0.3 mg) and glimepiride (2 mg)+metformin (1000 mg)+voglibose (0.2 mg) [Table/Fig-1]. In concomitant diabetic medications, the proportion of patients receiving Dipeptidyl Peptidase-4 Inhibitors (DPP4i) 908 (34.3%) was highest followed by Sodium-Glucose Co-Transporter-2 Inhibitors (SGLT2i) 349 (13.2%). Concomitant non diabetic medications were antiallergic, antianxiety, antiasthmatic, anticonvulsant, antidepressant, antiemetic, antiepileptic, antifungal, antimalarial, antiplasmodic, antituberculosis, antibiotic, antipyretic, antihistamine, laxative, mucolytic agent, probiotic, steroids and medications for bowel disease, coronary heart disease, erectile dysfunction, and liver disease. In concomitant non diabetic treatments, the most common class of drugs were antihypertensives 1601 (60.4%) and lipid lowering drugs 999 (37.7%) [Table/Fig-1]. Among co-morbid conditions, hypertension 1656 (62.5%) and dyslipidaemia 1109 (41.9%) were the most common across the study population [Table/Fig-2].

Before starting triple FDC, among previously prescribed medication, 1513 (57.1%), 533 (20.1%), and 405 (15.3%) patients were receiving a combination of metformin and sulfonylurea, metformin alone, and metformin plus DPP4i, respectively {with a mean (SD) duration of 33.9 (30.5), 23.7 (24.4), and 30.8 (24.2) months, respectively}. Remaining patients were receiving insulin 143 (5.4%) and other medications 53 (2%) with a mean duration of 40.6 (47.3) and 18.8 (15.8) months, respectively [Table/Fig-3]. Overall, 2616 (98.7%) patients had poor glycaemic control prior to the study (HbA1c ≥7.0%). Among reasons for starting the triple FDC of glimepiride,

Parameters		Number of patients (N=2650)* n (%)
Age (years), mean (SD)		54.2 (11.4)
Age group (years)		
≥20 to ≤40		350 (13.2)
>40 to ≤60		1530 (57.7)
>60 to ≤80		770 (29.1)
Sex		
Male		1689 (63.7)
Female		961 (36.3)
Height (cm), mean (SD)		163.1 (9.9)
Weight (kg), mean (SD)		72.2 (11.5)
BMI (kg/m^2), mean (SD)		27.2 (4.3)
Concomitant diabetic medication		
DPP4i		908 (34.3)
SGLT2i		349 (13.2)
TZD		111 (4.2)
Insulin		192 (7.2)
GLP1 agonist		18 (0.7)
Concomitant non diabetic medication (n=3581)		
Antihypertensive		1601 (60.4)
Lipid lowering		999 (37.7)
Neuropathic pain		143 (5.4)
Nonsteroidal anti-inflammatory		166 (6.3)
Antacids		162 (6.1)
Vitamins and multivitamins		143 (5.4)
Antiplatelet		59 (2.2)
Hypothyroidism		27 (1.0)
Others		281 (10.6)
Treatment pattern and frequency		
Glimepiride (1 mg)+metformin (500 mg) +voglibose (0.2 mg)	BD	349 (13.2)
	OD	98 (3.7)
	TID	2 (0.1)
Glimepiride (2 mg)+metformin (500 mg) +voglibose (0.2 mg)	BD	878 (33.13)
	OD	221 (8.33)
	TID	1 (0.03)
Glimepiride (1 mg)+metformin (500 mg) +voglibose (0.3 mg)	BD	156 (5.9)
	OD	28 (1.05)
Glimepiride (2 mg)+metformin (500 mg) +voglibose (0.3 mg)	BD	472 (17.8)
	OD	54 (2.03)
	TID	1 (0.03)
Glimepiride (1 mg)+metformin (1000 mg)+voglibose (0.2 mg)	BD	125 (4.7)
	OD	31 (1.2)
Glimepiride (2 mg)+metformin (1000 mg) +voglibose (0.2 mg)	BD	207 (7.8)
	OD	10 (0.4)
Other (combinations)	-	16 (0.60)

[Table/Fig-1]: Patient demographics and treatment related observations.
Data shown as n (%), unless otherwise specified. *N=2650, unless otherwise specified; DPP4i, dipeptidyl peptidase-4 inhibitors; FDC, fixed dose combination; GLP1, glucagon-like peptide-1; SGLT2i, sodium-glucose co-transporter-2 inhibitor; TZD, thiazolidinedione; BD, twice a day; OD, once a day; TID, thrice a day

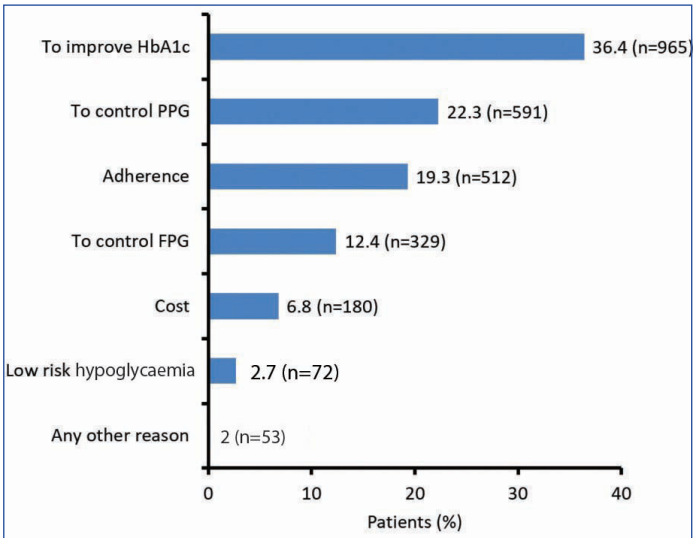
metformin, and voglibose, the most common reason was to improve HbA1c 965 (36.4%), followed by to control PPG levels 591 (22.3%) adherence to medication 512 (19.3%) to control FPG 329 (12.4%), cost 180 (6.8%) low risk of hypoglycaemia 72 (2.7%) and other reasons 53 (2%) [Table/Fig-4]. The mean HbA1c levels significantly decreased post-treatment with triple FDC of glimepiride, metformin, and voglibose with mean change of 1.45% (95% CI, 1.41-1.49; p<0.001) [Table/Fig-5].



[Table/Fig-2]: Comorbidities associated with T2DM.
CAD: Coronary artery disease; ED: Erectile dysfunction; NAFLD: Non-alcoholic fatty liver disease; PAD: Peripheral arterial disease; TIA: Transient ischemic attacks

Previously prescribed medications	Number of patients (N=2650) n (%)	Duration of treatment, Mean (SD)
Metformin+Sulfonylurea	1513 (57.1)	33.9 (30.5)
Metformin	533 (20.1)	23.7 (24.4)
Metformin+DPP4i	405 (15.3)	30.8 (24.2)
Insulin	143 (5.4)	40.6 (47.3)
Any other	53 (2)	18.8 (15.8)

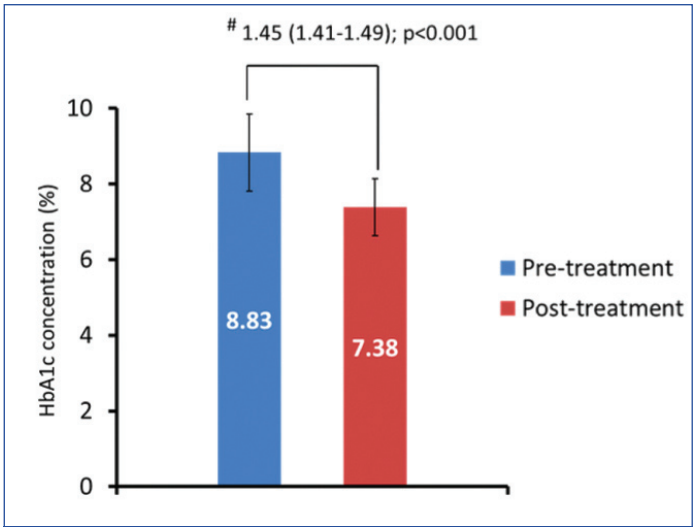
[Table/Fig-3]: Duration of previous medication before starting the FDC (months).
DPP4i: Dipeptidyl peptidase-4 inhibitors



[Table/Fig-4]: Reason for starting the triple FDC of glimeperide, metformin, and voglibose.
FPG: Fasting plasma glucose; HbA1c: Glycated haemoglobin; PPG: Postprandial plasma glucose

A total of 1645 (62.1%) patients experienced weight changes during the therapy. Out of these, the majority of patients 1106 (67.2%) had decreased weight while the remaining 539 (32.8%) patients had increased weight. Most of the patients had weight elevation or reduction up to 2 kilograms (kg). A total of 2449 (92.9%) patients were compliant with the triple FDC and 2585 (97.9%) achieved the glycaemic goal with triple FDC treatment. A total of 25 adverse events were reported and gastritis was the most common [Table/Fig-6]. Physician global evaluation of efficacy and tolerability showed a majority of patients on a good to excellent scale 2603 (98.7%) and 2603 (99%) [Table/Fig-7].

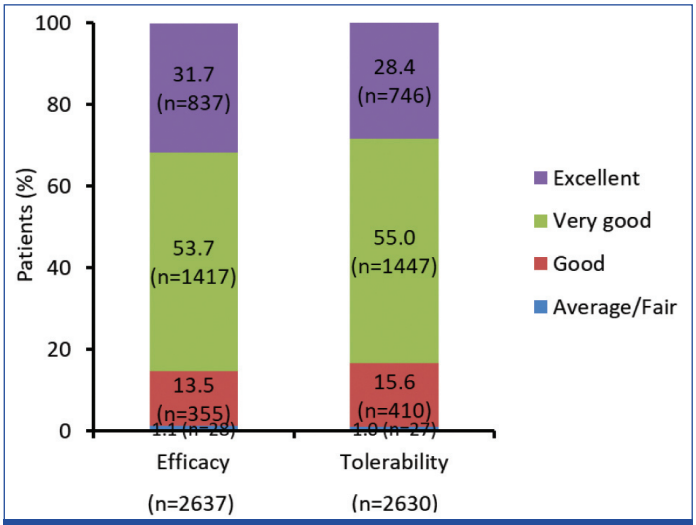
In gender-wise analysis, the median (IQR) age of males was significantly higher than females {55.0 (47.0-63.5) versus (vs.) 52.0 (46.0-60.0) years,



[Table/Fig-5]: Mean change in HbA1c levels from pre-treatment to post-treatment.
#Mean change from pre-treatment to post-treatment (95% CI)

Parameters	Number of patients (N=2650)
Patients with weight changes during the therapy, n (%)	1645 (62.1)
a) Increased weight (kg)	
0-2	399 (24.3)
2-4	132 (8.0)
>4	8 (0.5)
b) Decreased weight (kg)	
0-2	841 (51.1)
2-4	239 (14.5)
>4	26 (1.6)
Compliance (n=2635)	
Fully compliant, n (%)	2449 (92.9)
Not fully compliant, n (%)	186 (7.1)
Patients with glycaemic goal achieved (n=2639)	
Yes, n (%)	2585 (97.9)
No, n (%)	54 (2.1)
Adverse events (n=25), n (%)	
Gastritis	16 (64.0)
Diarrhea	4 (16.0)
Fullness of abdomen	4 (16.0)
Flatulence	1 (4.0)

[Table/Fig-6]: Observations related to weight alterations, FDC compliance, glycaemic control, and adverse events.
n: No. of subjects; kg: Kilograms



[Table/Fig-7]: Physician global evaluation of efficacy and tolerability.

p<0.001}. Majority of patients of either sex belonged to age group >40 to ≤60 years (males, n=946, 56.0% and females, n=584, 60.8%) followed by the elderly age group (>60 to ≤80 years) (males, n=541, 32.0% and females, n=229, 23.8%). The median (IQR) BMI was significantly higher in females {27.2 (24.7 to 30.1) kg/m^2} compared to males {26.6 (24.2 to 29.1) kg/m^2} (p<0.001). In both males and females, the majority of patients were overweight (n=786, 47.4% and n=445, 47.2%, respectively) [Table/Fig-8].

Characteristics	Males (n=1689)	Females (n=961)	p-value
Age (years)	55 (47.0-63.5)	52 (46-60)	<0.001*
Age group (years), n (%)			
≥20 to ≤40	202 (12)	148 (15.4)	<0.001*
>40 to ≤60	946 (56)	584 (60.8)	
>60 to ≤80	541 (32)	229 (23.8)	
Height (cm)	(n=1663) 168 (160-172)	(n=944) 158 (152-163)	<0.001*
Weight (kg)	(n=1681) 74 (67-80)	(n=954) 68 (61-75)	<0.001*
BMI (kg/m^2)	(n=1659) 26.6 (24.2 to 29.1)	(n=942) 27.2 (24.7 to 30.1)	<0.001*
Underweight, n (%)	12 (0.7)	8 (0.8)	<0.001*
Normal, n (%)	535 (32.2)	239 (25.4)	
Overweight, n (%)	786 (47.4)	445 (47.2)	
Obese, n (%)	326 (19.7)	250 (26.5)	
Duration of diabetes (years)	(n=1557) 5 (3-10)	(n=908) 5 (3-8)	0.101
Duration of treatment (months)	(n=1688) 4 (3-12)	4 (3-12)	0.426
Risk factors, n (%)			
Smoking	895 (52.9)	52 (3.1)	
Family history of DM	734 (43.4)	511 (30.2)	
Obesity	647 (38.3)	427 (25.2)	-
Sedentary lifestyle	517 (30.6)	321 (19.0)	
Alcohol consumption	318 (18.8)	25 (1.5)	
Intake of excess salt	272 (16.1)	160 (9.4)	
Tobacco chewing	226 (13.3)	18 (1.1)	
Emotional stress	217 (12.8)	259 (15.3)	

[Table/Fig-8]: Gender-wise analysis.
Data shown as median (IQR), unless otherwise specified. BMI: Body mass index; IQR: Interquartile range; cm: Centimeters; kg: Kilograms; m: Meters; n: No. of subjects; DM: Diabetes mellitus. *p<0.001 was considered statistically significant. As the present study was a retrospective study, some of the data was missing in the records, hence different "n" can be seen for above parameters

In male population, more than half of patients 895 (52.9%) were smokers, 734 (43.4%) of patients had a family history of DM, 647 (38.3%) were obese and 517 (30.6%) were living sedentary lifestyle [Table/Fig-8]. Excess alcohol consumption, intake of excess salt, tobacco chewing and emotional stress were the other risk factors observed in 318 (18.8%), 272 (16.1%), 226 (13.3%), and 217 (12.8%) male patients, respectively. Whereas, in female patients, family history of DM 511 (30.2%) was the most common risk factor followed by obesity 427 (25.2%). A total of 321 (19%) females were living sedentary lifestyle while 259 (15.3%) had emotional stress [Table/Fig-8].

Administration of glimepiride (2 mg) +metformin (500 mg) +voglibose (0.2 mg) was the most common treatment in both males and females (n=739, 43.7% and n=361, 37.5%, respectively) followed by glimepiride (2 mg) +metformin (500 mg) +voglibose (0.3 mg) (n=352, 20.8% and n=175, 18.2%, respectively) and glimepiride (1 mg) +metformin (500 mg) +voglibose (0.2 mg) (n=251, 14.8% and n=198, 20.6%, respectively) [Table/Fig-9a].

A total of 350 (13.21%), 1530 (57.74%), and 770 (29.06%) patients belonged to age groups ≥20 to ≤40 (group A), >40 to ≤60 (group B),

and >60 to ≤80 (group C), respectively. The median (IQR) age of patients was 37 (34-39), 52 (48-56), and 67 (63-71) years in group A, B, and C, respectively (p<0.001). More than half of the patients had elevated BMI {overweight:38.6% (n=134), 49.6% (n=743), and 46.8% (n=354)} and {obese: 28.0% (n=97), 20.7% (n=310), and 22.4% (n=169)} as compared to normal BMI {32.0% (n=111), 29.0% (n=435), and 30.2% (n=228)} across all the age groups (p=0.009).

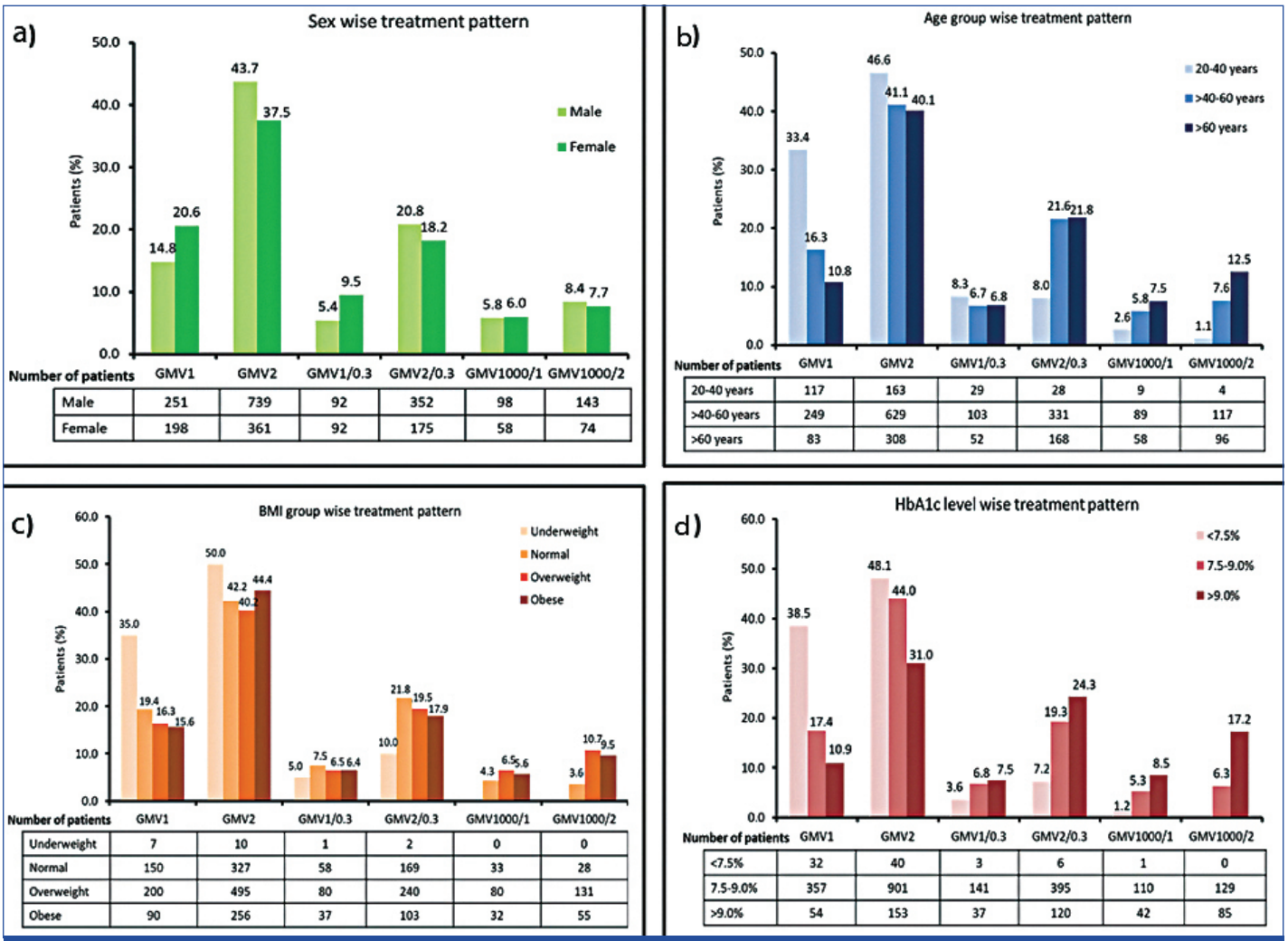
Administration of glimepiride (2 mg)+metformin (500 mg)+voglibose (0.2 mg) was the most common treatment given to patients from all the age groups {46.6% (n=163), 41.1% (n=629), and 40.1% (n=308)}. In the age group ≥20 to ≤40, the second most common treatment was glimepiride (1 mg)+metformin (500 mg)+voglibose (0.2 mg) (n=117, 33.4%); whereas, in age group >40 to ≤60 and >60 years, it was glimepiride (2 mg)+metformin (500 mg)+voglibose (0.3 mg) (n=331, 21.6% and n=168, 21.8%) [Table/Fig-9b].

Administration of glimepiride (2 mg)+metformin (500 mg)+voglibose (0.2 mg) was the most common treatment given to patients from all the BMI wise groups, i.e., underweight, normal, overweight, and obese {50.0% (n=10), 42.2% (n=327), 40.2% (n=495), and 44.4% (n=256), respectively}. In underweight patients, the second most common treatment was glimepiride (1 mg)+metformin (500 mg)+voglibose (0.2 mg) (n=7, 35.0%); whereas, in normal, overweight and obese patients, it was glimepiride (2 mg)+metformin (500 mg)+voglibose (0.3 mg) {21.8% (n=169), 19.5% (n=240), and 17.9% (n=103)} [Table/Fig-9c].

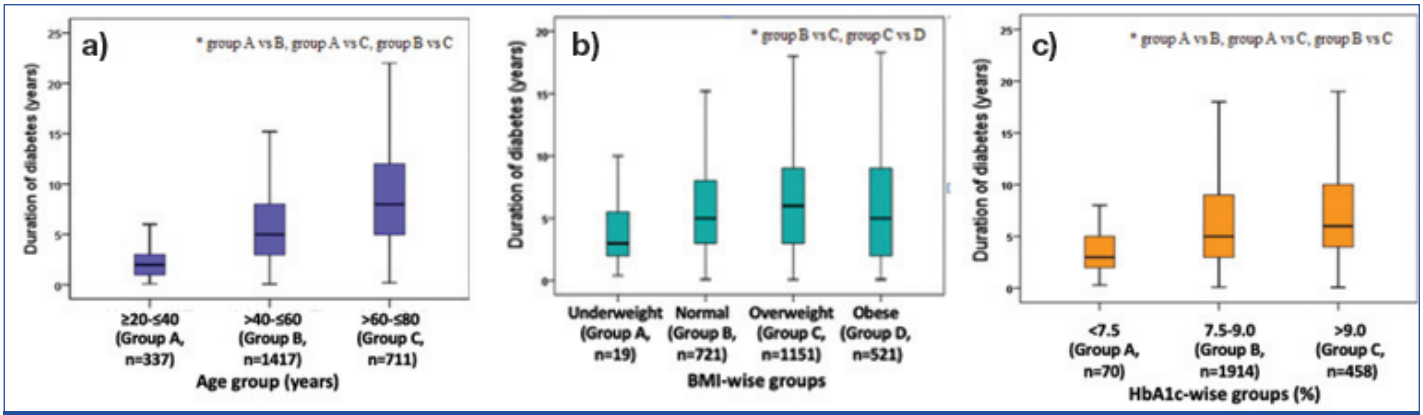
The median (IQR) duration of treatment was significantly higher in youngest age group {≥20 to ≤40 years, six (1-12) months} as compared to other two age groups {>40 to ≤60 years, four (3-12) months (p=0.003) and >60 to ≤80 years, three (3-12) months (p=0.002)}. The median (IQR) duration of diabetes was significantly increased with increasing age and there was a significant difference between group A vs. B {two (1-3) vs. five (3-8) years, p<0.001}, group B vs. C {five (3-8) vs. eight (5-12) years, p<0.001), and group A vs. C {two (1-3) vs. eight (5-12) years, p<0.001} [Table/Fig-10a].

The majority of patients across all the four BMI-wise groups had HbA1c level in the range of 7.5 to 9.0%. The median (IQR) duration of treatment was significantly higher in normal BMI group {six (3-12) months} as compared to overweight {three (3-12) months} and obese {three (2-10) months} groups (p<0.001). Also, a significant difference was observed between overweight {three (3-12) months} and obese {three (2-10) months} groups (p<0.001). The median (IQR) duration of diabetes was significantly higher in overweight group {six (3-9) years} as compared to obese {five (2-9) years, p=0.001} and normal BMI group {five (3-8) years, p=0.007} [Table/Fig-10b].

Administration of glimepiride (2 mg)+metformin (500 mg) +voglibose (0.2 mg) was the most common treatment given to patients from all the three HbA1c-wise groups, {48.1% (n=40), 44.0% (n=901), and 31.0% (n=153)}. Second most common treatment in patients with HbA1c <7.5% was glimepiride (1 mg) +metformin (500 mg) +voglibose (0.2 mg) (n=32, 38.5%); whereas, in those with HbA1c 7.5 to 9.0% and >9.0%, it was glimepiride (2 mg) +metformin (500 mg) +voglibose (0.3 mg) (n=395, 19.3%, and n=120, 24.3%, respectively) [Table/Fig-9d]. Therefore, among various treatment options, glimepiride (2 mg) +metformin (500 mg) +voglibose (0.2 mg) was the preferred FDC treatment prescribed by majority of physicians irrespective of HbA1c concentration.



[Table/Fig-9a-d]: Treatment patterns across the study population.
GMV1, glimepiride (1 mg)+metformin (500 mg)+voglibose (0.2 mg); GMV2, glimepiride (2 mg)+metformin (500 mg)+voglibose (0.2 mg); GMV1/0.3; glimepiride (1 mg)+metformin (500 mg)+voglibose (0.3 mg); GMV2/0.3, glimepiride (2 mg)+metformin (500 mg)+voglibose (0.3 mg); GMV1000/1, glimepiride (1 mg)+metformin (1000 mg)+voglibose (0.2 mg); GMV1000/2, glimepiride (2 mg)+metformin (1000 mg)+voglibose (0.2 mg)



[Table/Fig-10a-c]: Comparison of duration of diabetes among different study groups.
*p-value <0.05 was considered as statistically significant. BMI: Body mass index; HbA1c: Glycated haemoglobin

The median (IQR) duration of diabetes was significantly higher in patients with HbA1c >9.0% {six (4-10) years} than those with 7.5-9.0% {five (3-9) years} and <7.5% {three (2.0-5.3) years} (p<0.001) [Table/Fig-10c]. The median (IQR) age was significantly higher in patients with HbA1c >9.0% {57 (49-64) years} as compared to those with HbA1c 7.5%-9.0% {53 (42-62)} and <7.5% {52 (43-60)} (p<0.001). A significant difference in median (IQR) BMI was observed between patients with HbA1c >9.0% {27.2 (24.8 to 29.7) kg/m^2} and HbA1c <7.5% {25.0 (22.5 to 28.7) kg/m^2}; and between patients with 7.5%-9.0% {26.8 (24.2 to 29.4) kg/m^2} and HbA1c <7.5% {25.0 (22.5 to 28.7) kg/m^2} (p<0.001). Overweight and obese patients were associated with increasing HbA1c levels (p<0.001) [Table/Fig-11].

Characteristics	Group A <7.5% (n=83)	Group B 7.5-9.0% (n=2046)	Group C >9.0% (n=493)	p-value
Age (years)	52 (43-60)	53 (46-62)	57 (49-64)	0.244[a], 0.001[b, c]
BMI (kg/m^2)	(n=81) 25.0 (22.5 to 28.7)	(n=2025) 26.8 (24.2 to 29.4)	(n=467) 27.2 (24.8 to 29.7)	0.001[a, b], 0.156[c]
BMI range, n (%)				
Underweight	4 (4.9)	16 (0.8)	0	<0.001*
Normal	36 (44.4)	607 (30.0)	123 (26.3)	
Overweight	29 (35.8)	949 (46.9)	241 (51.6)	
Obese	12 (14.8)	453 (22.4)	103 (22.1)	

[Table/Fig-11]: HbA1c level-wise treatment distribution.
Data shown as median (IQR), unless otherwise specified; BMI: Body mass index; IQR: Interquartile range, *p<0.05 was considered statistically significant.; [a]Group A vs B; [b]Group A vs C; [c]Group B vs C

DISCUSSION

At present, achieving an optimal glycaemic control for long-term in patients with T2DM is a key challenge for the healthcare system. However, the growing prevalence of T2DM makes this situation worse with increasing disease burden on developing nations including India. There are various diabetes medications currently used as monotherapies or as a combination of multiple drugs in the management of T2DM. In spite of the sufficient data that provide favourable efficacy and safety outcomes for triple FDC use, there is a need for a firm evidence in support of these medications for long-term use.

In spite of metformin being a widely accepted first-line therapy for the management of T2DM, glycaemic variability is often a challenge. Consequently, there is uncertainty about the add-on drug to metformin for better glycaemic control. The use of metformin and sulfonylureas (mainly glimepiride) is the most common treatment of T2DM in India and this approach is even recommended by Indian guidelines [21-23]. However, the use of FDC has opened a new avenue in the treatment choices and helped in increased medication adherence to oral antidiabetic medications. One such triple FDC is glimepiride, metformin, and voglibose which has been studied for its effectiveness and tolerability among various populations of patients with T2DM [18].

The present study investigated treatment patterns of glimepiride, metformin, and voglibose as a triple-drug FDC in the management of T2DM along with co-morbidities, glycaemic control, changes in HbA1c and weight post-treatment with the study intervention in the real-world Indian setting. The key observations are as follows: More than half of the patients had elevated BMI indicating the overweight and obese population. Hypertension and dyslipidaemia were the most common associated co-morbidities. In the overall population, majority of patients had uncontrolled glycaemia (7.5-9.0%). The triple FDC of glimepiride, metformin, and voglibose was effective in significantly reducing the mean HbA1c levels post-treatment demonstrating efficacy in terms of achieving the glycaemic target. Among patients who experience weight alterations, 67.2% of the patients had decreased weight. Higher compliance rate to the triple FDC regimen and higher proportion of patients who achieved the glycaemic goal with triple FDC treatment demonstrated the efficacy of the glimepiride, metformin, and voglibose treatment. The safety profile observations indicate that the triple FDC of glimepiride, metformin, and voglibose was well-tolerated in the Indian population. Physician global evaluation of efficacy and tolerability showed overall good response. Administration of glimepiride (2 mg) +metformin (500 mg) +voglibose (0.2 mg) was the most common treatment received in overall population followed by glimepiride (2 mg) +metformin (500 mg) +voglibose (0.3 mg). The median duration of diabetes was significantly increased with increasing age and was significantly higher in the overweight group as compared to obese and normal BMI group.

In a postmarketing surveillance, Rao C and Faruqui AA assessed efficacy and safety of triple FDC of glimepiride, metformin and voglibose and its impact on glucose triad. They demonstrated significantly decreased HbA1c value, FPG level and PPG level after three months of treatment [18]. The present study observations corroborate with this study and demonstrate efficacy of triple FDC in achieving target reduction of uncontrolled glycaemia.

A recently published real-world study that determined the levels of glycaemic control among patients with T2DM revealed a high burden of uncontrolled diabetes with three-fourths of patients (76.6%) having poor glycaemic control. The study also reported a high prevalence of neuropathy, hypertension and obesity [24]. Other previous studies have also demonstrated a high prevalence of patients with poor glycaemic control [25-28]. Similarly, the present study also reported the majority of population with uncontrolled glycaemia. Although, present study population was previously receiving other antidiabetic medications for a long duration, the majority of patients could not achieve glycaemic control. Therefore, the administration of triple FDC was a good option for the management of uncontrolled glycaemia in these patients and helped to improve compliance with the triple FDC. Further, hypertension and dyslipidaemia were the most commonly observed co-morbidities in this study population. These observations are in concordance with the previously published studies [25,29,30].

A significant association of poor glycaemic control with a duration of diabetes, age of onset, family history, antidiabetic drugs, BMI, hypertension, lipid and FPG levels were observed in a study by Kayar Y et al., [28]. A study by Borgharkar SS and Das SS revealed an inverse relationship between duration of diabetes and glycaemic control. They showed that the risk of poor glycaemic control is associated with the increasing duration of diabetes even with the use of combination therapies. The progressive nature of diabetes may contribute to this inverse relationship observed [25]. Another study from China has reported similar observations. They demonstrated that more than four years of diabetes duration was associated with higher odds (OR=5.98, 95% CI 4.09 to 8.75) of poor glycaemic control [31]. The present study observations are in accordance with these studies and showed poor glycaemic control with increasing duration of diabetes. Additionally, the present study showed that the median duration of diabetes was significantly higher in overweight group as compared to obese and normal BMI group suggesting an increase in duration of diabetes is associated with elevated BMI.

One of the key benefits of using triple FDC of glimepiride, metformin, and voglibose is to reduce the risk of weight gain as a result of the efficacy of voglibose, an alpha-glucosidase inhibitor, in reducing body weight along with controlling PPG target levels [32]. In the present study, patients who experienced weight alterations showed that more than 65% of the patients had reduced weight up to 4 kg. This observation supports the fact that triple FDC of glimepiride, metformin, and voglibose was effective in reducing the risk of weight gain in patients with T2DM thereby alleviating the risk of developing co-morbidities associated with weight gain (obesity and dyslipidaemia). Voglibose was most commonly added with metformin and sulfonylureas. It was well tolerated by the participants with T2DM without significant weight change. However, a meta-analysis of the comparison of the efficacy of alpha-glucosidase inhibitors in Asians and Caucasians showed that treatment with different alpha-glucosidase inhibitors (acarbose, voglibose and miglitol) lead to comparable changes of HbA1c and body weight in T2DM patients in Asian and Caucasian population when compared with placebo and other active oral hypoglycaemic agents [33].

Limitation(s)

One of the key limitations of this study was the retrospective collection of data which limits the strength of the inference. The collection of data did not include fasting and post-prandial blood glucose levels of the patients which have limited the analysis power of the comparative study parameters. Absence of long-term follow-up of glycaemic parameters was another obstruction and would have added the value to this study in terms of reporting long-term effectiveness of this triple FDC. Therefore, well-structured, appropriately designed studies with long-term follow-up that will evaluate the real-world effectiveness of the triple FDC of glimepiride, metformin, and voglibose in achieving long-term glycaemic control in patients with T2DM are necessary to validate these observations and will aid in further understanding of the clinical effectiveness and safety of this triple FDC in the management of T2DM.

CONCLUSION(S)

The therapeutic intervention that will aid in achieving optimal glycaemic control is the key for better prognostic outcomes. The overall observations from this real-world study demonstrated that the triple FDC of glimepiride, metformin, and voglibose was effective in reducing HbA1c along with weight which helps in achieving the target glycaemic control, and was well-tolerated in Indian patients with T2DM. Furthermore, the compliance rate of 92.9% indicates overall good adherence of patients to this triple FDC regimen. Therefore, triple FDC of glimepiride, metformin, and voglibose is a promising treatment option for the clinical management of T2DM among the Indian cohort.

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