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A SINGLE -BLIND CROSS-OVER STUDY OF NATEGLINIDE AND VOGLIBOSE IN COMBINATION WITH METFORMIN IN TYPE 2 DIABETES MELLITUS PATIENTS.

K.Punyavathi Poojitha[*1], Syed Mubishera Begum[2], K. V. Siva Prasad[3]

[1]Associate Professor, Department of Pharmacology, GITAM Institute of Medical Sciences and Research, Visakhapatnam, Andhra Pradesh, India

[2]Assistant Professor, Department of Pharmacology, Guntur Medical College, Guntur, Andhra Pradesh, India

[3]Professor and Head, Department of Pharmacology, Government Medical College, Rajamahendravaram, Andhra Pradesh, India

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Abstract

Diabetes mellitus is a major global health issue, affecting around 300 million people. Type 2 diabetes mellitus (T2DM) is a chronic metabolic disorder characterized by elevated blood sugar levels, primarily due to insulin resistance, which over time can damage organs and tissues. High postprandial blood glucose levels have been associated with atherosclerosis. This study aims to compare the efficacy and safety of nateglinide and voglibose in patients with T2DM. It is a single-blind, randomized crossover study involving patients from the General Medicine outpatient department. Patients were divided into Group A and Group B. Group A received nateglinide followed by voglibose, both with metformin. Group B received voglibose followed by nateglinide, also with metformin. In Group A, the baseline mean postprandial blood glucose (PPBG) was 237.81 ± 14.05 mg/dL. After 12 weeks of nateglinide and metformin, PPBG dropped to 193.25 ± 8.64, and further reduced to 171.63 ± 8.09 after voglibose and metformin. In Group B, the baseline PPBG was 237.67 ± 11.12, reduced to 195.27 ± 8.37 after nateglinide and metformin, and to 177.27 ± 8.64 after voglibose and metformin. Both groups showed a significant reduction in glycated hemoglobin (HbA1c) levels. While both drugs effectively reduced PPBG and HbA1c, voglibose demonstrated a better safety profile, with fewer hypoglycemic episodes compared to nateglinide. Therefore, although nateglinide and voglibose are equally effective in glycemic control, voglibose is considered safer.

***Keywords*:** Type 2 Diabetes mellitus, nateglinide, voglibose, metformin, crossover design, postprandial hyperglycemia.

***Corresponding Author**
Dr. Kudupudi Punyavathi Poojitha
Department of Pharmacology,
GITAM Institute of Medical Sciences and Research, Visakhapatnam, Andhra Pradesh, India

INTRODUCTION

Type 2 Diabetes mellitus is associated with significant levels of morbidity and mortality. Morbidity is mainly due to expected complications like cardiovascular, cerebrovascular, peripheral vascular diseases, nephropathy, and infection leading to lower-extremity amputations. It is also a major risk factor for acute myocardial infarction, stroke, and chronic renal failure [1]. It is also associated with an increased risk of cancer, serious psychiatric illness, cognitive decline, chronic liver disease, accelerated arthritis, and other disabling or deadly conditions [2]. The risk of death is one-third higher among people suffering from diabetes mellitus when compared with people not having diabetes mellitus [3].

It is estimated by The World Health Organization (WHO) that by 2025 about 300 million people aged above 20 years will be suffering from diabetes mellitus [4]. Type 2 Diabetes mellitus is the predominant form of diabetes worldwide with 90% of cases globally. In India, the estimated number of adults with diabetes mellitus by 2025 is 57.2 million [5].The International Diabetes Federation states that the number of cases of diabetes will increase to 592 million cases and 175 million cases eluding diagnosis by 2035 [6, 7].

In 2019, the World Health Organization ranked diabetes as the 9th cause of death globally. That same year, direct global expenditure on diabetes mellitus reached an estimated US dollars 760 billion, and indicating a rise to US dollars 825 billion by 2045 [8]. Type 2 diabetes mellitus is the most prevalent form, accounts for 90% of all cases and is characterized by relative insulin deficiency, insulin resistance, and increased hepatic glucose output. Aging, excess body weight, physical inactivity, and increasing urbanization can lead to its progress [9].

The DIANA (DIAbetes and diffuse coronary Narrowing) study aimed to determine whether low levels of postprandial blood glucose levels with either voglibose or nateglinide could influence the progression of atherosclerosis in populationdiagnosed with early-stage type 2 diabetes mellitus. A subsequent analysis of the study data found that participants who achieved a reversion in their glycemic status – either from impaired glucose tolerance back to normal glucose tolerance, or from newly diagnosed type 2 diabetes mellitus to either impaired or normal glucose tolerance – exhibited less disease progression. These findings suggest that lowering postprandial glucose may offer a benefit in reducing atherosclerosis in patients with early-stage type 2 diabetes mellitus [10].

A cohort study recently reported that patients with type 2 diabetes mellitus who maintained low HbA1c levels the first year after diagnosis experienced a reduced risk of macro vascular complications over the subsequent 10 years [11].

The concept of "metabolic memory" or the "legacy effect," supported by post-trial monitoring studies, explained the long-term impact of hyperglycemia on cardiovascular disease [12]. The fact that myeloid cells and bone marrow precursors retain proatherogenic properties even after blood glucose levels are normalized contributes to the development of atherosclerosis. Newly diagnosed T2DM patients, who have likely experienced more prolonged hyperglycemia than those with IGT, may exhibit a stronger "trained immunity" response. This could explain why improvements in postprandial glucose control in newly diagnosed T2DM patients do not always result in sustained benefits after the trial concludes [13].

Increased levels of postprandial blood glucose are proved to damage endothelial function resulting in cardiovascular disease. There is a need to control the upsurge of postprandial blood glucose levels to prevent this damage. So the present study is aimed to evaluate better effective therapy between nateglinide and voglibose to control postprandial hyperglycemic upsurge.

AIM AND OBJECTIVES

1. To evaluate efficacy of Nateglinide and Voglibose both individually in combination with metformin in type 2 diabetes mellitus patients.
2. To find out safety of nateglinide and voglibose with respect to number of adverse drug reactions.

MATERIALS AND METHODS

This study is conducted prospectively in single-blind cross-over design from November 2015 to April 2016.

Study site and study population: Patients diagnosed with type 2 Diabetes mellitus who came to the outpatient department of General Medicine in Government General Hospital, located in Kakinada, Andhra Pradesh.

Study design

This is a prospective, randomized, single blind; two arms cross-over study.

Inclusion criteria:

1. Patients diagnosed with type 2 Diabetes mellitus on metformin monotherapy but HbA1c levels between 7 – 8 gm.percent.
2. Age group from 30-60 years for both genders.

Exclusion criteria

1. Patients suffering with other co-morbid conditions like hypertension, cardiac failure, hepatic or renal impairment, and other endocrine disorders.
2. Women who are pregnant andlactating mothers.
3. Patients with any chronic illness or infections.

Study Process

Patients suffering from type 2 Diabetes mellitus who turned up at the outpatient department of General medicine were screened for a period of 2 weeks. Baseline investigations were done for 50 patients. Investigations done were fasting blood glucose, postprandial blood glucose, and glycosylated hemoglobin. Glycosylated hemoglobin was analyzed using the ion exchange resin method.

Ethical Consideration

The study protocol (IEC/RMC/2014/045) was approved by the Institutional Ethics Committee of the Rangaraya Medical College (ANNEXURE1). The participants were explained and were given complete information about the study drugs. The study was discussed with them and written informed consent was taken before subjecting them to the study (ANNEXURE 2& 3). 60 patients who fulfilled inclusion criteria were selected and informed consent was taken from them in the local language (Telugu). 12 patients did not give the consent. 8 patients were excluded from the study based on exclusion criteria. 40 patients were assigned to two different intervention groups using random numbers. The patients who completed the study duration of 24 weeks were considered for analysis. Brand names of the drug are metformin generic, NATELIDE 60 mg tablets, and GLYBOSE 0.2mg tablets. Group A received nateglinide (60mg) thrice daily and metformin (500mg) twice daily for 12 weeks followed by voglibose (0.2mg) thrice daily and metformin (500mg) twice daily for the next 12 weeks (NV group). Group B received voglibose (0.2mg) thrice dailyand metformin (500mg)twice daily for 12 weeks followed by nateglinide (60mg) thrice daily and metformin (500mg)twice daily for the next 12 weeks as this is cross over study.

A significant wash-out period was not given at end of 12 weeks in this cross-over study. Nateglinide is a short-acting drug and is eliminated from the body; voglibose remains in the gastrointestinal tract and is not absorbed into the body. Therefore no scope for drug interaction between the two drugs during the cross-over period [14].

The patients received study medication according to their allocation into the groups. Nateglinide and voglibose are to be taken before food. Information regarding follow-up and subsequent blood tests was given to the patients. Patients were investigated for postprandial blood glucose and glycated hemoglobin levels at end of 12 weeks and also at end of 24 weeks. Patients were explained about possible adverse effects and symptoms of hypoglycemia. They are also asked to observe for improvement of symptoms with intake of glucose in case of hypoglycemia. During a follow-up visit at 12 weeks, the blood sample was collected from patients and they were enquired about the occurrence of adverse events. Study medication for the next 12 weeks was given. At the end of 24 weeks, the blood sample was collected for postprandial blood glucose level and glycated hemoglobin.

During follow-up visit at 12 weeks, the blood sample was collected from patients and they were enquired about the occurrence of adverse events. Study medication for the next 12 weeks was given. At end of 24 weeks, the blood sample was collected for postprandial blood glucose level and glycated hemoglobin.

RESULTS

A total of 40 patients were assigned to 2 groups and study medication was given. 20 patients in group A received nateglinide and metformin for 12 weeks and later switched over to voglibose and metformin. By end of 12 weeks, 18 patients came for follow-up, in the remaining two, one patient developed hypoglycemia and discontinued study medication and another patient was lost in follow-up. A Blood sample of patients was taken for postprandial blood glucose and glycated hemoglobin levels and study medication for the next 12 weeks was given. By end of 24 weeks, 2 more patients were lost in follow-up. The blood sample was collected again for postprandial glucose and glycated hemoglobin levels. Results were analyzed for 16 patients. 20 patients in group B received voglibose and metformin for 12 weeks and later switched over to nateglinide and metformin. By end of 12 weeks, 3 patients were lost in follow-up for unknown reasons. Blood sample of patients was taken for postprandial blood glucose and glycated hemoglobin levels and study medication for the next 12 weeks was given. By the end of 24 weeks, 2 patients were lost in follow-up. The blood sample was collected again for postprandial glucose and glycated hemoglobin levels. Results were analyzed for 15 patients. At the end of the study, based on the symptoms explained to them, 5 patients taking nateglinide experienced hypoglycemic attacks. 5 patients taking voglibose complained of abdominal fullness and discomfort. All 31 patients took the medication every day as directed by the physician in both groups.

STATISTICAL ANALYSIS

Group A (N V group) has 16 patients at the time of analysis of results. The distribution of patients on the basis of gender and age is given in table 1.The weight of all patients was noted. The mean weight of male patients is 71.27 and the mean weight of female patients is 60.06. The baseline mean fasting blood glucose value in group A is 151.81and in group B it is 154.33.

EFFICACY PARAMETERS

Glycated hemoglobin and postprandial blood glucose levels were taken as efficacy parameters. The baseline mean postprandial blood glucose for group A is 237.81 ± 14.05, at end of 12 weeks with nateglinide and metformin it was reduced to 193.25 ± 8.64. At end of 24 weeks, with voglibose and metformin, the value was reduced to 171.63 ± 8.09. The baseline mean postprandial blood glucose for group B is 237.67 ± 11.127, at end of 12 weeks with nateglinide and metformin it was reduced to 195.27 ± 8.371. At end of 24 weeks, with voglibose and metformin, the value was reduced to 177.27 ± 8.64. This date is depicted in figure 2 and table number 1.

Baseline mean glycated hemoglobin values for group A is 7.38 ± 0.286, at end of 12 weeks with nateglinide and metformin it was reduced to 6.794 ± 0.169. At end of 24 weeks, with voglibose and metformin, the value was reduced to 6.52 ± 0.19. The baseline mean glycated hemoglobin values for group B is 7.35 ± 0.253, at end of 12 weeks with nateglinide and metformin it was reduced to 6.807 ± 0.128. At end of 24 weeks, with voglibose and metformin, the value was reduced to 6.52 ± 0.12. This data is depicted in figure 3 and table 2.

The mean difference values of postprandial blood glucose levels from baseline in group A at 12 weeks is 44.563 ± 9.423 with p value<0.001. This significant difference is seen with the nateglinide and metformin combination. The mean difference values of postprandial blood glucose levels from baseline in group B at 12 weeks is 39 ± 9.03 with p value< 0.001. This significant difference is seen with voglibose and metformin combination.

The mean difference values of glycated hemoglobin from baseline in group A at 12 weeks is 0.581 ± 0.164 with p value<0.001. This significant difference is seen with the nateglinide and metformin combination. The mean difference values of glycated hemoglobin levels from baseline in group B at 12 weeks is 0.54 ± 0.168 with p value< 0.001. This significant difference is seen with voglibose and metformin combination.

Table 1 – Mean ± SD Values of Postprandial Blood Glucose

	GROUPA (16)	GROUPB (15)	P VALUE
BASELINE	237.81±14.05	234.67±11.127	0.49
3 MONTHS	193.25±8.64	195.27±8.37	0.514

6 MONTHS	6.52 ±0.19	6.52 ±0.12	0.465

Table 2 – Mean ± SD Values of Glycated Haemoglobin

	GROUPA (16)	GROUPB (15)	P VALUE
BASELINE	7.38 ±0.286	7.35 ±0.253	0.326
3 MONTHS	6.794±0.169	6.807±0.128	0.81
6 MONTHS	6.52 ±0.19	6.52 ±0.12	0.465

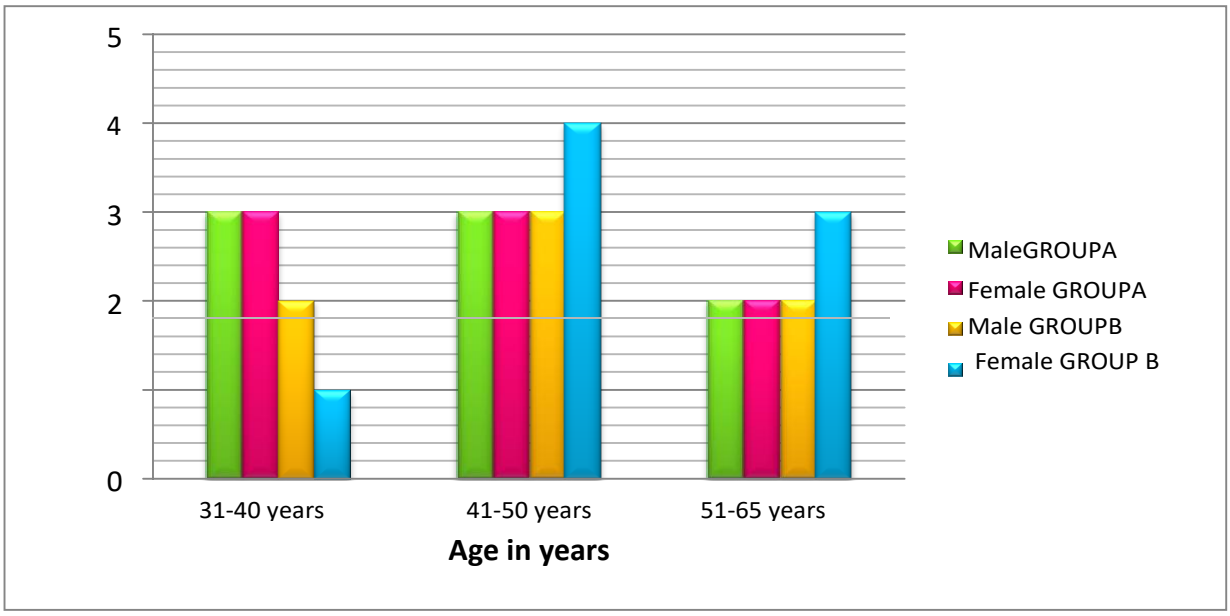

FIGURE 1. Gender and age distribution of study subjects

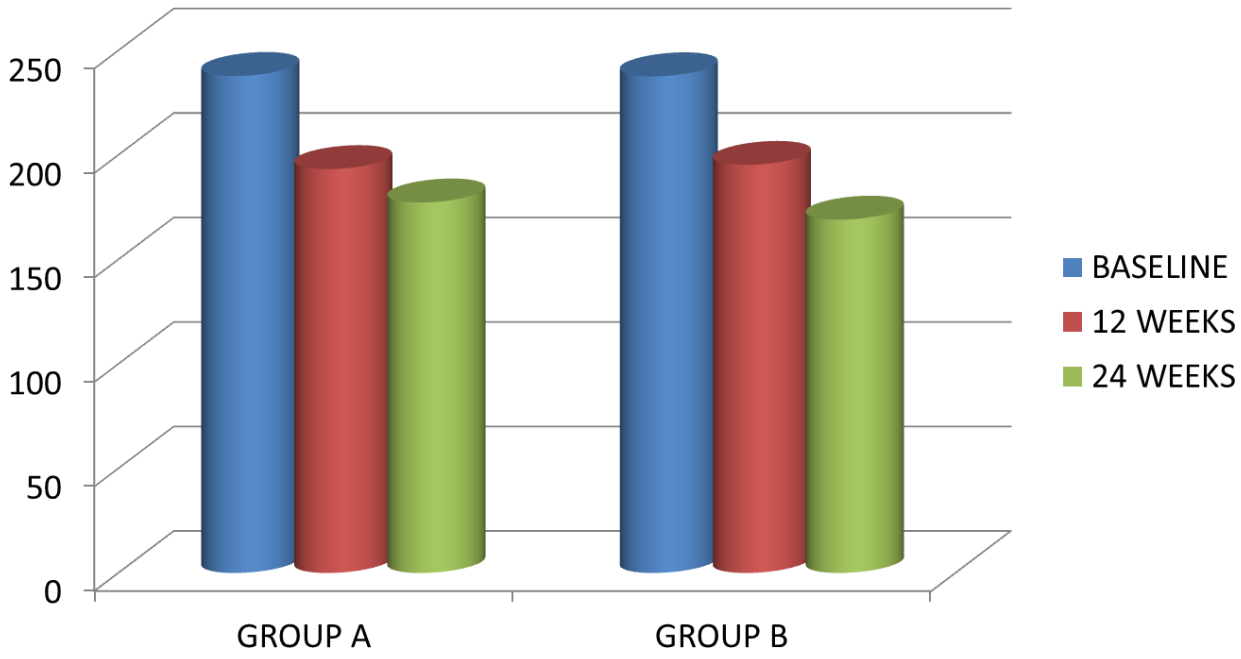

Figure 2: Comparison of PPBS Values

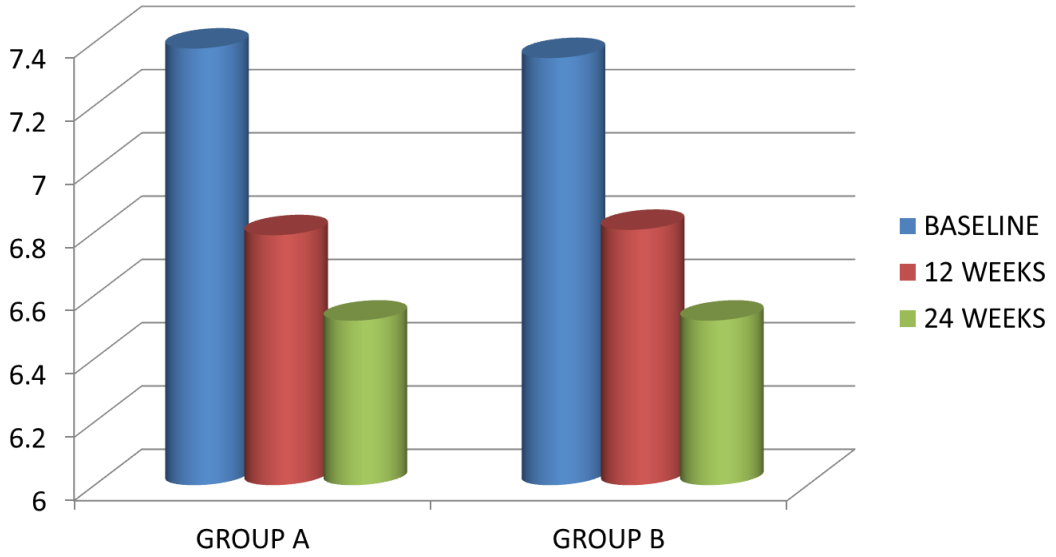

Figure 3: Comparison of Glycated Haemoglobin Values

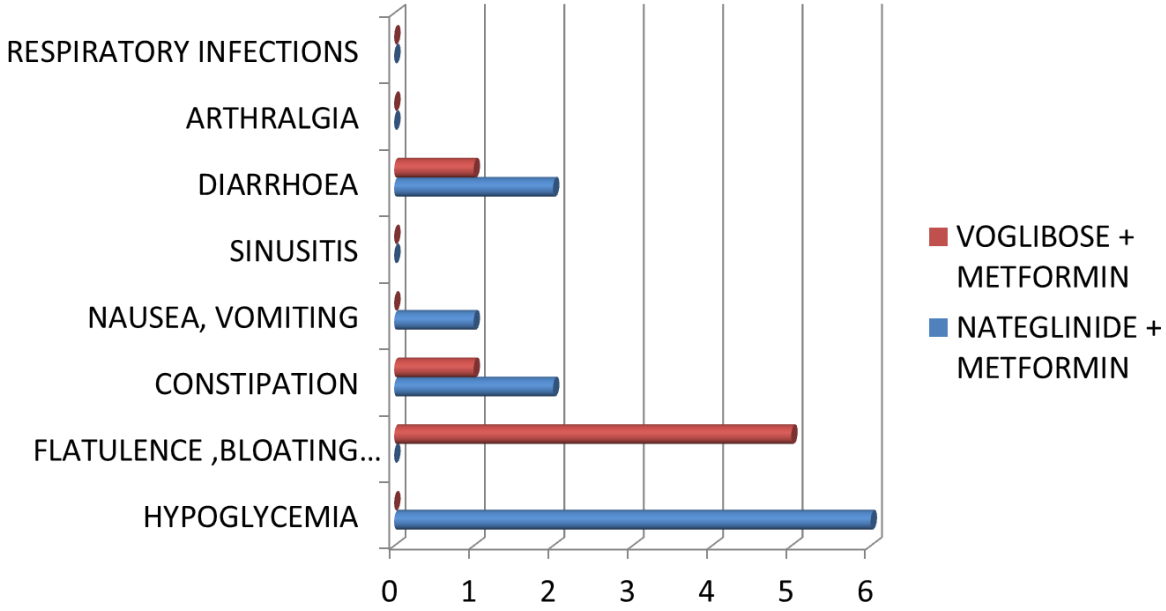

Figure 4: Frequency of Adverse Drug Reactions (ADRs)

SAFETY PARAMETERS

The adverse effects which are expected - are hypoglycemia, headache, sinusitis, upper respiratory tract infection, gastrointestinal discomfort, diarrhea, nausea, vomiting, constipation, bloating sensation, flatulence, headache, dizziness, arthralgia, sinusitis and upper respiratory tract infection for the study medication. Safety parameters (number of adverse events that occurred) were observed for 32 patients including one patient who withdrew from the study before follow-up. The data regarding occurrence of adverse effects is depicted in figure 4.

DISCUSSION

This studyis conducted to explore the efficacy of nateglinide and voglibose in type 2 diabetes mellitus patients. Some studies have shown an increased risk of cardiovascular disease in diabetic patients which was attributed to increased postprandial levels. Previous studies have shown that the study drugs in the present study reduce post-prandial blood glucose levels.Efficacy parameters taken in the present study are postprandial blood glucose and glycated hemoglobin levels.

DIANA (DIAbetes and diffuse coronary NArrowing) studywhich was done at various institutes in Japan demonstrated that postprandial blood glucose can lead to the development of coronary atherosclerosis. In the study, 302 patients were randomly allocated into 3 groups – lifestyle intervention, voglibose therapy, and nateglinide therapy. They demonstrated significantly less postprandial glucose levels by the voglibose treated people at follow-up. They concluded that an

improvement in glycemic status is significantly associated with less atherosclerotic change. This study provides link between glycemic changes and coronary atherosclerosis, especially in early-stage DM [15].

In a study done by KEILSON et al, nateglinide showed a rise in plasma insulin concentrations and fall in mealtime plasma glucose excursions when administered before food to people with type 2 diabetes mellitus [16].

Kulkarnietal stated that voglibose is the preferred drug in the management of postprandial hyperglycemia in the treatment of type-2 diabetes mellitus. Voglibose is a product of Takeda Pharma, a Japan company and is recommended in doses of 0.2mg and 0.3mg. Voglibose acts by reducing the release of small sugars by inhibiting the hydrolysis of a-1, 4-glycosidic bonds in complex carbohydrates [17].

In a study conducted by RIYAZ et al, 2-hour postprandial glucose levels were low in the voglibose group than in the placebo group. They concluded that voglibose significantly improved glucose tolerance and delayed disease progression [18].

Shogo kurebayashi et al [14] conducted a study in Japan comparing nateglinide and voglibose in the cross-over design. Glycated hemoglobin was taken as efficacy parameter. The dose of nateglinide taken was 270 mg per day and that of voglibose is 0.2 mg thrice a day before meals. The results of our study were almost similar and comparable to those of the previous study. They concluded that nateglinide is good at efficacy and is safe drug for the treatment of early T2DM patients like voglibose. Hypoglycemic attacks occurred more commonly in patients taking nateglinide whereas abdominal discomfort and gastrointestinal side effects were common in patients taking voglibose. One patient taking nateglinide and 5 patients taking voglibose combination reported hypoglycemia in their study. But in this study, 6 patients taking nateglinide metformin combination reported hypoglycemic episodes and no such events occurred with voglibose metformin combination. 21 patients on voglibose combination complained of abdominal discomfort and borborygmi of varying degrees in their study whereas, in this study, only 5 patients complained of such discomfort.

Raskin et al [19] conducted an open-label, randomized, multicenter trial to compare the efficacy and safety of repaglinide and nateglinide when used in a combination with metformin for treatment of Type 2Diabetes mellitus. Efficacy parameters taken were glycated hemoglobin and fasting blood glucose levels. 60 Minor hypoglycemic episodes occurred in 7% of the patients in the repaglinide/ metformin group compared with 2% of the patients in the nateglinide/ metformin group. The most frequent adverse event in both groups was upper respiratory tract infection. The repaglinide/ metformin group had 5% incidence of arthralgia and 5% incidence of chest pain, as compared with 1% for each in the nateglinide/metformin group. They concluded that combination therapy of repaglinide and metformin was safe and effective therapy in the treatment of type 2 diabetes mellitus patients.

Obesity is a key contributor to the development of type 2 diabetes mellitus (T2DM). It induces insulin resistance in peripheral tissues and inflammation in metabolically active adipose tissue, making it a significant genetic and environmental risk factor. The study medication reduces intestinal glucose absorption, LDL, and VLDL cholesterol. Decreases in triglycerides and free fatty acids suggest a cardio protective effect and potential improvement in insulin sensitivity. Metformin, included in both study groups, lowers hepatic glucose production by suppressing gluconeogenesis. This occurs through activation of AMP-activated protein kinase and inhibition of mitochondrial respiratory chain complex I, leading to increased NADH oxidation and reduced ATP synthesis. Therefore, metformin was selected as the common drug for both treatment groups [20, 21].

Repaglinide and nateglinide are the most commonly used brand-name meglitinides. Repaglinide was the first meglitinide approved for T2DM. These drugs are short-acting insulin secretagogues that, like sulfonylureas, bind to the sulfonylurea receptor on pancreatic cells, though with lower affinity. They stimulate insulin release by blocking KATP channels. Genetic variations, such as in the SLCO1B1 gene (which influences repaglinide uptake in the liver), can affect how well meglitinides work [22].

Three alpha-glucosidase inhibitors - acarbose, miglitol, and voglibose-are currently used in diabetes management. These agents have been shown to lower postprandial blood glucose levels and improve cholesterol profiles, blood pressure, and other cardiovascular risk factors [23]. These drugs function by inhibiting the brush border enzymes sucrase-isomaltase and maltase-glucoamylase, which are essential for carbohydrate digestion. Voglibose is a commonly prescribed AGI for T2DM. Compared to other diabetes medications like sulfonylureas and biguanides, they generally carry a lower risk of serious adverse effects [24].

This study has several strengths. Random patient allocation into two groups eliminates selection bias. The single-blind design, where patients are unaware of their treatment assignment, further minimizes bias. All patients received combination therapy, as metformin was added to the test drugs. Finally, while similar research exists internationally (e.g., in Japan), there is a relative scarcity of such studies conducted specifically within India.

This study has several limitations. The relatively small sample size may limit the ability to detect rare adverse drug reactions. The efficacy assessment relied solely on glycated hemoglobin and postprandial blood glucose levels, which may not provide a comprehensive picture of treatment effects. Furthermore, with only one follow-up visit during the 24-week study period, it was difficult to adequately monitor patient compliance.

CONCLUSION

Based on the data collected and statistical tests done, it is concluded that both nateglinide and voglibose are equally effective in reducing glycated hemoglobin and postprandial glucose levels. Voglibose is considered a safer drug when compared to nateglinide as more hypoglycemic attacks in the study population were because of nateglinide. Based on the data collected and statistical tests done, both nateglinide and voglibose are equally effective in reducing postprandial blood glucose and glycated hemoglobin levels. Therefore the importance of these drugs comes into focus in the perspective of preventing cardiovascular complications which are directly linked to upsurge postprandial blood glucose levels.

AUTHOR CONTRIBUTION STATEMENT

Dr. Mubishera Begum's support was crucial to the success of the study. She assisted with statistical analysis of the cross-over results, participant allocation, and data collection. Under the mentorship of Dr. Siva Prasad, I received comprehensive support throughout the study. He was always available to answer our questions, bridge any knowledge gaps, and provide guidance. His expert input was also crucial to the article's development, where he offered constructive criticism and refined our writing.I developed the study protocol and conducted the research, with the invaluable support and guidance of my colleague and my advisor.

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