Original Research Article

An open randomized study to compare effect of metformin versus acarbose monotherapy on glycemic control and lipid profile in newly diagnosed type 2 diabetes mellitus patients

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ABSTRACT

Background: Type 2 DM is one global health problem and a main cause of morbidity and mortality. It is epidemic in many industrialized and developing areas and is considered to be one of the most challenging health problems of the 21st century. Metformin and acarbose both are used as monotherapy and in combination with other anti-diabetes drugs for treatment of type 2 DM. There are very sparse evidences regarding comparative efficacy and safety of metformin versus acarbose, especially in Asian region. In addition to glycemic control, improvement in lipid profile, weight loss and post-prandial sugar level are important therapeutic objectives for better management of type 2 DM patients.
Methods: In this study, 60 newly diagnosed type 2 DM were randomly assigned (1:1) to oral acarbose (titrated doses upto 300 mg daily) or oral metformin (titrated doses up to 2500 mg daily) monotherapy and were followed-up for 12 weeks for effects on glycaemic control [serum HbA1C, fasting blood sugar and post prandial sugar and serum LDL, HDL, triglycerides and total cholesterol.
Results: Reduction in FBS, HbA1C and body weight was found significantly greater with metformin while acarbose yielded greater improvement in PPS, total cholesterol and triglyceride levels. Both metformin and acarbose yielded significant improvement in FBS, PPS, HbA1C, lipid profile and body weight after 12 weeks of therapy and yielded similar improvement in LDL and HDL levels.
Conclusions: Acarbose can be considered as an alternative initial therapy in newly diagnosed type 2 diabetes patients, particularly those with isolated post-prandial hyperglycemia and those who are intolerant to metformin therapy.

Keywords: Metformin, Acarbose, Type 2 diabetes, Post-prandial hyperglycemia, Lipid profile

INTRODUCTION

Diabetes mellitus (DM) is a metabolic disorder characterized by hyperglycemia resulting from defects in insulin secretion, insulin action or both. Type 2 diabetes mellitus (T2DM) is a major global health problem and an increasing cause of morbidity and mortality globally. It is considered to be one of the most challenging health problems of the 21st century. According to International Diabetes Federation, globally the prevalence of diabetes is around 415 million people in 2015 and this number is

expected to rise to 642 million by 2040. In India more than 69 million people diagnosed with the disease.[1]

T2DM is a complex progressive disorder, associated with various macrovascular and microvascular complications. Diabetic nephropathy, neuropathy, and retinopathy are main microvascular complications while cardiovascular disease (CVD), peripheral vascular disease (PVD), and cerebrovascular disease are the major macrovascular complications. The risk for developing coronary heart disease or other adverse cardiovascular (CV) events is

increases by almost three-times in patients with impaired glucose tolerance (IGT) compared to people with normal glucose tolerance.[2]

Postprandial hyperglycemia is a hallmark in most individuals with impaired glucose tolerance and early type 2 diabetes and has been established as a key pathophysiological component for mechanism underlying the development of both microvascular and macrovascular complications.[3] Therefore it is important to treat the most inappropriately elevated and longest lasting component of aberrant diurnal glucose that is post-prandial hyperglycemia.

Acarbose mainly targets post-prandial hyperglycemia and also significantly reduces fasting blood glucose (FBG) and HbA1C. These effects are more in eastern as compared with western populations.[4,5] as eastern diet contains higher proportion of starch than western diet.

Acarbose is a pseudo-carbohydrate that competitively and reversibly inhibits alpha-glucosidases i.e. membrane-bound intestinal enzymes located in the brush-border of the small intestine mucosa that process oligosaccharides, trisaccharides, and disaccharides to glucose and other monosaccharides. Inhibition of this glucoside hydrolase activity by acarbose delays hydrolysis and digestion of complex carbohydrates, subsequently retards absorption of glucose and 'blunts' postprandial hyperglycaemia. In addition, acarbose exerts the same degree of irreversible blockade on pancreatic alpha-amylase, which hydrolyses complex starches to oligosaccharides in the lumen of the small intestine. Intact acarbose is poorly absorbed and is excreted in feces, mostly intact but with up to 30% undergoing metabolism predominantly via fermentation by colonic microbiota.[6] Accumulating evidence has revealed that intensive glycemic control significantly decreases rate of microvascular and macrovascular complications in patients with T2DM.[7] Therefore controlling blood glucose continues to be a major therapeutic strategy.

Metformin is the first-line oral antidiabetic drug for type 2 diabetes with proven efficacy and safety that is recommended by international guidelines.[8] Robust evidence for metformin has been generated mostly from white populations with results being extrapolated to other populations, only few studies have assessed metformin in other populations, especially in Asian patients with exaggerated postprandial glucose excursion.[9,10]

In this study we compare effect of metformin versus acarbose monotherapy on glycemic control and lipid profile in newly diagnosed type 2 diabetes mellitus patients.

METHODS

The study was conducted in the department of pharmacology, in collaboration with the department of endocrinology of Vardhman Mahavir Medical College and Safdarjung Hospital, New Delhi after obtaining clearance from the institutional ethical committee VMMC. Informed consent was obtained from all the patients included in the study. The current study was an open label, randomized, prospective, interventional study. The study was done from May 2019 to November 2020.

Total 60 patients were enrolled in the study. Randomisation codes were generated with a computer programme (SAS version 9.10) for eligible patients. Patients were randomly assigned (1:1) in to two groups viz. group I (metformin) and group II (acarbose), with 30 patients in each group. Neither patients nor investigators involved in the study were masked to treatment allocation. On the basis of previous literature.[11,12]

Inclusion criteria

Newly diagnosed with type 2 diabetes (both drug naive and those received less than 1 month treatment) older than 18 years with suboptimum glucose control (HbA1c ≥47.5 mmol/mol (6.5%) and/or fasting blood sugar (FBS)≥126 mg/dl and/or post prandial sugar (PPS) ≥200 mg/dl).

Exclusion criteria

The following patients were excluded from the study: history of renal disease (plasma creatinine concentration of 1·5 mg/dl or more), cardiac disease (unstable angina or myocardial infarction within the previous 6 months or New York Heart Association class III or IV congestive heart failure), hepatic disease (aspartate aminotransferase or alanine aminotransferase concentration at least twice as high as the upper limit of the normal range), chronic hypoxic diseases (emphysema or corpulmonale); **m**alabsorptive gastrointestinal diseases, past history of intestinal surgery**; a**cute illness, requirement for insulin therapy, diabetic ketoacidosis or hyperosmolar non-ketotic coma; women preparing for conception, or who are pregnant or breastfeeding; participation in any drug clinical trials during the past 3 months before enrolment; mental disorders; and drug or other substance misuse, history of allergic reaction or intolerance to study drugs.

Drug treatment

Patients were assigned to receive metformin hydrochloride up to 2500 mg, daily or up to 300 mg of acarbose, daily.

Acarbose was started from 50 mg once a day at dinner time during the first week and titrated upwards to 50 mg twice a day at lunch and dinner in the second week, 50 mg three times a day with three meals in the third week, and 100 mg three times a day from the fourth week onwards. Metformin was started at 500 mg once a day after dinner for the first 2 weeks and titrated up to 1000 mg per day in the third week and up to 2500 mg per day from the fourth week onwards.

All the data (history, clinical examination and lab investigations) were recorded in one standard case record form.

Data collection

After thorough history, physical and clinical examination, data was collected at baseline and after 12 weeks for the following parameters: HbA1C, FBS, PPS, serum creatinine, lipid profile (HDL, LDL, triglycerides, total cholesterol), LFT (SGOT, SGPT), BMI–calculated [BMI=weight (in kg)/ (height in meters^2)], weight and height. The primary end points were change in HbA1C, FBS, and PPS from base line after drug treatment. The secondary end points were change in lipid profile and body weight from base line.

Statistical analysis

The analysis was carried out in Microsoft Excel and SPSS software version 17. A p value of ≤0.05 was taken as level of statistical significance. The results were expressed as mean±standard deviation. Changes in parameters from baseline within the group were evaluated using paired t-test. Comparison between the groups at 12 weeks were evaluated using independent t-test.

RESULTS

In the present study, 60 patients of newly diagnosed type 2 diabetes were recruited and randomly divided in to two groups – group I and group II, with 30 subjects in each group. Group I received metformin up to 2500 mg per day and group II received acarbose up to 300 mg per day.

Both the groups were followed for 12 weeks. Blood samples were collected at base line and again at 12 weeks.

The results of the study are tabulated in Table 1.

Primary end points after 12 weeks of therapy.

Glycosylated hemoglobin (HbA1C)

At baseline, mean HbA1c in the metformin group was 65.1 mmol/mol (8.1%) while in the acarbose group it was 70.1 mmol/mol (8.6%). T-test analysis suggested that there was no significant difference in mean HbA1C at baseline between the two groups (P value was >0.05).

After 12 weeks of therapy mean HbA1c was found to be significantly decreased in both the groups. However percentage reduction was found to be greater in the metformin group compared to the acarbose group.

Fasting blood sugar

At base line, mean FBS in the metformin group was 154.6 mg/dl while in the acarbose group it was 158.2 mg/dl. T-test analysis suggested that there was no significant

difference in mean FBS of the subjects between these two groups (P value was >0.05)

After 12 weeks of therapy FBS was found to be significantly decreased in both the groups. (P value <0.05). However percentage reduction was found to be greater in the metformin group compared to the acarbose group (30.3% versus 26.9%) and this difference was found as statistically significant.

Post prandial sugar

At base line, mean PPS in the metformin group was 252 mg/dl while in the acarbose group it was 261 mg/dl. T-test analysis suggested that there was no significant difference in mean PPS of the subjects between these two groups (P value was >0.05)

Both metformin and acarbose caused significant reduction in PPS from baseline. However, significantly greater percentage reduction in PPS was seen with acarbose (42.5%) than with metformin (37.3%) (p value<0.05).

Secondary end points after 12 weeks of therapy

Lipid profile

At baseline lipid profile parameter in the metformin group was as follows Total cholesterol (TC)-167.6 mg/dl, triglyceride (TG)-136.6 mg/dl, LDL-74.6 mg/dl and HDL-46.8 mg/dl. While in the acarbose group- total cholesterol-153.9 mg/dl, triglyceride-121.8 mg/dl, LDL-75 mg/dl and HDL-47.27 mg/dl t-test analysis suggested that there was no significant difference in lipid profile parameter at baseline (p value>0.05)

After 12 weeks of therapy both metformin and acarbose caused significant improvement in all lipid profile parameters from baseline but acarbose yielded significantly greater reduction in TC (23.9% versus 15%) and TG (27.4% versus 20.3%) when compared to metformin group while improvement in HDL and LDL was found to be similar in both the groups.

Body weight after 12 weeks of therapy

At baseline weight in the metformin group was 64.84 kg while in the acarbose group it was 67.3 kg. After 12 weeks of therapy mean weight in the metformin group was 60.3 kg while in the acarbose group it was 64.7 kg. Both metformin and acarbose were found to cause significant reduction in mean body weight after 12 weeks of therapy. However decrease in body weight was more with metformin than with acarbose (7% versus 3.8%) which was found to be significant (p value <0.05).

Renal parameters

Base line mean urea in the metformin group was 20.7 mg/dl while in the acarbose group it was 19.1 mg/dl. Mean

serum creatinine in the metformin group was 0.8 mg/dl while in the acarbose group it was 0.9 mg/dl. After 12 weeks of therapy no significant change was found in renal parameters in both the groups. (P value>0.05).

Chi square test analysis suggested that acarbose group of subjects had significantly higher incidence of side effect than metformin group of subjects.

Table 1: Demographic comparison of groups.

Characteristics	Metformin group (N =30)	Acarbose group (N=30)	P value
Age (years)	49.7±7.9	47±6.9	0.16
Weight (kg)	64.8±10.7	67.3±8.7	0.33
Height (meter)	1.6±0.1	1.6±0.1	0.12
BMI (kg/m^2)	25.9±3.6	25.2±3.4	0.44
Sex (men/women)	13/17	18/12	0.196
	43.3%/56.7%	60%/40%	

Primary end points after 12 weeks of therapy

Table 2: Comparison of renal parameters.

Parameter		Metformin group	Acarbose group	P value (between groups)
Urea (mg/dl)	baseline	20.7±5.2	19.1±4.9	0.23
	At 12 weeks	17.1±4.2	16.4±4.6	0.54
	P value	0.06	0.08	
Creatinine (mg/dl)	baseline	0.8±0.2	0.9±0.2	0.37
	At 12 weeks	0.8±0.1	0.7±0.2	0.80
	P value	0.07	0.1	

Table 3: Comparison of side effects.

Side effect	Metformin group (number of patients out of total 30)	Acarbose group (number of patients out of total 30)	Chi square value	P value
Dyspepsia	1	5		
Flatulence	1	3	4.320	0.037
Total	2	8		

DISCUSSION

The management of diabetes includes diet control, exercise and pharmacological therapy. As per American diabetic association (ADA) guidelines metformin is first line OAD for type 2 diabetes with proven efficacy and safety data.[13,14]

However, majority of data available on metformin has been generated from white population with results being extrapolated to other population. The socioeconomic status and diet composition of Asian population is significantly different from western population. Asian population consume more carbohydrate than western ones which probably results in to exaggerated postprandial glucose excursion which is key pathophysiologic component for the development of both microvascular and macrovascular complications of diabetes specifically cardiovascular complications. Alpha glucosidase inhibitor such as acarbose mainly targets post-prandial hyperglycemia. However, there is paucity of data on acarbose as initial therapy in newly diagnosed type 2 diabetes.

In the present study, we aimed to ascertain the effectiveness of the α-glucosidase inhibitor acarbose, compared with metformin as the initial therapy in newly diagnosed type 2 diabetes.

Although both metformin and acarbose significantly reduced HbA1C, FBS and PPS. However significantly greater reduction in HbA1C and FBS was seen with metformin than with acarbose. Some previous studies.[11,15] have also reported greater decrease in HbA1C and FBS with metformin than with acarbose. This could be because of the fact that metformin, in comparison to acarbose has additional mechanism of action, other than reduction in intestinal glucose absorption including improved peripheral glucose utilization, reduced hepatic glucose production, increasing insulin sensitivity of peripheral tissues, at molecular level action on cyclic AMP.[16]

This may partly explain greater reduction in HbA1C and FBS. On the other hand acarbose caused significantly greater decrease in PPS compared to metformin. This may be explained by mechanism of action of acarbose which inhibit intestinal enzyme α-glucosidase inhibitor and

prevent breakdown of complex carbohydrates in to simple absorbable form. This ultimately leads to reduced absorption of carbohydrates.

Similar results were seen in a German trial by Hoffmann et al where 96 patients were randomized into three groups- metformin, acarbose and placebo group, after 24 weeks they concluded that both metformin and acarbose yielded significant reduction in FBS, PPS and HbA1C compared with placebo.[11] Another study by Gu and colleagues, they compared the glucose-lowering effects of metformin andacarbose and they concluded that metformin was more effective in reducing FPG and HbA1C while acarbose caused grater reduction in PPG.[16]

In another study by Pan et al, they studied the effect of metformin and acarbose in newly diagnosed type 2 diabetes, they concluded that acarbose treatment exhibited greater effectiveness in decreasing PPG, TG whereas metformin treatment resulted in greater decreases in FPG.[17]

Both the drugs showed significant improvement in all lipid profile parameters –TC, TG, LDL and HDL. No significant difference was seen between the two groups with respect to LDL and HDL. However, acarbose caused significantly greater decrease in TC and TG levels compared to metformin group. This may be explained by the mechanism of acarbose, which mainly targets PPS, as decrease PPS prevent lipolysis causing reduced TC and TG. Similar results were seen in previous studies.[16,17]

Thus, from the results of present study it can be said that acarbose can be considered as alternative initial therapy in patients intolerant to metformin and those with isolated postprandial hyperglycemia.

In majority of these studies patients were followed for 24 to 48 weeks while in our study patients were followed for only 12 weeks. Majority of these studies enrolled more number of patients than our study.

CONCLUSION

Acarbose can be considered as an alternative initial therapy in newly diagnosed type 2 diabetes patients, particularly those with isolated post-prandial hyperglycemia and those who are intolerant to metformin therapy.

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