

Effect of Acarbose on Glycemic Control, Serum Lipids and Lipoproteins in Type 2 Diabetes

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Abstract

Objective: To assess the efficacy of acarbose monotherapy during 12-weeks treatment on the fasting glycemic level, lipid and lipoproteins profiles, in patients with type 2 diabetes mellitus.

Setting: Type 2 diabetics were selected from out patient department of Baqai Diabetes and Endocrine Centre, and one other diabetic clinic of Karachi, during 1996-97.

Design: A prospective intervention trial, and a 10 days screening period with a follow-up of 12 weeks.

Methods: Forty-four patients (36 men and 8 women, mean age 55.09 ± 1.72 years) were included of whom 25 (56.81%) patients were previously treated with diet alone, 11(25%) with diet and glibenclamide, 5(11.36%) with diet and gliclazide, and 3(6.81%) with diet and chlorpropamide, more than at least 3 months known duration of diagnosed type 2 diabetes, body mass index (BMI) 23.69 ± 0.49 kg/m², were insufficiently controlled on diet alone, or diet plus sulfonylureas, were studied. The dosage of acarbose was started with 50 mg t.i.d with each meal, if necessary, was titrated upward on subsequent visits to 100 mg t.i.d with each meal, based on tolerability and efficacy. Fasting blood glucose, lipid and lipoprotein profiles were determined at the baseline and at the end of the study.

Results: Acarbose treatment was associated with significant reduction in fasting blood glucose from (mean $\pm$ SE) 173.89 ± 3.89 mg/dl at day 0 to 161.29 ± 3.41 mg/dl at day 90 ($P < 0.01$). The serum total triglyceride level was (mean $\pm$ SE) 188.85 ± 5.91 mg/dl at entry, and was also significantly decreased to 158.57 ± 4.48 mg/dl at day 90, this reduction was found statistically significant ($P < 0.01$). Whereas very-low density lipoprotein cholesterol reduced significantly from 33.08 ± 1.09 mg/dl at day 0 to 31.02 ± 0.95 mg/dl at day 90 ($P < 0.01$). Acarbose had no significant effect on serum total cholesterol, low-density lipoprotein cholesterol, and High-density Lipoprotein cholesterol concentrations. Almost, all adverse experiences, as reported by patients on acarbose, were related to the digestive system and included diarrhea, flatulence, bloating and nausea. Most symptoms were of mild to moderate intensity and tended to improve with time. Overall, acarbose was well tolerated and the adverse experience profile was clinically acceptable.

Conclusion: In type 2 diabetic patients, acarbose as monotherapy for 12 weeks resulted in beneficial effects on glycemic control, fasting blood glucose, mean serum total triglyceride and very-low density lipoprotein cholesterol decreased significantly. Perhaps attainment of normoglycemia on a long-term basis would result in more normal lipid and lipoprotein levels. Furthermore use of acarbose can be considered as a useful alternative in such type 2 patients, if they are difficult to control with diet alone or diet plus sulfonylureas UPMA 50:1 52, 2000).

Introduction

One of the main goals of treating patients with type 2 diabetes mellitus is to produce near-normal glucose levels to prevent the development of diabetic complications¹. Patients with type 2 diabetes have abnormalities in the metabolism of both glucose and lipids that probably contribute to diabetic complications². Near normalization of blood glucose has not been demonstrated to reduce the risk of atherosclerotic vascular disease, however, in diabetic patients with lipoprotein abnormalities, improved glycemic control is frequently associated with a less atherogenic lipid profile³. The treatment of type 2

diabetes includes an appropriate diet and prudent exercise program. If these measures are insufficient to control the blood sugar, oral agents (sulfonylureas or biguanides) or insulin are added to the therapeutic regimen. Although the diet prescription has been the traditional treatment for type 2 diabetes for nearly 40 years. Recently a new class of oral agents, the alpha-glucosidase inhibitors, has become available⁴. Acarbose is a novel oral anti-hyperglycemic agent approved for the treatment of non-insulin dependent diabetes mellitus. It inhibits alpha-glucosidases in the small intestine, an action that delays the digestion and absorption of complex carbohydrates⁵. Acarbose reduces postprandial plasma glucose and may improve metabolic control in non-insulin dependent diabetes mellitus when combined with diet⁶. Other effects include a reduction in postprandial insulin and variable changes in plasma lipid concentrations⁷. This is important since improvement in glycaemic control has been associated with reduction in the lipoprotein abnormalities that are believed to accelerate atherogenesis in the diabetic population. Studies that have examined the effect of acarbose on lipid profile in type 2 diabetes have yielded conflicting results, and little information is available about the action of acarbose on fasting blood glucose and lipids. This study was designed to evaluate the therapeutic potential of acarbose, an alpha-glucosidase inhibitor as monotherapy in patients with type 2 diabetes on glycaemic control, lipid and lipoproteins, who were insufficiently controlled on either diet alone, or diet plus sulfonylurea.

Patients and Methods

This study was carried out in the Department of Pharmacology and Therapeutics, Basic Medical Sciences Institute, Jinnah Postgraduate Medical Centre, Karachi. Forty-four patients with type 2 diabetes, 36 males and 8 females, whose ages ranged from 35- 76 years were studied. The patients were selected from the outpatient department of Baqai Diabetes and Endocrine Centre, and one other Diabetic Clinic of Karachi. Entry criteria was: Type 2 diabetic patients in concomitant dietary follow-up, age > 35 years and with stable body mass index (BMI < 30 kg/m²), more than at least 3 months known duration of diagnosed type 2 diabetes. The diagnosis of diabetes was made according to World Health Organization's criteria⁸. Patients to whom no previous antidiabetic medication had been given, or previous treatment consisted of diet alone and or oral hypoglycemic agents (Sulfonylureas) were also included. The exclusion criteria were history of significant ketosis, intake of medications known to affect lipid metabolism or carbohydrate metabolism or those who were taking medications that might affect blood pressure or likely to alter gut motility or absorption. Previous treatment with glucocorticoids, or non-selective β -blocking agents or a significant gastrointestinal, cardiovascular or renal disease by history, physical examination, or laboratory evidences were excluding factors. Patients with severe diabetic complications, or concurrent medical illness requiring immediate treatment were also excluded. All hypoglycemic medications were discontinued at least 10 days prior to admission to the study. During that period patients were treated with individualized weight maintaining diets (carbohydrate, 60%; fat, <30%; protein, 12-20%) with caloric content adjusted to the patient's age, body weight, and physical activity as recommended by the dietitians. All the patients then received tablets acarbose (taken orally) along with diet control for 12 weeks. The initial dosage of acarbose was 50 mg with each meal, three times daily, and if necessary, was titrated upward on subsequent visits to 100 mg three times daily with each meal and was adjusted according to the patients' tolerance to the drug and the glycaemic status.

The study period consisted of 12 weeks (90 days) with weekly follow-up visits. On each visit, fasting blood glucose (FBG) levels were recorded. Tolerability was determined on the basis of patient's reports of treatment emergent adverse events and by review of laboratory test results. When adverse events and side effects occurred, they were documented. Hypoglycemic reactions were also noted. Drug compliance was ascertained by counting the tablets returned. Body weights were recorded and caloric intake was assessed by the dietitians. Subjects were forbidden to take any other medication during the study.

Before each visit, all study participants were instructed to fast for 12-14 hours for the estimation of blood glucose. Lipid profile was measured at weeks 0 and 12. Fasting blood glucose was determined by using Accutrend Blood Glucose Analyzer (Boehringer Mannheim, Mannheim, Germany). Serum total cholesterol, high-density lipoprotein cholesterol and Serum total triglycerides were measured by enzymatic colorimetric methods by using commercial kits (Spinreact, S.A. Spain). Low-density lipoprotein cholesterol was calculated using Friedewald's equation⁹. LDL-cholesterol (mg/dl)=Total cholesterol-(Triglycerides/5)-HDL cholesterol. Very-low density lipoprotein cholesterol was calculated, according to formula proposed by Wilson. cited by DeLong et al¹⁰: VLDLcholesterol (mg/dl) = 0.20 x Triglycerides.

Statistical Analysis

All calculations were performed using the Minitab program release 11.12. The results are expressed as mean±SE. Comparison between baseline and at the end of acarbose treatment values of the same group was made using paired student's t test to obtain P values. Differences were considered statistically significant if P<0.05.

Results

Fifty patients with type 2 diabetes were initially selected in this study. out of which 44 (36 males, 8 females) continued for the entire whole period. Of the 6 who dropped out, four did not tolerate acarbose, one showed poor compliance and one refused to follow up further. The data of 44 patients (36 men and 8 women, mean± SE age 55.09 ± 1.72 years. duration of diabetes mean± SE 2.1±0.2 years) were included for statistical analysis. Out of 44 study subjects 25 (56.8%) were previously treated with diet alone and of the remaining 19 (43.2%), 11 had been on diet and glibenclamide, 5 on diet and gliclazide, and 3 on diet and chlorpropamide. Of the 19 subjects on sulfonylureas, 11(25%) patients were on glibenclamide mg/day and 3 on 20 mg/day]. Of the 5(11.36%) patients on gliclazide mg/day]. Only 3(6.81%) patients were taking chlorpropamide. all in the maximal dose of the drug, 500 mg/day.

Table 1. Baseline demographic characteristics of type 2 diabetic patients (n=44).

Variables	at day 0	at day 90
Age (years)	55.09±1.72	-
Sex (M/F)	36/8	-
Duration of diabetes (years)	2.1±0.2	-
Body Weight (kg)	68.05±0.85	67.69±0.85*
Body mass index (kg/m ²)	23.69±0.49	24.17±0.62*

Results are expressed in mean±SEM, * = Non significant.

Figure in parentheses shows the number of patients.

Table-1 shows the baseline demographic characteristics of the patients. The effects of 12 weeks

treatment of acarbose on (mean $\pm$ SE) fasting blood glucose levels in type 2 diabetic patients, previously treated with either diet alone or with diet and sulfonylureas can be seen in table 2.

Table 2. The effects of acarbose on (mean $\pm$ SEM) fasting blood glucose levels in type 2 diabetic patients previously treated with diet alone, glibenclamide, gliclazide and chlorpropamide therapy.

Treatment Group	Baseline (day 0)	After treatment (day 90)	Δ Difference	P value*
Diet Alone (N=25)	172.9 $\pm$ 8.8	163.6 $\pm$ 4.7	-9.3 $\pm$ 7.12	NS
Oral Hypoglycemics (N=19)				
Glibenclamide (N=11)	169.8 $\pm$ 7.05	161.6 $\pm$ 5.2	-8.2 $\pm$ 6.3	NS
Gliclazide (N=5)	159.6 $\pm$ 15.6	146.6 $\pm$ 14.4	-13 $\pm$ 2.9	0.0054
Chlorpropamide (N=3)	165.7 $\pm$ 9.0	165.3 $\pm$ 4.5	-0.3 $\pm$ 7.2	NS

Data are expressed as mean $\pm$ SE. NS= Non significant. All observations were measured in mg/dl. Δ Difference between baseline and after the treatment at day-90. *P value comparing changes from baseline to last visit at day-90.

Acarbose treatment significantly decreased mean fasting blood glucose concentrations ($P < 0.005$) from 159.6 $\pm$ 15.6 mg/dl to 146.6 $\pm$ 14.4 mg/dl (Difference -13 $\pm$ 2.9 mg/dl) in subjects previously treated with gliclazide. Whereas no-significant changes were observed in patients previously treated with diet alone, glibenclamide and chlorpropamide. These non-significant changes in fasting glycaemic control could be related to small number of patients in each treated group.

Table 3. Effects of acarbose treatment on (mean±SEM) fasting blood glucose, plasma lipids and lipoproteins in type 2 diabetic patients.

Parameters	Baseline (day 0)	at day 90	P value*
FBG (mg/dl)	173.89±3.89	161.29±3.41	<0.01
T-CHOL (mg/dl)	220.39±5.02	209.64±4.70	NS
TRIG (mg/dl)	188.85±5.91	158.57±4.48	<0.01
HDL-C (mg/dl)	35.08±0.76	36.22±0.86	NS
LDL-C (mg/dl)	147.24±4.82	140.98±4.86	NS
VLDL-C (mg/dl)	33.08±1.19	31.02±0.95	<0.01

Results are expressed in mean±SEM, NS = Non significant. Figure in parentheses shows the number of patients. All observations were measured in mg/dl.

Table 3 shows the main metabolic characteristics of all study subjects regardless of their previous therapy, at base line day 0 and at the end of the treatment period, at day 90.

Acarbose led to an improvement of fasting blood FBG = glucose from 173.89 ± 3.89 mg/dl to 161.29 ± 3.41 mg/dl (mean ± SE) which was a significant ($P < 0.01$) fall. It is apparent that these patients had unequivocal fasting hyperglycemia before acarbose therapy, and that this was associated with elevated serum triglyceride and reduced HDL-cholesterol concentrations. The serum total triglyceride level was 188.85 ± 5.91 mg/dl at entry, and was significantly decreased to 158.57 ± 4.48 mg/dl (mean ± SE) at day 90, which was statistically significant ($P < 0.01$). Very-low density lipoprotein cholesterol also reduced significantly from 33.08 ± 1.09 mg/dl at day 0 to 31.02 ± 0.95 mg/dl (mean ± SE) at day 90 ($P < 0.01$). The mean fasting serum total cholesterol, high-density lipoprotein cholesterol and low-density lipoprotein cholesterol concentrations did not seem to be affected by acarbose, the changes were found insignificant at day 90. All these favorable biological effects occurred without exposing the patient to hypoglycemia or weight gain.

Mean body weight did not change significantly, which showed statistically non-significant change in body mass index at the end of acarbose therapy, as shown in table 1. This reflects their constant dietary intake during the 12-week period of treatment, which was evaluated by dietary recall information by dietitians. The mean daily dose of the acarbose was 204.5 mg/day at the start of therapy, and the mean daily dose of acarbose at the final assessment (i.e. after 12 weeks of treatment) was 195.5 mg/day. The average daily dose, which remained throughout the study, was 224 mg/day. The only adverse events that could be linked to the drug were gastrointestinal symptoms. Many patients complained of mild to moderate intestinal adverse effects. The most common reason for discontinuation of the drug was gastrointestinal symptoms. The most frequently reported adverse side effects was abdominal discomfort or cramps, experienced by 19 (43.18%) subjects, diarrhea was reported by 10 (22.72%), flatulence by 6 (13.63%), and 9 (20.45%) tolerated the acarbose well. In this study, abdominal discomfort or flatulence was the only significant side effect that led to treatment withdrawal in a few

acarbose treated patients. In accordance with previously reported experience, no hypoglycemic reaction was observed.

Discussion

Diabetes, particularly type 2, is commonly associated with abnormalities in plasma lipid and lipoprotein levels. In particular, it usually presents with concomitant elevations in plasma triglyceride (TG) levels and reductions in plasma HDL-cholesterol concentrations¹¹. These abnormalities certainly play a role in the increased risk for cardiovascular disease, particularly coronary artery disease. The current study was undertaken to see if acarbose treatment of patients with type 2 diabetes resulted in changes in fasting blood glucose and lipid metabolism. presumed to increase the risk of coronary artery disease. The results presented indicated that this was not the case. In contrast, the data presented suggest that the changes in lipid and lipoprotein concentrations observed in patients treated with acarbose would, if any thing, lead to a decrease in coronary risk factors.

The greatest change in serum lipid concentrations associated with acarbose treatment was a fall in serum total triglyceride concentration; the mean reduction was modest in magnitude ($P < 0.01$). The ability of acarbose treatment to lower serum total triglyceride concentrations is likely to be related to the degree of diabetic control achieved with therapy. Indeed, it appears that successful treatment can lead to a beneficial effect in this instance. Moroney et al¹² cited that, high concentrations of LDL-cholesterol are known to be independently associated with coronary heart disease, we did not find any significant change in the LDL-cholesterol concentration at the end of acarbose therapy. The effects of acarbose therapy on serum total cholesterol and HDLcholesterol concentrations were modest in magnitude, and in neither instance were the changes statistically significant in our study. However, it should be noted that the changes in both cases, i.e., lower serum total cholesterol and HDLcholesterol levels, would be viewed by current concepts as representing an improvement in cardiovascular risk factors¹³. The study of Toeller et al¹⁴ reported that, alphaglucohydrolase inhibitors generally improve metabolic control in NIDDM patients regardless of whether acarbose is administered in addition to other oral anti-diabetic agents or with diet alone. The most significant finding is the reduction of postprandial blood glucose concentrations. In this study we assessed efficacy of acarbose by estimating fasting blood glucose, which showed significant decline ($P < 0.01$). Although in this study the level of fasting blood glucose did not fall into the acceptable levels. The relatively small effect of acarbose on fasting blood glucose levels is not unexpected because the drug delays the absorption of glucose from the gastrointestinal tract^{15,16} and therefore should affect mainly the post prandial plasma glucose levels. The lowering effect of acarbose on fasting blood levels might be explained by decreased glucose toxicity with improvement in insulin sensitivity and β -cell response to glucose¹⁷. Although most studies in patients with non-insulin dependent diabetes mellitus have not shown any effect of acarbose on fasting plasma glucose¹⁸⁻²⁰, a few have shown small beneficial effect of the drug on those levels^{21,22}. In these studies, the initial fasting plasma glucose levels were relatively low to start with (<10 mmol/L 178.57 mg/dl). The results of our study show, that acarbose therapy improved fasting glycemic levels, though they did not fall in the acceptable range, regardless of the antidiabetic treatment regimen used previously.

The study of Hanefeld et al²¹ also showed significant decrease in fasting blood glucose with 24 weeks of acarbose treatment in patients with type 2 diabetes, uncontrolled with diet alone, whereas no significant change in serum total cholesterol levels was seen. The study of Chan et al²³ also found significant reduction of fasting blood glucose during treatment with acarbose. These findings are in agreement with our results. It is an established fact the prevalence of atherosclerosis is increased in patients with diabetes. Since triglyceride biosynthesis in the liver is stimulated by the availability of glucose as well as by the presence of insulin, therefore acarbose also exerts an inhibitory influence on

hepatic lipogenesis which is secondary to its effects on glucose absorption and thus insulin secretion²⁴. Our observation reflects the decrease in serum total triglyceride concentrations which indicates a decrease in the lipase activity. This may be due to increase in the insulin sensitivity or indirectly effected by an improved glycemic control which also decreased the VLDL cholesterol. Four patients dropped out of the study due to intolerance to acarbose therapy. Abdominal discomfort or cramps were the major symptoms expressed by 43.18% of the study subjects. Generally acarbose was well tolerated and the adverse reactions were transient and self-limited. The reason is inhibition of the intestinal α -glucosidase, causing maldigestion of complex carbohydrates. When these reach the colon, they are fermented by bacteria resulting in severe meteorism, abdominal cramps and diarrhea. In our experience, lowering the acarbose dose can prevent such unacceptable side effects. In the present study, there were no significant reductions in body weight, which was due to insignificant change in dietary intake.

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