



STUDY ON EFFICACY OF ACARBOSE (WITH AND WITHOUT CORNSTARCH DIET) IN COMPARISON WITH ROSIGLITAZONE IN DIABETIC RATS

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ABSTRACT

The aim of this study is to compare metabolic effects of acarbose and rosiglitazone, especially in controlling hyperglycemia and hypercholesterolemia. We have selected acarbose and rosiglitazone for the present study among various currently approved oral hypoglycemics. As diet is also an important component in diabetic therapy, effects of resistant starch diets (e.g. cooked cornstarch) on carbohydrate and lipid metabolism were also studied. The metabolic effects of the drugs were investigated and significant changes with respect to blood glucose levels, HbA1c along with lipids profile of drug-treated animals were compared with untreated animal after 7, 15 and 30 days. The experimental result showed excellent glycemic control when acarbose was administered alone. Acarbose along with cooked cornstarch diet produced a more favorable lipid profile, but with significant increased level ($p<0.001$) of triglycerides. These findings suggest that acarbose and acarbose along with cooked cornstarch are more effective in controlling hyperglycemia with more favorable lipid profile when compared with rosiglitazone.

Keywords: Resistant starch, hyperglycemia, oral hypoglycemic, hypocholesterolemia, alpha-glucosidase inhibitor.

INTRODUCTION

Altered metabolism of carbohydrates and lipids in diabetes mellitus is frequently accompanied with imbalances in LDL, HDL and triglyceride levels and thought to be responsible for increased risk of developing atherosclerosis and other related cardiovascular disorders. The present study is aimed to compare metabolic effects of acarbose and rosiglitazone, especially in controlling hyperglycemia and hypercholesterolemia. Since diet therapy is very helpful for patients in achieving their appropriate metabolic and physiologic goals of blood glucose, lipids, blood pressure and body weight¹ and also because cooked cornstarch diet help minimizing GI adverse effects associated with acarbose therapy², in our present study we have evaluated the antidiabetic and hypocholesterolemic properties of resistant starch diet (e.g. cornstarch) when administered along with acarbose and compared with rosiglitazone. Previous studies reported that resistant starch modifies carbohydrate and lipid metabolism and clinically significant in controlling hyperglycemia and hypercholesterolemia³.

One of the possible mechanism for low glycemic response of resistant starch is delayed digestion and delayed absorption of dietary carbohydrate. Another mechanism may be the fermentation of dietary starches by colonic microflora and release of short-chain fatty acids (acetate, propionate and butyrate)⁴. Recent study⁵ reported that in rat hypocholesterolemic effect of cornstarch is not mediated by cecal fermented products, but enlarged bile acid pool and increased fecal bile may be the cause.

Acarbose is classified as alpha-glucosidase inhibitors. The mechanism of antihyperglycemic effect of acarbose is competitive, reversible inhibition of pancreatic alpha-amylase and membrane-bound intestinal alpha-glucosidase. This enzyme inhibition results in a delayed glucose absorption and lowering of postprandial hyperglycemia which is the goal of diabetic therapy⁶. Since acarbose specifically target postprandial plasma glucose so it is effective in controlling sustained elevated hemoglobin A1c⁷. However, tolerability is the major issue which has limited its use⁸. Acarbose is metabolized within the gastrointestinal tract and is

completely excreted by the kidneys. The recommended initial acarbose dose is 25 mg orally t.i.d. with the first bite of each meal. The most common side effects with acarbose therapy are abdominal pain, diarrhea and flatulence and increase in liver enzymes⁹.

Rosiglitazone belong to the class thiazolidinedione or glitazone and is indicated either as monotherapy or in combination with other antidiabetics¹⁰. It is a highly selective and potent agonist for the peroxisome proliferator-activated receptor-gamma (PPAR γ). Activation of PPAR γ receptors regulates the transcription of insulin-responsive genes involved in the control of glucose production, transport, and utilization. In addition, fatty acid metabolism is also regulated by these PPAR γ -responsive genes¹¹. Rosiglitazone is extensively metabolized in the liver and excreted through kidneys. It may be administered at a starting dose of 4 mg daily. Plasma rosiglitazone concentrations may be significantly increased in patients with pre-existing hepatic impairment¹⁰.

MATERIALS AND METHODS

Selection of Animal & Treatment

The present study was carried out on 40 adult albino rats (either sex) of Wistar strain weighing 200-300 gram. Animals bred locally in animal house of Department of Pharmacology, University of Karachi, were used in this study. The animals were housed in iron cages as groups of 3 animals per cage. Before induction of diabetes and administration of drugs the animals were fed on regular rat pellet diet and water ad libitum. One of the groups was fed with cooked cornstarch diet. All the animals were maintained under constant environment condition $21 \pm 1^\circ\text{C}$ and humidity (50-60%) and maintained 12:12 light and dark cycle. Body weight, food intake, water intake, urine volume, lack of activity, diarrhea, edema, ulceration and blood glucose levels were closely monitored in pre-experimental period.

Animals were handled as per specifications provided in Helsinki Resolution 1964 and study is approved by our Board of Advanced Studies and Research vide Resol. No. 12(30) dated: 14-04-2010.

Induction of Diabetes

To induce diabetes, animals were injected with a single dose of freshly prepared aqueous solution of alloxan monohydrate (intraperitoneally at a dose of 150mg/kg body weight¹²). Since alloxan is capable of producing total hypoglycemia as a result of massive pancreatic insulin release, the rats were kept for the next 24 hours on 5% glucose solution orally¹³. Controlled rats treated identically and served as diabetic control.

After 48 hours, the blood samples were drawn in order to ensure that hyperglycemia has been induced. Blood glucose levels were determined by using a portable glucose analyzer (Abbott Medisense Optium Blood Glucose analyzer). The levels of blood glucose considered to be normal ranges from 50-135mg /dl. Animals with glucose levels >200mg/dl were considered as diabetic and selected for experimental study¹⁴.

Preparation of Diet

The animals were kept on regular rat pellet diet. Since flatulence, diarrhea and GI distention are major adverse effects associated with acarbose therapy so one of the groups was fed on cooked cornstarch diet to minimize these effects². Cooked cornstarch diet was prepared by the method described by¹⁵ in her study using corn starch as a source of carbohydrate and no sugars.

Experimental Protocol

The animals were divided into 4 groups of 10 animals each:

- Group I was alloxan treated (served as diabetic control).
- Group II was acarbose with regular diet treated at a dose of 1.66 mg/kg/three times a day.
- Group III was acarbose with cooked cornstarch diet treated at a dose of 1.66 mg/kg/three times a day.
- Group IV was rosiglitazone treated at a dose of 0.034 mg/kg/ twice a day.

The doses of acarbose and rosiglitazone were prepared in distilled water in concentration of 50 mg/5 ml and 2mg/2ml respectively by serial dilution method. The control group animals were given distilled water only. Diabetic rats were subjected to drug treatment on the 2nd day after induction. Drug samples were administered orally for a period of total four weeks. Blood samples were collected from caudal vein of each animal and plasma/serum was separated out by centrifuging the blood samples in Humax 14 K (Germany) at 3000 RPM for 15 minutes. Effects of drugs on blood glucose and on lipid profile were monitored on day 7, 15 and 30.

BIOCHEMICAL ESTIMATION**Blood Glucose Levels**

Fasting blood glucose and random blood glucose were analyzed within 3 hours of sample collection by GOD-PAP Enzymatic Colorimetric test method¹⁶ on Humalyzer 3000 (Semi-automatic chemistry analyzer Model # 16700 by Human Germany) using standard kits supplied by Human.

Lipid Profile

Total cholesterol was estimated by cholesterol liquicolor, CHOD-PAP Enzymatic Colorimetric Test Method for cholesterol with Lipid Clearing Factor¹⁷. Serum triglycerides were measured by triglyceride liquicolor, GPO-PAP Enzymatic Colorimetric Test Method for triglycerides with lipid clearing factor¹⁸.

Estimation of HbA1c, HDL, LDL

For estimation of HbA1c, LDL and HDL samples were sent to Dr. Punjwani Center for Molecular Medicine and Drug Research (PCMD) diagnostic laboratory located in H.E.J Research Institute, University of Karachi within 1 hour after collection.

STATISTICAL ANALYSIS

Results were expressed as mean \pm SEM. Differences were statistically analyzed by one-way ANOVA, followed by Students-Newman-Keuls post hoc analysis. P- Values < 0.005 were considered as statistically significant, $p<0.0025$ as more significant and $p<0.001$ as highly significant.

RESULTS AND DISCUSSION

In our present study, fasting blood glucose level was significantly decreased within 7 days in group III (table #1), indicating if diet is controlled and if given with cooked cornstarch diet the drug efficacy is increased. Same drug, but with regular diet (group II), only produces its effect after two weeks dosing. In comparison rosiglitazone (group IV), belongs to other class of antidiabetic, decreased fasting blood glucose after 15 days (table #1). This result indicates that acarbose could be beneficial where we require significant reduction in fasting blood glucose within 7 days time. Only thing we should consider is to give acarbose along with cooked cornstarch as lengthening of carbohydrate digestion and absorption appears to be the major factor responsible to show the response of decreasing plasma glucose¹⁹. Same results were found after 30 days.

Table 1: Effect of drugs on blood glucose level

| Groups | Fasting blood glucose level (mg/dl) | | | | | |
|-----------|-------------------------------------|--------|-------------------|--------|-------------------|--------|
| | Day 7 | | Day 15 | | Day 30 | |
| | Mean \pm S.E | P | Mean \pm S.E | P | Mean \pm S.E | P |
| Group I | 276.30 \pm 97.4 | - | 264.2 \pm 77.3 | - | 289.8 \pm 57.1 | - |
| Group II | 151 \pm 116 | 0.019 | 80.50 \pm 3.63 | 0.0000 | 160.4 \pm 43.1 | 0.0000 |
| Group III | 114 \pm 41.4 | 0.0004 | 159.9 \pm 49.9 | 0.0027 | 88.7 \pm 3.33 | 0.0000 |
| Group IV | 210.80 \pm 48.9 | 0.08 | 112.5 \pm 21.4 | 0.0001 | 128.5 \pm 3.81 | 0.0000 |
| Groups | Random blood glucose level (mg/dl) | | | | | |
| | Day 7 | | Day 15 | | Day 30 | |
| | Mean \pm S.E | P | Mean \pm S.E | P | Mean \pm S.E | P |
| Group I | 349.8 \pm 80.7 | - | 366.9 \pm 5.67 | - | 338.4 \pm 24.1 | - |
| Group II | 106.8 \pm 10.5 | 0.0000 | 131.2 \pm 5.63 | 0.0000 | 221.1 \pm 61.6 | 0.0002 |
| Group III | 130.3 \pm 63.8 | 0.0000 | 106.6 \pm 16.13 | 0.0000 | 318.75 \pm 3.36 | 0.031 |
| Group IV | 263.9 \pm 78.7 | 0.028 | 131.7 \pm 7.02 | 0.0000 | 288.2 \pm 4.66 | 0.0001 |
| Groups | HbA1c level (%) | | | | | |
| | Day 7 | | Day 15 | | Day 30 | |
| | Mean \pm S.E | P | Mean \pm S.E | P | Mean \pm S.E | P |
| Group I | 6.23 \pm 0.27 | - | 6.07 \pm 0.25 | - | 8.87 \pm 0.42 | - |
| Group II | 5.05 \pm 0.058 | 0.0000 | 4.97 \pm 0.300 | 0.0000 | 4.95 \pm 0.33 | 0.0002 |
| Group III | 4.96 \pm 0.47 | 0.0000 | 4.94 \pm 0.36 | 0.0000 | 8.44 \pm 0.32 | 0.020 |
| Group IV | 4.92 \pm 0.061 | 0.0000 | 5.11 \pm 0.21 | 0.0000 | 5.70 \pm 0.35 | 0.0000 |

Values are mean \pm S.E. (n=10). Significant differences by Newman-Keuls test * $p<0.005$, ** $p<0.0025$ and

*** $p<0.001$ as compared to control rats, following one-way ANOVA df(3,39)

Table 2: Effect of drugs on Lipid Profile

| Groups | Cholesterol level (mg/dl) | | | | | |
|-----------|----------------------------|--------|-------------------|--------|-------------------|--------|
| | Day 7 | | Day 15 | | Day 30 | |
| | Mean \pm S.E | P | Mean \pm S.E | P | Mean \pm S.E | P |
| Group I | 59.60 \pm 3.81 | - | 69 \pm 4.40 | - | 110.28 \pm 4.20 | - |
| Group II | 14.67 \pm 2.85 | 0.0000 | 57.89 \pm 4.05 | 0.0000 | 60.52 \pm 3.48 | 0.0000 |
| Group III | 53.69 \pm 3.02 | 0.0013 | 48.54 \pm 4.31 | 0.0000 | 32.87 \pm 2.98 | 0.0000 |
| Group IV | 84.90 \pm 4.53 | 0.0000 | 48.92 \pm 4.24 | 0.0000 | 72.81 \pm 3.11 | 0.0000 |
| Groups | HDL level (mg/dl) | | | | | |
| | Day 7 | | Day 15 | | Day 30 | |
| | Mean \pm S.E | P | Mean \pm S.E | P | Mean \pm S.E | P |
| Group I | 36.3 \pm 3.47 | - | 36.5 \pm 3.63 | - | 6.71 \pm 0.40 | - |
| Group II | 30.7 \pm 3.59 | 0.0025 | 38.2 \pm 3.43 | 0.30 | 2.73 \pm 0.33 | 0.0000 |
| Group III | 25.5 \pm 3.24 | 0.0000 | 30.53 \pm 3.03 | 0.0009 | 19.96 \pm 3.54 | 0.0000 |
| Group IV | 53.10 \pm 3.84 | 0.0000 | 35.7 \pm 4.22 | 0.66 | 5.29 \pm 0.34 | 0.0000 |
| Groups | LDL level (mg/dl) | | | | | |
| | Day 7 | | Day 15 | | Day 30 | |
| | Mean \pm S.E | P | Mean \pm S.E | P | Mean \pm S.E | P |
| Group I | 18.7 \pm 4.19 | - | 12.80 \pm 3.83 | - | 12.70 \pm 3.33 | - |
| Group II | 9.80 \pm 3.01 | 0.0001 | 10.78 \pm 3.58 | 0.24 | 12.19 \pm 3.27 | 0.73 |
| Group III | 8.3 \pm 3.13 | 0.0000 | 4.92 \pm 2.50 | 0.0001 | 5.59 \pm 2.10 | 0.0000 |
| Group IV | 15.10 \pm 3.35 | 0.049 | 12.14 \pm 3.48 | 0.69 | 13.90 \pm 3.48 | 0.44 |
| Groups | Triglyceride level (mg/dl) | | | | | |
| | Day 7 | | Day 15 | | Day 30 | |
| | Mean \pm S.E | P | Mean \pm S.E | P | Mean \pm S.E | P |
| Group I | 65.90 \pm 3.84 | - | 64.4 \pm 3.95 | - | 65.20 \pm 3.88 | - |
| Group II | 75.19 \pm 3.45 | 0.0000 | 102.07 \pm 3.75 | 0.0000 | 56.27 \pm 3.36 | 0.0000 |
| Group III | 78.56 \pm 9.00 | 0.0015 | 292.2 \pm 28.9 | 0.0000 | 174.80 \pm 3.61 | 0.0000 |
| Group IV | 132.1 \pm 3.67 | 0.0000 | 39.61 \pm 3.71 | 0.0000 | 40.70 \pm 3.17 | 0.0000 |

Values are mean \pm S.E. (n=10). Significant differences by Newman-Keuls test *p<0.005, **p<0.0025 and *** p<0.001 as compared to control rats, following one-way ANOVA df(3,39)

Reduction in random blood glucose level suggest that acarbose is very effective in maintaining the glycemic control throughout the day especially after meals no matter it was used with regular diet or with cornstarch diet (table #1). This effect was not seen by rosiglitazone in 7 days indicating that rosiglitazone require at least two weeks dosing before it can control random blood glucose²⁰. The control of random blood glucose was more prominent in group II than with group IV (table #1). In group III the level was decreased but not significantly probably because within two weeks it significantly lowered the random blood glucose and maintained it thereafter (table #1).

Significant decrease in HbA1c level in group II and IV indicate good control of diabetes (table #1). However, significantly increased HbA1c level was observed in group III after 30 days (table #1). This effect was due to delayed absorption of carbohydrate by acarbose as well as cornstarch²¹ when administered for prolonged period of time. Delayed carbohydrate absorption resulted in increased gluconeogenesis from excessive dietary protein and fat breakdown²².

Hence, the present findings indicate that acarbose may be useful in condition where reduction in blood sugar level is required within 7 days and not only fasting blood glucose is decreased but also the random blood glucose is also controlled with an HbA1c level of <6%. If acarbose is given with cooked cornstarch diet the efficacy of the drug will be enhanced within two weeks as far as glycemic control is concerned. However, in the long run acarbose along with cooked cornstarch diet administration showed increased random blood glucose level with an increased level of HbA1c (table #1).

Based on above findings, it is concluded that patients with type 2 diabetes should not be maintained on cooked cornstarch diet for prolonged period, instead other resistant starch diets may be given in combination with cooked cornstarch for better glycemic control in the long run²¹.

There was a significant reduction in cholesterol level in group II but result was very significant in group III (table#2). In comparison, the cholesterol level was decreased significantly after 15 days in group IV (table#2) indicating that rosiglitazone requires at least two-weeks dosing to produce same effect.

As shown by ²³ that plasma cholesterol and triglycerides levels were reduced as the dietary level of cornstarch increased in rats. One possible explanation is fermentation of cornstarch to produce additional propionate in the large intestine ²⁴, and/or increase in the intestinal pool and biliary excretion of bile acids ^{5, 25} reported that an enlargement of the bile acid pool will increase portal bile acid concentration, which may affect cholesterol metabolism in the liver, including decrease in cholesterol synthesis and VLDL secretion. Therefore, an increase in the intestinal pool of bile acids may be another possible mechanism of the hypocholesterolemic effect of cornstarch.

Another study ²⁶ indicated that rats fed on high resistant starch diet showed increased propionate production, slow glucose absorption and relatively low insulinemia in parallel to high rate of short chain fatty acid absorption, which could be the factors responsible for depressed cholesterologenesis and lipogenesis. In our present study, both HDL and LDL cholesterol concentrations were reduced by acarbose in group II (table #2). Synergistic effect was also observed in group III (table#2). Reduced LDL levels were due to reduction in hepatic VLDL production (LDL precursor) which is thought to be mediated by decreased synthesis of cholesterol, a required component of VLDL ²⁷. However, the level of HDL was significantly increased in group III on 30th day (table#2). It has been reported that plasma LDL and HDL levels are more specific and sensitive biochemical markers of cardiovascular disease risk and also believed that HDL do help protect against the development of atherosclerosis ²². So, we can say that the risk of developing atherosclerosis may be greatly reduced when acarbose was administered along with

cooked cornstarch diet. Treatment with rosiglitazone, however, showed non-significant change in level of LDL. Decrease in HDL level was significant after 30 days of dosing (table#2).

Rosiglitazone treatment has been shown to reduce hypertriglyceridemia and to improve the insulin-mediated glucose utilization in type 2 diabetes patients and several animal models of type 2 diabetes²⁸.

In our present study, treatment with rosiglitazone in group IV showed an initially elevated TG level, which was then decreased after 15th and 30th days (table#2). Group IV also showed an elevated blood glucose level at day 7 but later rosiglitazone decreased these levels by increasing insulin sensitivity via stimulating PPAR- γ ²⁸.

Triglyceride levels in both acarbose treated groups (II and III) were significantly greater than those in the controls but increase in the level was more intense in group III. However, on long run there was a reduction in TG level in group II also (table#2).

CONCLUSION

Based on the above findings, it is concluded that although acarbose is believed to decrease TG levels, as reported in previous studies²⁹, our present study showed increase in the TG levels when acarbose was administered along with cooked cornstarch diet which may be the effect of high carbohydrate diet³⁰. It could be important that if person has elevated triglycerides then use of acarbose with cooked corn starch should be with caution or may require an addition of antihyperlipidemic agent.

So we can conclude that acarbose and acarbose along with cooked cornstarch are more effective in controlling hyperglycemia with more favorable lipid profile when compared with rosiglitazone.

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