



## **Effects of acarbose (with and without corn starch diet) and rosiglitazone on kidney functions in alloxan-induced diabetic rats**

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### **ABSTRACT**

So far, it has been very difficult to express that any particular antidiabetic drug is more effective in terms of nephroprotection. Present study was conducted to evaluate the potential of rosiglitazone and acarbose in minimizing diabetic nephropathy in type 2 diabetes. 40 Wistar albino rats were divided into 4 groups. Group I was alloxan-treated diabetic control. Groups II, III, IV were treated with acarbose, acarbose along with cooked cornstarch diet and rosiglitazone respectively. Diabetes was induced with single dose of alloxan monohydrate intraperitoneally. After induction drug samples were administered orally and effects were studied on day 7, 15 and 30 for determination of renal functions. Highly significant decrease ( $p < 0.001$ ) in creatinine level after 7 days and then significant increase ( $p < 0.001$ ) was observed after 15 and 30 days in all treated groups. BUN level of groups II and III were significantly decreased ( $p < 0.001$ ) after 7 and 15 days. Group III showed a highly significant ( $p < 0.001$ ) increase after 30 days. Group IV showed an initially elevated BUN level after 7 days. The levels were then decreased after 15 and 30 days. Acarbose use is associated with less risk of drug-induced nephropathy.

**Key words:** Diabetic nephropathy, drug-induced interstitial nephritis, acarbose, rosiglitazone.

### **INTRODUCTION**

Prevalence of diabetic nephropathy is greatly increased in many countries, and become the leading cause of end-stage renal disease [1]. A large number of diabetic subjects have an altered renal function at some point in their life. On the whole, the significant increase in diabetic patients with end-stage renal disease is largely due to rising incidence of type 2 diabetes, the prolonged use of oral hypoglycemic and population age. Recently Stamm et al confirm a considerable increase in the number of diabetic dialysis subjects over an 8-year period [2]. A 2.6 fold increase in risk of chronic kidney disease [3] and 3-fold increase in renal death [4] due to diabetes is reported. Monitoring of renal function is therefore recommended for all adult diabetic subjects for at least once in a year with the determination of serum creatinine,  $^{\circ}$ GFR and urinary albumin/creatinine ratio [5]. Since some oral hypoglycemic drugs are contraindicated or may require dose adjustment in impaired kidney functions [6], it is recommended to re-evaluate a patient's antidiabetic therapy if estimated

glomerular filtration rate ( $^{\circ}$ GFR) falls below 60 ml/min [5]. Since adequate control of diabetes leads to lower risk of complications including kidney failure (requiring dialysis or transplant), blindness, heart disease and limb amputation, so good glycaemic control either by oral hypoglycemic drugs or insulin is the only effective therapeutic intervention for the primary prevention of diabetic kidney disease [7].

There are presently four classes of oral antihyperglycemic agents [8]:

- Sulfonylureas: Which are Insulin Secretagogues.
- Non-Sulfonylurea Secretagogues: e.g. Meglitinides,
- Sensitizers: Agents which increase the sensitivity of target organs to insulin, e.g. Biguanides and Thiazolidinediones
- Alpha-glucosidase inhibitors: Agents which decrease the rate at which glucose is absorbed from the gastrointestinal tract [8].

These agents differ greatly in terms of mechanisms of action, efficacy, side effect profiles, and cost. So far, it has been very difficult to express that any particular antidiabetic drug is more effective than any other in terms of nephroprotection [9]. Except for Acarbose, all classes decrease the glycosylated hemoglobin by a similar magnitude: 1.0 to 1.5%. In chronic renal failure, the oral agents that can be used include the insulin secretagogues repaglinide and nateglinide and the thiazolidinediones (rosiglitazone and pioglitazone) with caution. Insulin also can be used safely in renal failure [10]. However, there is few data available regarding the use of acarbose in patients with renal disease. Current recommendations therefore state that acarbose should not be given to patients with severe renal impairment [11]. Drug-induced acute interstitial nephritis is also an important reversible cause of acute renal failure [12]. In 2006, Castledine reported one case of rosiglitazone-induced acute interstitial nephritis [13]. Data from previous studies do not exhibit acarbose-induced nephrotoxicity. Results of one systemic review and meta-analysis regarding the use of acarbose as a monotherapy in patients with type 2 diabetes mellitus showed that acarbose has very clear beneficial effects on glycemic control and postload insulin levels with no evidence for an effect on morbidity and mortality. Most frequent adverse events associated with acarbose use were flatulence, diarrhea and stomachache [14].

## MATERIALS AND METHODS

**Selection of animal & treatment:** The present study was conducted on 40 adult Wistar albino rats (either sex) weighing 200-300. 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%).

**Ethical consideration:** 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 solution of alloxan monohydrate (dissolved in ice-cold water) intraperitoneally at a dose of 150mg/kg body weight [15]. Since alloxan is capable of

producing total hypoglycemia as a result of massive pancreatic insulin release, rats were kept on 5% glucose solution orally for the next 24 hours [16]. Controlled rats treated identically and served as diabetic control. The blood samples were drawn after 48 hours 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 analyser). The levels of blood glucose considered to be normal ranges from 50-135mg/dl. Animals with glucose levels  $>200\text{mg/dl}$  were considered as diabetic and selected for experimental study [17].

**Preparation of diet:** The animals were kept on regular rat pallet diet. Since major adverse effects associated with acarbose therapy are related to GI disturbances, one of the groups was fed on cooked cornstarch diet to minimize these effects [18]. Cooked cornstarch diet was prepared by the method described by [19] in her study using corn starch as a source of carbohydrate and no sugars.

**Drug treatment:** The effect of the following drugs on animals were studied

- Acarbose in a dose of 1.66 mg/kg/three times a day.
- Rosiglitazone in a dose of 0.034 mg/kg/twice a day.

**Experimental protocol:** The animals were divided into 4 groups of 10 animals each:

- Group I: Alloxan treated (served as diabetic control) treated with distilled water only.
- Group II: Acarbose treated. Administered 1.66 mg/kg acarbose three times a day for 30 days.
- Group III: Acarbose + cooked cornstarch diet treated. Administered 1.66 mg/kg acarbose three times a day for 30 days.
- Group IV: Rosiglitazone treated. Administered 0.034 mg/kg rosiglitazone twice a day for 30 days.

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. Diabetic rats were subjected to drug treatment on the 2<sup>nd</sup> day after induction. Drug samples were administered orally for a period of total four weeks and effects of drugs have been studied on day 7, 15 and 30 for determination of renal function.

**Sample collection and estimation of serum creatinine and BUN:** Blood samples were collected and 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 for estimation of serum creatinine and BUN.

**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 statistically significant.

## RESULTS

Results of our present study showed a highly significant decrease ( $p < 0.001$ ) in level of creatinine in all treated groups after 7 days but levels were significantly ( $p < 0.001$ ) increased in all treated groups after 15 and 30 days (table#1).

In the present study when acarbose was administered (Group II and III) it showed a significantly decreased BUN level after 7 days (table#2). Results showed highly significant decrease ( $p < 0.001$ ) in BUN level in both groups II and III after 15 days (table#2). The levels were decreased non significantly in group II after 30 days. When acarbose was administered along with corn starch diet (group III) results showed a highly significant increase ( $p < 0.001$ ) in BUN level (table#2).

Treatment with rosiglitazone (group IV) showed an initially elevated BUN level ( $p < 0.001$ ) after 7 days (table#2). The levels were then decreased significantly ( $p < 0.001$ ) after 15 days and continue to decrease after 30 days, although the decrease was non-significant (table#2).

## DISCUSSION

In the development of diabetic nephropathy advanced glycation end products (AGEs) were found to play a critical role via induction of extracellular matrix (ECM) accumulation. Plasminogen activator inhibitor-1 (PAI-1) that plays an important role in degrading ECM, was found to significantly increase in diabetics and nondiabetics due to increase in various factors including metabolic factors (glucose and lipoproteins) [20]. The fact that PPAR- $\gamma$  agonist treatment significantly decreased PAI-1 expression [21], encouraged [22] to assume that PPAR- $\gamma$  activation by its agonists e.g. rosiglitazone prevent diabetic nephropathy through suppression of PAI-1.

Results of our present study also support previous findings that rosiglitazone has been proven to be safe in chronic kidney disease patients since

Castledine et al (2006) first time reported only one case which showed rosiglitazone as a cause of acute interstitial nephritis [13]. Most recently, [23] also submitted a case report and concluded that cause of acute renal failure with rosiglitazone use may be idiosyncratic since patient failed to return to pre-morbid serum creatinine level despite the cessation of rosiglitazone.

As far as acarbose is concerned, the results of our present study is in accordance to our previous findings [24] which showed a significant control of random blood glucose and a therapeutic level of HbA1c when acarbose was administered with regular diet (Group II) for 30 days. However, administration of acarbose along with corn starch diet (Group III) showed a poor glycemic control as indicated by increased random blood glucose as well as HbA1c level [24]. It has already been reported that adequate diabetes control is required to lower the risk of diabetic complications including renal failure [7]. Based on these findings it is concluded that decline in kidney function may not be associated directly with acarbose use rather it may be due to delayed absorption of carbohydrate by acarbose as well as cornstarch [25]. Delayed carbohydrate absorption for prolonged period of time resulted in increased gluconeogenesis from dietary protein as well as fat breakdown [26] as evident by hyperglycemia.

## CONCLUSION

Based on above findings it has been concluded that although acarbose has beneficial effects on glycemic control and are associated with less risk of drug-induced nephropathy in the treatment of type 2 diabetes mellitus, it is recommended that patients with type 2 diabetes should not be maintained on cooked cornstarch diet for prolonged period while on acarbose therapy. For better glycemic control in those patients other resistant starch diet may be given in combination with cooked cornstarch [25], [27]. Our results although support the fact that rosiglitazone prevents diabetic nephropathy by PPAR- $\gamma$  activation through suppression of PAI-1, it requires some more studies to support our findings.

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**Conflict Of Interest Statement:** None declared. The contents of this paper have not been published previously in whole or part.

**Table 1: EFFECT OF DRUGS ON SERUM CREATININE LEVEL**

Groups	Serum creatinine mg/dl					
	Day 7		Day 15		Day 30	
	Mean ± S.E	P	Mean ± S.E	P	Mean ± S.E	P
I	0.88±0.051	-	0.36±0.032	-	0.28±0.030	-
II	0.72±0.036	0.0000	1.08±0.055	0.0000	1.06±0.046	0.0000
III	0.69±0.039	0.0000	0.66±0.037	0.0000	0.49±0.034	0.0000
IV	0.76±0.036	0.0000	0.61±0.037	0.0000	0.34±0.029	0.0005

Values are mean ± 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 BUN LEVEL**

Groups	BUN mg/dl					
	Day 7		Day 15		Day 30	
	Mean ± S.E	P	Mean ± S.E	P	Mean ± S.E	P
I	35.60±2.91	-	39.96±2.96	-	35.90±3.81	-
II	24.00±3.30	0.0000	33.34±3.54	0.0003	32.82±3.36	0.072
III	20.08±2.69	0.0000	24.81±3.30	0.0000	51.63±3.21	0.0000
IV	56.63±4.19	0.0000	24.73±3.54	0.0000	38.70±3.27	0.096

Values are mean ± 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)

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