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Original Research Article

Effect of atorvastatin and rosuvastatin on glucose intolerance in low dose streptozotocin induced hyperglycemic Albino rats

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ABSTRACT

Background: Dyslipidemia and glucose intolerance are closely associated with each other especially as a part of metabolic syndrome. Statins are the drug of choice for treatment of dyslipidemia and for primary prevention of coronary heart disease in diabetics. Recent studies indicate risk of new onset diabetes in patients receiving statins. Hence it was worthwhile to study the effect of two most commonly used statins, which differ in their lipophilicity, on glucose tolerance in prediabetic animal model.
Methods: The study consisted of 3 groups with 6 wistar rats in each and hyperglycemia was induced by intraperitoneal injection of low dose (25mg/kg) streptozotocin. Group 1 served as control, group 2 and 3 were given Atorvastatin and Rosuvastatin respectively for 8 weeks. Oral glucose tolerance test (OGTT) was performed at 0,1 and 2 hrs after glucose load on days 0, 14, 28, 42 and 56 days.
Results: Starting from 28th day onwards both the treatment groups showed progressive worsening of glucose tolerance throughout the study period in comparison to the control. The impairing effect on glucose tolerance was less pronounced in Rosuvastatin group as compared to Atorvastatin.
Conclusions: Hydrophilic Rosuvastatin showing less impairing effect on glucose tolerance can be a rational choice than lipophilic Atorvastatin for prevention and control of dyslipidemia in patients at risk of developing frank diabetes or having impaired glucose tolerance.

Keywords: Atorvastatin, Glucose tolerance, Hydrophilic, Rosuvastatin, Streptozotocin

INTRODUCTION

An important modifiable risk factor for the development of atherosclerosis and cardiovascular disease (CVD) is Dyslipidemia.[1] The prevalence of dyslipidemia is steadily rising in developing countries.[2] Effective management of dyslipidemia by pharmacological treatment is known to reduce the rate of CVD morbidity and mortality.[3] Statins, the main drugs used for treatment of dyslipidemia, are 3-Hydroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase competitive inhibitors which catalyze an early, rate-limiting step in cholesterol biosynthesis.[4]

Diabetes manifests itself typically in the context of other abnormalities, especially the principal components of metabolic syndrome, namely hypertension and hyperlipidemia.[5] Metabolic syndrome is often associated with prediabetes i.e. Impaired fasting glucose (IFG) and/or Impaired glucose tolerance (IGT).[6] During the pre-diabetic state also, the risk of a CVD event is modestly increased.[7]

The transition from prediabetes to diabetes usually results from failure of compensatory mechanisms especially defects in insulin secretion. Even transient impaired glucose tolerance may be associated with an increased

risk of deterioration to diabetes.[8] Diabetes mellitus is considered to be a CVD-equivalent disorder. So dyslipidemia treatment guidelines is the same as that for patients with established.[4]

Although statins are the cornerstone of lipid-altering therapy for reducing CVD risk in diabetics and non-diabetics, recent studies have suggested that statins cause worsening of blood glucose profile and increase the risk of diabetes.[9-12] Two meta-analyses of available randomized placebo-controlled trials-HPS (simvastatin 40mg), LIPID (pravastatin 40mg), ASCOT (atorvastatin 10mg), CORONA (rosuvastatin 10mg), and JUPITER (rosuvastatin 20mg) showed a slight increase in the risk of diabetes.[10,13]

All statins are similar in mode of action and their potency being comparable in reducing low density lipoprotein (LDL) Cholesterol; however, they show difference in their pleotropic effects- attributable to marked differences in lipophilicity.[14] The presence or absence of polar moieties on their largely hydrophobic structures influence solubility and localisation due to which metabolic differences among the statins occur.[15,16]

Atorvastatin, fluvastatin, pitavastatin, simvastatin, cerivastatin and lovastatin are lipophilic, while pravastatin and rosuvastatin are hydrophilic.[16]

Hydrophilic statins are more hepatocyte specific and less likely to enter extrahepatic cell membranes such as β cells of pancreas, adipocytes or skeletal muscles whereas lipophilic statins can more readily penetrate these tissues therefore it has been hypothesized that the latter might be more diabetogenic.[17] Lipophilic statins enter into cells by passive diffusion, whereas hydrophilic statins employ carrier-mediated mechanisms for uptake.[17] Lipophilic statins may be incorporated into various organs such as pancreas, adipose tissue and muscle which are important for glucose metabolism, while hydrophilic statins are incorporated mainly into liver.

A small excess percentage of those taking statins may develop diabetes but the benefits from reduction in cardiovascular events due to their use overweigh the risk of development of diabetes; and so, this effect do not change the recommendation of use of statins in CVD.[18] Hence it was worthwhile to study the effect of two most commonly used statins (Atorvastatin and Rosuvastatin), which differ in their lipophilicity, on glucose tolerance in prediabetic (hyperglycaemic) animal model.

METHODS

This was an animal experimental study done in the Animal Laboratory of Department of Pharmacology, RIMS, Ranchi. The total study period was 8 weeks (56 days). Only healthy and active rats weighing 200-250gms with random blood sugar i.e. 140-199mg/dl (Impaired glucose tolerance range) were included. The diabetic animals were allowed free access to tap water, standard laboratory pellet diet along with added fat (butter) and glucose, and were kept at room temperature and optimum humidity in their cages.

Drugs

1. Atorvastatin [Storvas 20mg tablet- Ranbaxy (Cardiovasculars)] (1.8mg/kg body wt).
2. Rosuvastatin [Rosuvas 10mg tablet - Ranbaxy] (0.9mg/kg body wt)

Dose calculation

On the basis of body surface area: Surface area ratio of 200g rat to 70 kg man is 0.018 (conversion factor for rat). Thus, human dose of any drug (for a 70kg person) multiplied by 0.018 gives the value of that drug for 200g of rat. Multiplying the product with 5 gives mg/kg value.[19]

Induction of hyperglycemia

Rats were fasted for 12 hours overnight before inducing β cell destruction. Freshly prepared streptozotocin (STZ) solution in 0.1 M citrate buffer (pH 4.2) was used for a single intra-peritoneal injection of 25mg/kg (i.e., about half the diabetes induction dose) of streptozotocin. After 3 days of stabilization period oral administration of statins and Normal Saline (with the help of gavage feeding tube) was started and continued on once a day basis at a fixed time for 8 weeks.

Sample size

18 male Wistar (albino) rats were divided into 3 groups having 6 rats each (Table 1).

Table 1: Grouping of rats.

Groups	All (STZ) induced	Drugs
Group 1	Hyperglycemic control	Given normal saline
Group 2	Hyperglycemic treated	With atorvastatin
Group 3	Hyperglycemic treated	With rosuvastatin

Oral glucose tolerance test

Oral glucose tolerance test (OGTT) was performed after oral administration of 0.5g/ml glucose solution at 1ml/100g body weight (5g/kg) to an overnight-fasted conscious rat through a gavage tube.[20] Blood glucose was measured just before glucose load (0 hour) and after 1 and 2 hours of glucose load. Oral glucose tolerance test was performed in all groups on day 0, 14th, 28st, 42th and 56th day of starting statin administration. The blood sample were taken from tail vein of rats and were estimated by a glucose oxidation method.

Statistical analysis

Data were expressed as Mean±Standard deviation. Data were analysed with IBM-SPSS version 23 software. Statistical comparisons were performed by one-way ANOVA followed by Post hoc Multiple Comparison Tukey HSD (Honestly significant difference) Test. Values were considered statistically significant when P <0.05.

RESULTS

Table 2 shows Mean±SD data representation of hour '0' for all three groups throughout 8 weeks of study period. The OGTT values were higher than normal range in all groups. The value did not change appreciably throughout in group 1. But treatment groups 2 and 3 showed a rising trend as the study progressed from 28 days onwards. The rise in values differed in both treated groups. The increase in blood glucose values in 0 hours was higher in Atorvastatin group than Rosuvastatin.

Table 3 shows data of hour '1' for all the groups throughout 56 days of study. The value did not change appreciably from day 0 throughout in group 1. But treatment groups i.e. 2 and 3 showed a rising trend as the study progressed from 4th week onwards. Both statin treated groups showed difference in rise of blood glucose.

Table 2: Hour "0" data of all the groups throughout the study period (Mean±SD).

Hour 0	Day 0	Day 14	Day 28	Day 42	Day 56
	Mean±SD	**Mean±SD**	**Mean±SD**	**Mean±SD**	**Mean±SD**
Group 1	104.16±1.47	104.00±2.36	104.16±1.47	104.50±2.42	104.16±2.63
Group 2	105.16±1.47	105.50±2.42	117.00±1.41	119.16±1.47	122.33±1.21
Group 3	105.83±2.48	105.33±1.21	110.00±1.41	113.66±1.63	118.66±1.63

Table 3: Hour "1" data of all the groups throughout the study period (Mean±SD).

Hour 1	Day 0	Day 14	Day 28	Day 42	Day 56
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Group 1	171.16±5.63	171.83±6.43	171.33±7.25	171.16±5.91	171.33±6.02
Group 2	171.83±2.78	171.66±5.71	198.16±2.31	210.16±2.31	222.83±3.54
Group 3	171.33±2.87	171.83±3.65	188.50±1.87	198.33±2.16	209.00±2.60

Table 4: Hour "2" data of all the groups throughout the study period (Mean±SD).

Hour 2	Day 0	Day 14	Day 28	Day 42	Day 56
	Mean±SD	Mean±SD	Mean±SD	Mean±SD	Mean±SD
Group 1	146.66±2.80	147.00±4.81	146.83±3.06	147.16±2.78	147.66±2.58
Group 2	147.00±2.60	147.16±2.04	167.50±1.87	176.83±2.31	187.50±1.87
Group 3	147.16±2.40	147.50±3.27	165.16±3.31	172.33±2.16	179.50±1.87

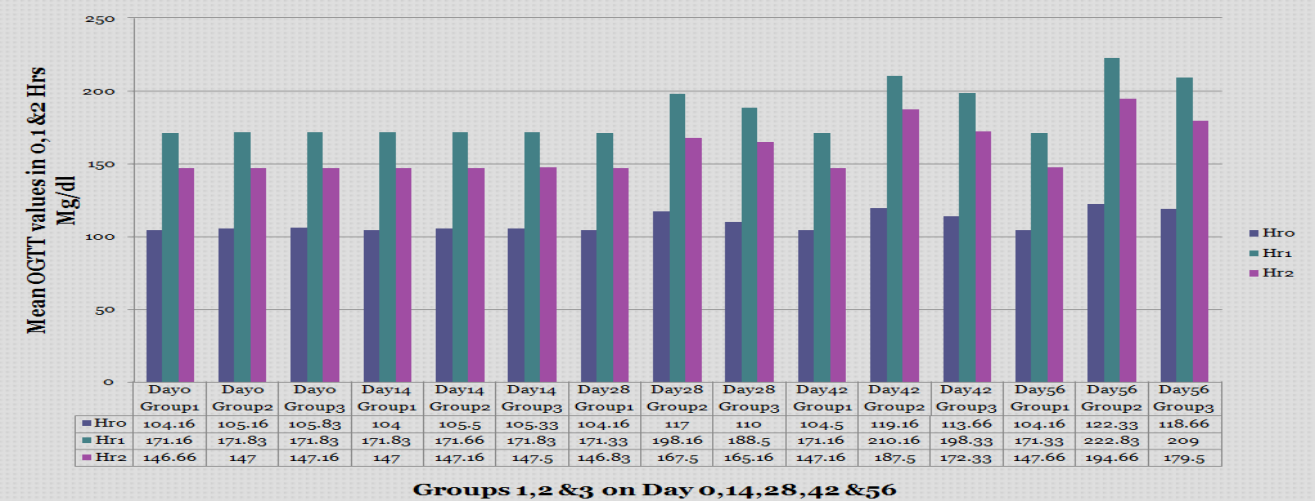

Figure 1: Comparison of 0, 1 and 2 hr OGTT of all groups throughout the study period.

In Table 4 also the values were higher than normal range. The value did not change appreciably throughout in group 1. But treatment groups i.e. Atorvastatin and Rosuvastatin showed increment as the study progressed from 28 days onwards, however there was no significant difference in values between group 2 and 3 at 28th day. It also shows that the increase in mean blood glucose values in 2 hours was higher in group treated with atorvastatin than in rosuvastatin from 42 days onwards.

Figure 1 gives the comparison between groups. The values for 0, 1 and 2 hours glucose levels were higher than normal range in group 1 but this group had negligible changes in OGTT as the study progressed. The values on 0 and 14th day of 2 and 3 groups were similar to that of group 1 (hyperglycaemic control). It indicates that the effect of statins on glucose metabolism was not apparent till 2 weeks but took 4 weeks to show their effects. There were significant differences in values in all hours between groups from 28th day onwards except 2hr value on 28th day between group 2 and 3.

DISCUSSION

We have chosen low dose of streptozotocin (25mg/dl) I.P to produce prediabetic state in rats i.e. by partial β cell destruction. The effect of statins on glucose tolerance in full dose (50-60mg/dl) STZ induced diabetic model rats, the diabetes induced may be too severe to detect mild influence of a drug on the glucose tolerance as observed by Makoto Kanda, Kumi Satoh, and Kazuo Ichihara.[21]

Ganda et al, have demonstrated a progressive increase in mean plasma glucose following administration of streptozotocin greater than 20mg/kg. The blood glucose and OGTT-induced increase in the glucose were progressively increased depending on the dose of streptozotocin (which gives a sigmoid curve).[22]

It seems that not only the glucose tolerance after a glucose load was affected but also the corresponding fasting levels (0 hrs) were also impaired both the instead of all statin treated groups. It means both muscle (IGT) and hepatic (IFG) insulin resistance may have been impaired. Moreover, both the first and early (IFG) and late phase (IGT) of insulin secretion might have been defective. Ding et al, in 2009 observed no change in fasting plasma glucose after treatment with atorvastatin (10mg-40mg) in 27 individuals compared to 21 controls.[23]

SPARCL (atorvastatin) study in 2006 and JUPITER (rosuvastatin) study in 2008 demonstrated a significant increase in the incidence of diabetes in patients on atorvastatin (8.71%) and rosuvastatin (3.0%) respectively compared to placebo.[24,25] The higher incidence with atorvastatin as compared to rosuvastatin supports our findings. Coleman et al, and Ratpathak et al, in their respective meta-analyses of RCTs HPS (simvastatin), LIPID (pravastatin), ASCOT (atarvastatin), JUPITER (rosuvastatin) and CORONA (rosuvastatin) found that there was increased risk of diabetes with these statins which is coherent with our study.[10,13] Sattar N, Preiss D, Murray HM et al, meta-analysed through pooled data from 13 trials between 1994 and 2009 revealed statin therapy was associated with a 9% increased risk of diabetes.[11,12] However their analysis differed from ours in the fact that Rosuvastatin was found to be most diabetogenic followed in sequence by atorvastatin.

Statins are known to modulate insulin secretion and sensitivity through various mechanisms which are as follows:[26-28]

The possible hypotheses through which the statins increased hyperglycemia may have involved both decreased insulin secretion and increased insulin resistance. The insulin secretion may be decreased (in both lipophilic and hydrophilic statins) due to proposed mechanisms like statin induced inhibition of the glucose induced cytosolic Ca^{2+} signaling and insulin secretion by blocking L-type Ca^{2+} channels in β cells (more with lipophilic statins); chronic cholesterol depletion causing dysregulation of SNARE proteins in pancreatic β cells and inhibition of the voltage gated Ca^{2+} channels and also inhibiting the activity of glucokinase the rate- limiting enzyme for intracellular glucose metabolism; the interplay between inflammation, oxidation, and apoptosis- all potentially triggered by increased abundance of plasma-derived LDL-cholesterol due to statin-induced blockade of de-novo cholesterol synthesis; interference with β cell insulin secretion by interfering with isoprenylation of guanosine triphosphate (GTP) binding proteins; and statin inhibited HMGCoA reductase suppression of synthesis of ubiquinone (CoQ), an essential factor in the mitochondrial electron transfer system, resulting in inhibition of insulin secretion due to reduced production of ATP.

The possible mechanisms through which statins (mainly lipophilic Atorvastatin) may have increased insulin resistance due to suppressed synthesis of isoprenoids causing downregulation of Glut-4 expression on skeletal muscles and adipocyte cells, leading to impaired glucose uptake; statin-induced cholesterol lowering per se contributing to myocyte damage of skeletal muscle fibre causing skeletal muscle insulin resistance; statin induced myalgia and fatigue may impair exercise capacity and aggravate sarcopenia, which is associated with impaired glucose intolerance; depletion of CoQ10 and subsequent mitochondrial damage in skeletal muscles and adipocytes limiting their glucose uptake; decrease in adiponectin (an insulin sensitizing cytokine released from adipocytes) levels by Rosuvastatin.

CONCLUSION

To conclude, both atorvastatin and rosuvastatin have impairing effects on glucose tolerance. Both atorvastatin and rosuvastatin also have impairing effects on fasting

blood glucose. Hydrophilic rosuvastatin had better effect on glucose tolerance and fasting blood glucose than the lipophilic atorvastatin. So, if statins have to be used Rosuvastatin and not atorvastatin may be a rational choice in patients with risk of hyperglycemia.

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