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Effect of Telmisartan On Blood Glucose Levels and Blood Lipid Levels in Streptozotocin Induced Diabetic Rats

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To evaluate the effect of telmisartan on blood glucose levels and blood lipid levels in streptozotocin induced diabetic rats. Eighteen Wistar albino rats weighing 150-200gms of either sex were randomly selected from the central animal facility, and divided into 3 groups. Diabetes was induced by injecting Streptozotocin intraperitonelly. The control group received 1% Gum acacia(oral), standard group received 0.5 mg/kg Glibenclamide (oral) and the test group received Telmisartan7.2mg/kg body weight (oral) from 0-28 days respectively. Body weight of the individual rats were measured on the respective days before blood glucose estimation on 0, 1, 3, 7, 14, 21 & 28th day and fasting blood glucose was estimated by (ACCUCHECK) glucometer. Estimation of fasting lipid profile by lipid screening strips on 1st and 28th day. When compared to control the capillary blood glucose (CBG) levels in the Telmisartan group was less at all the intervals but comparable with that of standard drug Glibenclamide in Streptozotocin induced diabetic rats. Improved lipid profile was seen with the Telmisartan group when compared to control group in Streptozotocin induced diabetic rats. Hypoglycemic activity and improved lipid profile action was seen with Telmisartan group which is comparable to standard drug glibenclamide in streptozotocin induced diabetic albino rats.

Keywords: Adiponectin, Angiotensin II, Diabetes, Hypoglycemia, PPAR a.

Diabetes is usually caused by a complex interaction of genetics, environmental, inflammation and autoimmune factors. The metabolic dysregulation and complications are associated with diabetes are due to glucotoxicity, lipotoxicity, formation of Advanced Glycation End Products (AGEs), Protein kinase C and Hexosamine pathway products, all these comprehensively causes secondary pathophysiologic changes in multiple organ systems that impose a tremendous burden on the individual with diabetes and on the health care system. All these lead to both morbidity and mortality in these patients as a result of microvascular (retinopathy, neuropathy, and nephropathy) and macrovascular (heart attack, stroke, peripheral vascular disease) complications and leading to end organ damage. [1, 2, 3]

When renin binds to Pro Renin Receptor (PRR) the catalytic activity of renin is augmented. However, pro renin or renin can dissociate from PRR to return to their original state. Non enzymatic activation of pro renin plays a major role in local Renin Angiotensin system (RAS), where pro renin exerts effects via Angiotensin II dependent and also through independent pathways.

Angiotensin II dependent action through AT receptor:-Activation of pro renin or renin generates Angiotensin I which is converted to

Angiotensin II by ACE (Angiotensin converting enzyme). Angiotensin II acts on AT_1 receptors on tissue cells to produce effects on cell growth, inflammation, and apoptosis.

Angiotensin II independent pathway:- Binding of pro renin or renin directly to PRR on cell surface triggers intracellular signaling via activation of Mitogen Activated Protein (MAP) kinases, plasminogen activator inhibitor-1, Janus Kinase-Signal Transducer and Activator of Transcription (JAK-STAT) pathway, transcription factors proto oncogenes.

Angiotensin II increases the synthesis and concentration of tumor necrosis factor á, interleukin 6, IL-1, chemokine monocyte chemo attractant protein 1 and nuclear factor kappa of activated B cells (NF êB) leading to inflammatory cell infiltration in â cells anda key role in the pathogenesis of type 2 diabetes mellitus. Inflammatory cytokines like IL-6 and IL-1 produce dyslipidemia, with increased VLDL and decreased HDL. IL-1â is known to activate the Inhibitor of êâ (Iêâ) and induce insulin resistance. [4, 5]

Adiponectin and Adipokines

Mesenteric adipocytes contain LTB4 inflammatory molecule which cause release in inflammatory molecules leading to type 2 diabetes. Resistant macrophages and immune cells are activated by extra fat particularly in the liver and mesentery. [6] LTB4 which is released causes positive feedback loop leading to release of more LTB4 from newly arriving macrophages. Inflammation in diabetes is a chronic process and LTB4 activates other cells.

LTB4 receptors are present in liver, fat and skeletal muscles. In obesity the cells become infammed. LTB4 receptors on macrophages surfaces are activated when LTB4 binds to them and release adipokines leading to insulin resistance. [7]

Adipocytes secrete biological products. Adipocytes products (adipokines) produce an inflammatory state, which modulate insulin sensitivity in skeletal muscles and liver.[8] Adiponectin is an adipokine and acts as an insulin sensitizing peptide. The concentration of adiponectin is reduced in Diabetes and this may contribute to pathogenesis of diabetes by insulin resistance.[9, 10]

Adiponectin has receptors on skeletal muscles and on liver and it plays a important role in regulation of glucose metabolism, lipid metabolism, inflammation and oxidative stress.

Expression of adiponectin receptors by small interfering RNA leads to globular and full length adiponectin and mediates AMP kinase, PPAR ã and PPAR-á ligand activities.[11, 12]

Insulin sensitizing action of adiponectin is through activating AMPK (5' Adenosine Monophosphate kinase) and by directly regulating glucose metabolism and insulin sensitivity.[13, 14, 15]

Thus, angiotensin II receptor inhibition through Telmisartan has blood glucose lowering effect and hypolipidemic action is due to adiponectic expression via PPAR ã, AMP kinases activation and decreasing the inflammatory response of IL1, IL6, and TNF-á etc. Lipid lowering effect by PPAR á expression, induction of hepatic ACSL1 (Acyl CoA Synthetase Long chain), CPT1A (Carnitine Palmitoyl Transferase) and reduction in catecholamine levels (noradrenaline).

HYPOTHESIS: Telmisartan decrease the blood sugar level and lipid level through its activity of blocking action of angiotensin II on AT_1 receptor and promoting the activity of adiponectin and decreasing the activity of adipokines.

METHODS AND MATERIALS

The study was conducted at Central Animal Facility, after getting the approval from Institutional Animal Ethics Committee (*IAEC)*. CPSEA approval number from IAEC of: JSSMC/ IAEC05/5657/DEC 2013.

Wistar albino rats of either sex of average weight 150-200gms aged 3-4 months were used in the experiments.Under suitable conditions of housing, temperature, ventilation and nutrition the rats were inbred in the central animal facility.The rats were acclimatized to the laboratory conditions for seven days prior to test before assigning animals to treatment group. The doses of drugs were based on human daily dose converted to that of rats according to Paget and Barnes (1962). The method employed in this study to induce diabetes was chemical method using streptozotocin, given intraperitoneally. Blood glucose estimation was done by using glucometer.

Drugs and Chemicals: Glibenclamide (*Sanofi Aventi, India),* Telmisartan (*Ranbaxy, India),*

Streptozotocin *(Sisco Research Laboratories Pvt. Ltd.)*.The rats were divided into 3 groups containing six animals(n=6) in each group (control, standard and test group).

Group 1: Diabetic control: 1% Gum acacia(oral)

Group 2: Standard: 0.5 mg/kg body weight, Glibenclamide (oral)

Group 3: Telmisartan7.2mg/kg body weight (oral).

- Blood was collected from 12 hr fasted rats by rat tail vein puncture method, 1hr after each dose administration of the respective drugs. Fasting blood glucose was estimated on 0, 1, 3, 7, 14, 21 & 28th day.
- Body weight of the individual rats was measured before blood glucose estimation on 0, 1, 3, 7, 14, 21 & 28th day.
- Fasting lipid profile was estimated by lipid screening strips on 1st and 28th day.

Statistical analysis

The results was analyzed and mean, standard deviations were calculated for each group. One way ANOVA followed by post hoc Tukey's test for statistical significance between groups. IBM SPSS statistics ©IBM Corporation and Other(s) 1989, 2012 software was used for statistical analysis purpose. $P < 0.05$ was considered as significant.

Table 1. Blood glucose levels in different groups

Groups(n=6)	D0	D1	D3	D7	D14	D21	D28
1 Diabetic control	351.16± 11.80	370.33± 15.85	382.16± 20.15	389.33± 23.82	405.5± 22.79	420.66± 23.76	438.83± 25.76
2 Standard	358.8± 15.94	351.66± 21.27	327.33± 17.52	301.33± 19.07	265.5± 22.75	200.16± 24.70	173.66± 24.48
3 Telmisartan	360.33± 12.53*	355.16± 22.06*	337.5± 21.19*	313.83± 24.44*	281.5± 22.89*	236.66± 28.77*	210.83± 21.02*

Data expressed in Mean ± SD values. *P<0.01 compared with control. SD: standard Deviation

D 0 = before giving the drug

D 1, D 3, D 7, D 14, D 21, D 28 = 1st , 3rd , 7th ,14th , 21st ,28th days of administration of the drugs respectively

Table 2. Statistical Analysis showing comparison of Total cholesterol levels between different groups on day 1 and day 28

Groups (n=6)	Mean+ SD on 1st day	Mean+ SD on 28th day	Difference in TC levels
Diabetic control	119.33±10.78	212.5±8.11	93.17±2.67
Standard	106.6±7.76	100.6±7.89	6±0.13
Telmisartan	111.5±11.84*	132.83±6.43*	21.33±5.41*

Data expressed in Mean ± SD, *P<0.05 compared with control.

Table 3. Statistical Analysis showing comparison of Triglyceride levels between different Groups on day 1 and day 28

Groups (n=6)	Mean+ SD on 1st day	Mean+ SD on 28th day	Difference in TG levels
Diabetic control	101.33±14.34	210.16±14.46	108.83±0.12
Standard	109.5±14.55	101.83±5.34	7.67±9.21
Telmisartan	120.5±8.31*	157.66±12.19*	37.16±3.88*

Data expressed in Mean + SD, *P<0.05 compared with control.

RESULTS

The diabetic control rats showed progressive increase in blood glucose levels and the standard drug showed persistent decrease in the blood glucose level from 1st to 28th day. The test drug, Telmisartan produced consistent decrease in blood glucose levels from 3rd day to 28th day. From 1st to 3rd day there was no consistent fall in blood glucose level.Telmisartan group showed lesser reduction in the first week when compared to the standard group. By the end of second week there was fall in the blood glucose levels in both the standard and telmisartan group.Both Telmisartan and standard group almost performed same activityat the end of 4th week.

In diabetic control there was a gross increase in total cholesterol, triglyceride and LDL level.In telmisartan group there was moderate decrease in total cholesterol and LDL. And there was moderate raise in Triglycerides when compared to control.The fall in HDL level in telmisartan group was very minimal with standard. There was gross decrease in HDL level in diabetic control group

There was 20%reduction in body weight in diabetic control. In standard group there was 7% increase in body weight. In the Telmisartan group there was 1.46% increase in the body weight.

DISCUSSION

In standard group the blood glucose level on day 0 was 358.8mg/dl and on day 28 it was 173.66mg/dl. This indicates the standard drug glibenclamide (0.5mg/kg) has good immediate and prolonged action which leads to fall in blood glucose level. In telmisartan group the blood glucose level on day 0 was 360.33mg/dl and on day 28 it was 210.83mg/dl. The fall in the blood glucose level in telmisartan group from day 0 to day 28 id 149.5mg/dl.

Progressive and consistant hypoglycemic effect was seen with telmisartan group but the maximum effectiveness was seen after 1st week of drug administration. The persistant hypoglycemic effect was seen upto the end of 4 weeks.

At the end of study when compared to standard the percent reduction of blood glucose level in Telmisartan group was 51.95%. While in standard it was 60.42%.The reduction in mean percent blood glucose level was statistically significant ($p<0.001$) compared to diabetic control group. This indicate that Telmisartan has significant

Table 4. Statistical Analysis showing comparison of LDL levels between different Groups on day 1 and day 28

Groups (n=6)	Mean+ SD on 1st day	Mean+ SD on 28th day	Difference in LDL levels
Diabetic control	127.83±10.14	213.66±9.11	85.83±1.03
Standard	111.33±9.89	114±10.75	2.67±0.86
Telmisartan	118.83±4.66*	150.5±8.11*	31.67±3.45*

Data expressed in Mean + SD, *P<0.05 compared with control.

Table 5. Statistical Analysis showing comparison of HDL levels between different Groups on day 1 and day 28

Groups (n=6)	Mean+ SD on 1st day	Mean+ SD on 28th day	Difference in HDL levels
Diabetic control	37.33±5.2	27.16±4.26	10.17±0.94
Standard	42.33±3.07	44.66±3.61	2.33±0.54
Telmisartan	39.5±1.87*	38.66±2.58*	0.84±0.71*

Data expressed in Mean + SD, *P<0.05 compared with control.

Table 6. Table showing mean values of body weight of rats in different groups on different days

Groups (n=6)	Before STZ	D0	D1	D3	D7	D14	D21	D28
Diabetic control	215	169	172	153	161	159	171	173
Standard	200	182	173	181	192	189	201	214
Telmisartan	205	180	178	160	168	188	200	208

Values in grams

and sustained hypoglycemic activity persisting till last day (28th day) compared to standard in their respective experimental dosages. The above data conclude at all-time intervalsin experimentally induced diabetes telmisartan has the capacity to improve the glycemic status and is almost equal to that of standard. [Table 1]

In diabetic control there was a gross increase in total cholesterol (93.17mg/dl), triglyceride(108.83mg/dl) and LDL level(85.83mg/dl), whereas there was gross decrease in HDL level (10.17mg/dl) compared to both standard and test group from 0-28 day. While, the test drug Telmisartan showed moderate increase in total cholesterol (21.33 mg/dl), triglyceride (37.16 mg/dl) and LDL levels (31.67 mg/dl). The decrease in HDL levels of Telmisartan was 0.84mg/dl from 0-28 day. Telmisartan was inferior to standard (6mg/dl) in reducing the total cholesterol from 0-28 days. Telmisartan was inferior to standard (7.67mg/dl) in reducing the triglyceride levels from 0-28 days. Telmisartan was inferior to standard (2.67mg/dl) in reducing the LDL levels from 0-28 days. Telmisartan was inferior to standard (2.33mg/dl) in increasing the HDL levels from 0-28 days. Thus to conclude the test drug Telmisartan is better in improving the lipid profile compared to control and is comparable with that of standard. [Table 2, 3, 4and 5]

As a consequence of induction of diabetes by Streptozotocin there was significant reduction in body weight in the control group of rats between 0-28 days. In the standard group of rats there was no reduction in the body weight rather there was slight improvement in weight from 0-28 days but in the Telmisartan group there was no much change in the body weight between 0-28 day of experimentation [Table 6]. Improved body weight of the treated animals indicates the efficacy of *Telmisartan* in controlling the glucose excretion and blood glucose level of diabetic rats. The activity and behavior of diabetic control was less and gradually decreased from 0-28th day but the activity and behavior was almost normal throughout the study in standard and Telmisartan group.

CONCLUSION

Thus the glucose lowering effect of Telmisartan was due to the mechanism like inducing adiponectin protein expression, via PPAR ã activation, AMP kinases activation, decreasing the inflammatory response of IL1, IL6, TNF-á and reduction in catecholamine levels (noradrenaline). Lipid lowering effect of Telmisartan was due to PPAR á expression, induction of hepatic ACSL1 (acyl coA synthetase long chain), CPT1A (carnitine palmitoyl transferase).

The present study concludes the hypoglycemic activity and improved lipid profile action of Telmisartan in Streptozotocin induced diabetic albino rats.

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